THE UNIVERSITY
of EDINBURGH

ALCOHOL RELATED CANCERS IN SCOTLAND

Ian Grant

DEGREE SUBMITTED FOR: DOCTOR OF PHILOSOPHY

THE UNIVERSITY OF EDINBURGH

APRIL 2015

Declaration

Thesis: Alcohol related cancers in Scotland

I, Ian Grant hereby declare that I am the sole author of this thesis. I developed the hypotheses examined in this thesis and conducted all aspects of the research except when contribution of colleagues is acknowledged. This thesis has not been submitted for any other degree or professional qualification.

Signature: …… Date: ……

Acknowledgements

Well it's taken a very long time to get to the 'end' and I would never have brought it to a close without the help and advice of a number of people.

I would like to thank my principal supervisor Professor Sarah Wild and my second supervisor, Dr Colin Fischbacher, for their guidance, comments and advice throughout the thesis. This thesis would not have been possible without their patience and fortitude.

I would like to thank Dr Diane Stockton, Public Health Specialist and Richard Lawder, Senior Information Analyst at ISD for providing advice on statistical matters. I wish to acknowledge Dr David Brewster who provided the original ideas on which this thesis was built. I also would like to thanks Lesley Bhatti at ISD for her help with accessing data from the Scottish Cancer Registry. I would also like to acknowledge the support of Susan Frame and Dr Diane Stockton at ISD for allowing me to juggle my ISD commitments with my PhD.

I wish to acknowledge ISD, National Services Scotland, for providing most of the funding for the thesis and for allowing me the opportunity to conduct this thesis.

Abstract

Introduction:

There is considerable epidemiologic evidence that drinking alcoholic beverages is associated with an increased risk for certain cancers (i.e. cancers of the upper-aero digestive tract) though the evidence of an increased risk for colorectal and breast cancer is controversial. For other cancers (e.g. kidney, bladder, lung, ovarian) the evidence remains inconclusive. Considering the high prevalence of many of these cancers in Scotland, even a small increase in cancer risk is of great importance, therefore from a public health perspective it is important that the evidence linking alcohol to an increased risk of cancer is continuously evaluated. Questions still remain, however, concerning the robustness and consistency of the alcohol information collected across studies. Furthermore, the heterogeneity of drinking levels, drinking patterns, and definitions of standard drinks internationally make it problematic to generalise the findings of these studies.

Aim:

To further clarify the role of alcohol in the occurrence of cancer in a country marked by high levels of alcohol consumption and rising incidence of many of the cancers linked with alcohol consumption. The aim of this study, therefore, is to (1) investigate the association between alcohol consumption and the risk of fourteen cancers using routine Scottish data sources and (2) to test the hypothesis that alcohol consumption increases the risk of these cancers in a sample of the Scottish population.

Methods:

A systematic review of the published literature between 1999, the date of the last major review, and 2009 on alcohol related cancers to determine the strength of evidence on the association between alcohol and cancer, and if it varies by amount drunk, by drinking pattern and drink type. Two cohort studies were formed; in the first a population based cohort study, based on a linkage between a representative general population sample and hospital, cancer registry and death records in Scotland, describes risk of cancer by amount of alcohol consumed per week and by drinking frequency and in a second study, based on a linkage between hospital and cancer and death records, the risk of cancer in a population that has been admitted to hospital (between 1981 and 2007) with an alcohol related diagnosis was investigated.

Results:

The present study provides weak evidence of a relationship, in a sample of the Scottish general population, between alcohol drinking frequency and amount consumed and cancers of the upper aero digestive tract. An increased risk (though non-significant) of colorectal cancer for daily drinkers was observed but no relationship was detected for amount consumed for this cancer. There was no

association observed between drinking frequency or amount consumed and risk of breast, lung and prostate cancer. People with an alcohol-related hospital admission, however, are at substantially higher relative risk of head and neck and upper gastrointestinal cancers compared to the general population, and relative risks increase with increasing levels of deprivation. It is likely that tobacco smoking also contributes to this excess risk.

Conclusions:

The generalisability of findings from the international literature to Scotland is problematic due to different measures of alcohol consumption. Although the present study provides evidence that people in Scotland who require in-hospital care for an alcohol related condition are at substantial subsequent relative risk of head and neck and upper gastrointestinal cancers and that the relative risk increases with increasing levels of deprivation, further prospective studies with longer-follow-up are required to assess the risk between alcohol consumption and cancer in the Scottish general population.

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Abbreviations

BMI	Body Mass Index
EASR	European age standardised rate
EPIC	European Prospective Investigation into Cancer and Nutrition
GLS	General Lifestyle Survey
HEPS	Health Education Population Survey
HMCE	Her Majesty's Custom and Excise
HR	Hazard ratio
IARC	International Agency for Research on Cancer
ICD	International Classification of diseases
ISD	Information Services Division, Scotland
NRS	National Records Scotland (formerly General Registrar Office for Scotland)
NOS	Newcastle-Ottawa Scale
OR	Odds ratio
QF	Quantity Frequency
RR	Relative risk
SCC	Squamous Cell Carcinoma
SES	Socio-economic status
SHeS	Scottish Health Survey
SIMD	Scottish Index of Multiple Deprivation
SMR	Scottish Morbidity Record
UK	United Kingdom
WCRF	World Cancer Research Fund
WHO	World Health Organisation

Chapter 1: Introduction

This chapter aims to provide the historical and policy perspectives on alcohol and health and to review the historical evidence of the link between alcohol and cancer. Finally, it details the thesis hypotheses and describes the thesis objectives.

1.1 A short history of alcohol

An alcoholic beverage is a drink containing ethanol (or *ethyl alcohol)*, commonly known as alcohol. Alcoholic beverages that have lower alcohol content (e.g. beer and wine) are produced by fermentation of sugar- or starch-containing plant material. Beverages of higher alcohol content (e.g. spirits) are produced by fermentation followed by distillation. The effects of alcohol (i.e., ethanol) on various tissues depend on its concentration in the blood (blood alcohol concentration [BAC]) over time. BAC is determined by how quickly alcohol is absorbed, distributed, metabolized, and excreted (Zakhari 2006). After alcohol is swallowed, it is absorbed primarily from the small intestine into the veins that collect blood from the stomach and bowels and from the portal vein, which leads to the liver. From there it is carried to the liver, where it is exposed to enzymes and metabolized. The major pathway for alcohol metabolism involves the enzyme alcohol dehydrogenase. This enzyme converts alcohol to acetaldehyde through a chemical process called oxidation. Acetaldehyde is highly toxic to the body, even in low concentrations. Normally, however, the enzyme aldehyde dehydrogenase rapidly oxidizes acetaldehyde to acetate (Maher 1997). Chronic alcohol consumption and alcohol metabolism are strongly linked to several pathological consequences and tissue damage (Zakhari 2006).

Alcoholic beverages have been used in human societies at least since the beginning of recorded history. Fermented beverages existed in early Egyptian civilization and there is evidence of an early alcoholic drink in China around 7000 B.C. In India, an alcoholic beverage called sura, distilled from rice, was in use between 3000 and 2000 B.C. The Babylonians worshiped a wine goddess as early as 2700 B.C. In Greece, one of the first alcoholic beverages to gain popularity was mead, a fermented drink made from honey and water (Hanson 1995, Walton 2001). During the time of the Roman Republic and Empire, trade in wine and other alcoholic beverages grew enormously. In this period, the Romans were essentially responsible for the beginnings of the European wine industry planting vineyards across Europe including England, France, Germany, Italy, Hungary and other parts of southeastern Europe (Blocker et al 2003). With the collapse of the Roman Empire and decline of urban life, religious institutions, particularly monasteries, became the repositories of the brewing and winemaking techniques that had been earlier developed (Babor et al 1986). As the end of the middle ages approached, the popularity of beer spread to England, France and Scotland (Austin 1985). Beer

brewers were recognized officially as a guild in England (Monckton 1966) and the adulteration of beer or wine became punishable by death in Scotland (Hanson 1995). The most important development, in Europe, regarding alcohol throughout the Middle Ages was probably that of distillation (Walton 2001). The knowledge of this process, first used in India and China from around 800BC, began to spread slowly among monks, physicians and alchemists, who were interested in distilled alcohol as a cure for ailments (Hanson 1995). Spirit drinking was still largely used for medicinal purposes throughout most of the 16th century. It has been said of distilled alcohol that, "the sixteenth century created it; the seventeenth century consolidated it; the eighteenth popularized it." (Braudel 1967, quoted in Hanson 1995). The industrial revolution and subsequent European colonial expansion changed the cultural position of alcohol nearly everywhere (Hanson 1995, Room et al 2005, Berridge 2006). New forms of alcoholic beverages were introduced especially around spirit based drinks e.g. gin. A product prepared within the household and community was gradually transformed into an industrial commodity, available at any time and virtually any place (Room et al 2005).

1.2 Alcohol and health: historical perspective

Accompanying the near ubiquity of alcoholic beverages in human history, has been an appreciation, documented in ancient texts from Greece, Palestine, or China, of the social and health problems caused by drinking (Babor 1986, Room et al 2005). During the Roman period came the first complaints of widespread public drunkenness and of what we now commonly describe as "binge drinking", for example alcohol was frequently distributed free at charge at festivals, large public gatherings etc., and often led to large-scale disorder (Hanson 1995). On the other hand, alcohol was also prized for its medical properties. Classical medical opinion generally held that wine had curative properties, particularly for gastric and urological ailments (Blocker et al 2003). What was most notable about responses to intoxication or excessive use of alcohol, was that concerns revolved around moral attitudes and social behaviours regarded as ‘licentious’, ‘sinful’ or ‘criminal’, that were associated with excessive drinking (Thom 2001). From the Middle Ages, through at least the beginning of the eighteenth century, attitudes toward alcohol and drinking were also generally characterized by a continued recognition of the positive nature of moderate consumption and an increased concern over the negative effects of drunkenness (Hanson 1995, Walton 2001). Drunkenness itself became a civil offence in England in 1552, and in 1606 an act was passed in England to allow authorities “to repress the odious and loathsome sin of drunkenness” (Thom 2001). Similar legislation was passed in Scotland in 1617. There is little evidence, however, that this legislation was rigoursly enforced (Thom 2001) and one reason for this, as Porter (1985) observes, was that heavy drinking was still prized as a ‘manly and sociable custom’ in Georgian Britain. Heavy

drinking, which was generally viewed as arising out of the increased self-indulgence of the time, was seen as a threat to spiritual salvation and societal well being (Hanson 1995). An early example of this, in the United Kingdom, can be seen in the language used the Royal College of Physicians in a statement to the House of Commons in 1726, which demanded an increase in taxes on spirits to act as a disincentive to 'this (gin drinking) great and growing evil' *(*Royal College of Physicians 1987). A similar tone was adopted by the then government, which in passing the 1736 Gin Act to control the sale of gin, stated that action was necessary because of the prevalence of gin consumption "among the people of lower and inferior rank, which led to the destruction of their healths, rendering them unfit for useful labour and business, debauching their morals, and citing them to all manner of vices" (Nicholls 2009).

While drunkenness was still an accepted part of life in the eighteenth century (Austin, 1985), the nineteenth century brought a change in attitudes as a result of increasing industrialization and the societal changes that followed (Porter 1990). From an early stage of the industrial revolution, alcohol was more available, stronger and cheaper than ever before. This led to sharp increases in the consumption of alcohol across Europe peaking in the 1870's (Wilson, 1940, p335 in Berridge 2006). The most significant increases in consumption occurred among the working classes (Knapp 1998). Drunkenness became progressively more common, more public and more associated with poverty (Porter 1985, Barrows and Room 1991, Anderson and Blaumberg 2001). As Walton (2001) observed, the new work patterns the Victorian era ushered in required labourers, however, to be available and fully functioning for a clearly defined major portion of their waking hours. Therefore, in the context of an industrialising society which needed adaptable, time-aware workers, sobriety became a virtue (Porter, 1990 Berridge 2006). In most countries where Protestant Christianity was strong, substantial temperance movements in the 19th century at first sought individual pledges to abstain from drinking and eventually pressed for national prohibition (Room et al 2005). In Scotland, the temperance movement first became organised in the 1820s and by the 1830s temperance societies had sprung up all over Glasgow and elsewhere in Scotland (Glatt 1958). In England, Joseph Livesey and seven Preston working men signed a pledge in 1832 stating that they would never again drink alcohol. Other groups of working men followed the example of Livesey and his friends, and by 1835 the British Association for the Promotion of Temperance was formed (Blocker et al 2003).

The issues of the health effects of alcohol in the late 19th and early 20th Century were, therefore, seen within the context of broader debates about the temperance movement and prohibition (Leon 2001). The most prominent leader of the temperance movement was Dr. Benjamin Rush. His ideas were the primary foundation of the temperance movement. Rush explained that alcohol consumption was detrimental to one's health, both physical and psychological. In 1784, he described what we would now call alcohol dependence as an involuntary condition. Rush subsequently laid the foundation for what is now called the disease concept or model of addiction and alcoholism (Thom 2001, Berridge

2006). By the end of the Eighteenth century, prominent physicians were observing, that a 'new and terrible source of mortality had been opened for the 'poor', and this marked a crucial transition in public assessment of what was problematic about drink. Alcohol as Edwards (2000) noted "had become, in the modern term, a public health issue". These issues came to the fore in an era of rapidly changing social conditions, new philosophical and political perspectives and the emergence of new power elites (Thom 2001). Medical temperance supporters worked with public-order interests in moves to establish a state-funded treatment system for 'inebriates' (the alcoholics of the day) and to divert drunkards out of the criminal justice system and into treatment (Berridge 2006). In Scotland, the temperance campaigners achieved a notable triumph in 1913 with the Temperance (Scotland) Act allowing electors to vote locally on whether their district should allow the sale of alcohol.

Although the outbreak of World War One meant implementation of the law was suspended until 1919, excessive drinking and drunkenness, especially among serviceman and factory workers, remained a significant problem. The then British Prime Minister, Lloyd George even observed in a speech to factory workers in 1915 that, "…we are fighting Germany, Austria, and drink; and, as far as I can see, the greatest of these three deadly foes is drink" (Chalmers 1915). During the First World War controls were put in place, which were the equivalent of a national alcohol strategy (Berridge 2006). The creation of the Central Control Board (Liquor Traffic) in 1915 initiated a more active governmental interest in alcohol policy. Existing restrictions on opening hours (i.e. the 'afternoon gap' and Sunday trading were tightened, excise duties on beer and spirits were increased significantly, and the strengths of both beer and spirits were reduced) (Berridge 2006, House of Commons 2009). The restriction on opening hours was enshrined in the 1921 Licensing Act. Once the war was over, many Scottish communities took advantage of the Temperance Act to ban the sale of alcohol. In 1922, Winston Churchill, then a Liberal MP for Dundee, even lost his seat in parliament to a prohibitionist candidate (Paton 1992).

The effect of the temperance movement was to result in a steady decline in alcohol consumption between 1900 and 1945, as measured by alcohol sales derived from Customs and Excise figures (Department of Health 1995). The spate of legislation to control manufacturing, distribution and consumption of alcohol (e.g. the 1921 Licensing Act) along with major changes in social and economic circumstances had resulted in a fall in consumption and related problems and a wane in policy attention to alcohol issues in general (Thom 2001). By the 1930s, the influence of the temperance movement was on the decline. In Britain, attention had strayed from the disease concept of alcoholism towards social harms such as loss of productivity, accidents and crime and poverty associated with excessive alcohol consumption rather (Thom 2001). Thom argues that by the 1970's, the disease concept of alcohol had been firmly supplanted by a concern for alcohol misuse and problem drinking (rather than 'alcoholism') and the extent of alcohol related harm in communities and populations as a whole. The term "preventive paradox" summed up the belief that a greater level

of harm accrued from drinking by the majority of the population, than from the minority of alcoholics or excessive drinkers (Rose 1981, Kreitmann 1986). The 'new public health approach' proposed that both change in individual lifestyles and public health measures were required to minimize the harms related to the use of alcohol (Thom 2001).

The idea of 'sensible' drinking was introduced, in the early 1980s by the UK government's Health Education Authority, in response to increasing concern about rising number of hospital admissions for alcoholism and alcoholic psychosis and death rates from cirrhosis of the liver, (Dight 1976, Donnan and Haskey 1977, Royal College of Psychiatrists 1979, Tuck 1980, Haskey et al 1983). In 1984, the Health Education Council (the predecessor of the Health Education Authority) published the first edition of its pamphlet "That's the Limit" (Health Education Council 1984) . This drew on material from a similar pamphlet which had been developed by health educators and clinicians working in the field of addiction in the North East of England (House of Commons Science and Technology Committee 2012). This gave advice on sensible drinking - described as the amounts, well within the "safe limits", to which people should limit their drinking. These were defined as 18 "standard drinks" (equivalent to units) a week for men and 9 for women. "Too much" was defined as 56 a week for men and 35 for women. Initial advice framed these guidelines in terms of 'standard' drinks, the common measure of alcohol consumption used in many North American studies (Room 1977); a 'standard' drink is a notional drink that contains a specified amount of pure alcohol (ethanol). One standard drink always contains the same amount of alcohol regardless of serving size or the type of alcoholic beverage. A 'standard drink generally contains between 10-14 grams of pure ethanol although the measure varies among countries (ICAP 2010). Further guidance from the Governments' Health Education Authority in 1987, replaced the 'standard drink' with the alcohol 'unit' (Cabinet Office 2004); the 'unit' was a construct first developed by Dight (1976) in a survey of drinking habits in Scotland to overcome the problem that the predominant Scottish beverage, beer, was sold primarily in two different drink sizes, a half-pint and a pint (Room 2000). As Room (2000) observed, Dight chose the smaller size as the ``standard unit", although an ordinary male drinker in Scotland would think of ``a drink" in terms of a pint (equivalent to two standard units). When British governments then moved to promoting ``sensible drinking guidelines", the Dight unit took on a new role as the metric for stating these guidelines. Sensible drinking guidelines were set at a maximum of twenty one units weekly for men and fourteen units weekly for women in the 1987 edition of the pamphlet 'That's the Limit' (Health Education Authority 1987). Three of the medical Royal Colleges issued reports on alcohol in 1986/7 (Royal College of Psychiatrists 1986, Royal College of General Practitioners 1986, Royal College of Physicians 1987) endorsing the 1987 Health Education Authority line on "sensible" drinking. The British Government officially adopted the 1987 advice of the Royal Colleges in the Lord President's (1991) report "Action Against Alcohol Misuse" with national targets for reducing people drinking beyond these "sensible" levels being set in both England and Scotland (Tuck 1980,

Paton 1988, Department of Health 1995). These “safe and sensible” drinking guidelines were further developed following a review of the “sensible” drinking message partly in response to evidence that alcohol may be protective from coronary heart disease, but also in recognition that weekly consumption levels can have little relation to single drinking episodes and may mask short term episodes of heavy drinking which often correlate strongly with both medical and social harm (Department of Health 1995). Therefore, in addition to weekly “sensible” guidelines, guidelines were set for daily alcohol intake: no more than four units a day for men and three units for women.

Over the last decade, governments in Scotland and England have responded to concerns about the health and social harm associated with excessive drinking with a number of strategies (Scottish Executive 2002, Cabinet Office 2004, Scottish Government 2007, Department of Health/Home Office 2007) combining harm reduction approaches with law and order initiatives to address excessive drinking patterns, including 'binge drinking' and regular drinking above the daily and weekly guidelines. More recently, however, and in an innovative departure from traditional post war alcohol policy, the Scottish Government have proposed the introduction of minimum retail pricing for alcohol to prevent loss-leading and below-cost selling of alcohol which has “generated the conditions for increasing levels of drinking and alcohol-related problems” (Scottish Government 2009). Although minimum pricing remains relatively untested and has not yet been implemented in many places nor evaluated extensively, some evidence exists that price control can lead to reductions in alcohol problems; in Canada with minimum pricing of beer, and the implementation in some Australian localities of bans on the sale of the cheapest form of alcohol (which amounts to raising the minimum price) (Babor et al 1986, Stockwell et al 2011). Work quantifying the potential impact of policies targeting pricing and promotion of alcohol on alcohol related harm in England (ScHARR 2008) and Scotland (ScHARR 2009) has demonstrated significant potential health gains for harmful drinkers drinking above safe levels, (usually beyond those of hazardous drinking, with evidence of alcohol-related problems), and also important health gains in hazardous (drinking over the recommended weekly guidelines) and moderate drinkers (Raistrick et al 2006). The potential health gains depend greatly on the level of minimum price. At a low threshold (e.g. 25 pence per unit) there is little impact at reducing harmful outcomes, however, as the minimum price threshold increases, alcohol-related hospital admissions and deaths are estimated to reduce: for example, in Scotland 3,600 admissions per annum (once the full effect on the risk of harm has been realised) for a 40p threshold compared to 8,900 per annum for a 50p threshold (ScHARR 2009). Purshouse et al (2010) reported on the estimated effect of a £0.50 minimum price on the yearly prevalence of illness in England 10 years after policy implementation; of an estimated 49,000 cases of illness prevented by £0.50 minimum price, approximately two-thirds (64%) occurred in diseases of the circulatory system (net of any

increased cases of ischaemic heart disease) 16.5% (8,150 cases) in 'alcoholic disorders'[1] and 2940 (6.0%) in cases of epilepsy. There were also smaller reductions in the number of cases in diseases of the digestive system (1490), diabetes (1300) and cancer (1050).

1.3 Alcohol and health: a developing science

Leon (2001) asserts that alcohol is the epidemiological 'risk factor' with the longest history of systematic study. Early epidemiological studies, in the late nineteenth century and early twentieth century, started to link excessive alcohol consumption with increased mortality. In 1851, one of the first scientific papers on alcohol and its effect on mortality was published in the Journal of Statistical Society. This study, which followed up 'intemperates', observed a mortality rate three times higher among excessive drinkers, than that in 'abstainers' (Neison 1851 *in* Edwards 2000). The most systematic evidence of alcohol's health effects occurred in 1904 when Moore (1904) published an analysis of mortality among over sixty thousand policy holders who had taken out life insurance with the United Kingdom Temperance and General Provident Institution over the period 1841-1901. Moore found the mortality rate among male non-abstainers was unexceptional by the standard used by the life-insurance industry at the time. However, mortality among abstainers was considerably lower, resulting in a 10% greater life expectancy from age 30 years, than among non-abstainers. Similar results were reported for women.

Despite these earlier studies, it is generally considered that the scientific study of alcohol related mortality began in the 1920s with Pearl's studies (1926) of alcohol and longevity (Leon 2001, Mann et al 2003). Pearl, in a study whose primary aim was to throw light on genetic factors in tuberculosis, also investigated death rates among various types of drinkers based on analyses of family history data collected in Baltimore in the early 1920s (Leon 2001). Pearl demonstrated that heavy drinkers had higher rates of overall mortality and of cirrhosis mortality than did lighter drinkers or abstainers. In the same study, it was also reported that abstainers had a slightly higher mortality rate than moderate drinkers, providing early evidence of a U-shaped associated between alcohol consumption and mortality. Over the next fifty years, from Pearl's work in Baltimore, studies continued to observe higher liver cirrhosis death rates among heavy drinkers than the general population (Pearl 1962, Sundby 1967, Schmidt and de Lint 1969, Schmidt and de Lint 1972, Pell and D'Alonzo 1973, Bruun et al 1975). From the early 1980's, a number of studies provided evidence that both non-drinkers (abstainers) and heavy drinkers of alcohol have higher total and cardiovascular mortality rates than light or moderate drinkers (Klatsky et al 1981, Marmot et al 1981). This U-shaped mortality curve has

[1] wholly alcohol-attributable conditions which include alcoholic psychoses, alcohol-dependence syndrome, alcoholic polyneuropathy, alcoholic cardiomyopathy, alcoholic gastritis, alcoholic liver cirrhosis, and ethanol toxicity, see Section 1.3 p25)

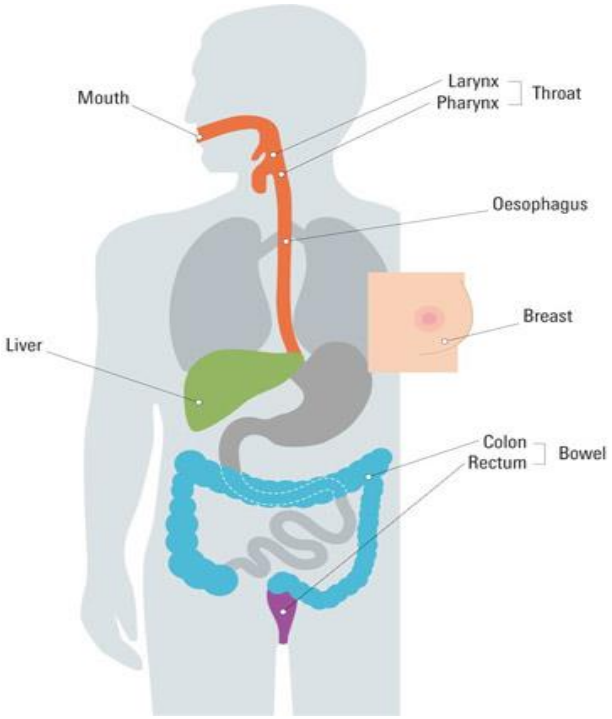
been interpreted as indicating that moderate alcohol intake may confer protection against cardiovascular disease in general, and against heart attacks in particular (Turner et al 1981, Marmot 1984, Moore and Pearson 1986). A number of biologically plausible mechanisms have been invoked to support the hypothesis, including the effects of alcohol on high-density-lipoprotein cholesterol and apolipoproteins, on fibrinolysis and coagulation, on blood pressure, and on coronary artery reactivity (Castelli et al 1977, Moore and Pearson 1986, Criqui et al 1987, Criqui 1990). Although the evidence of a lower risk of coronary heart disease among moderate drinkers is substantial and consistent, controversy remains about whether the relationship is truly causal-that is, whether moderate alcohol consumption really prevents coronary heart disease Mukamal and Rimm (2001). One of the major criticisms levelled at many of the studies is that non-drinkers will include people who have given up drinking because they were unwell. Such people would be expected to have an increased rate of disease. The argument suggests that it is the inclusion of "sick quitters" with the non-drinkers that accounts for the high incidence of coronary heart disease in non-drinkers compared with moderate drinkers (Shaper et al 1988).

By the end of the 1970s, the substantial increase in alcohol consumption in many European and North American countries after World War II, driven by a relative decrease in price and a relaxation of licensing laws had spurred a greater interest in the effects of alcohol consumption on health (BMJ 1981). In Britain, the relaxation of local licensing laws following the Errol report for England and Wales and the Clayson report for Scotland, published in 1973, resulted in both the British Medical Journal and Lancet producing editorials attacking these proposals, which were condemned as contrary to the interests of health. A Royal College of Physicians (1979) report towards the end of the decade commented on the relaxation of local licensing that ‘the relationship between normal drinking patterns and the country’s experience of alcohol related problems was ‘accidentally, but unequivocally put into the arena of debate’. In America, the disease model of alcoholism had shifted to one where alcoholism was viewed as an illness and government reports began to talk about problem drinking as opposed to ‘alcoholics’ (Hewitt 1995). The founding in 1970 of the National Institute on Alcohol Abuse and Alcoholism in America also coincided with a large increase in national government research funds, for studies of health problems resulting from heavy alcohol consumption (Voas and Fell 2010).

Spanning several decades since then, the literature now contains many reports linking alcohol with a broad array of adverse health outcomes and some beneficial health outcomes associated with alcohol use in individuals (IARC 1988b, Longnecker 1995, English et al 1995, Gutjahr et al 2001, Ridolfo and Stevenson 2001, Corrao et al 2000, Rehm et al 2003, Room et al 2005). Recent research has contributed substantially to our understanding of the relation of drinking to specific disorders and has shown that the relationship between alcohol consumption and health outcomes is complex and multidimensional. Alcohol has been shown to be ‘causally’ related to more than 60 different medical conditions, in most, but not all cases detrimentally, and in the majority of cases there is a dose-

response relation with the volume of alcohol consumption, with risk of disease increasing with higher volume (Corrao et al 1999, 2004, Rehm et al 2003, 2004). Alcohol consumption, above recommended daily drinking guidelines, significantly increases the risk of various diseases, and it has been suggested to be a significant contributory factor to a range of chronic conditions (WCRF/AICR 2007, BMA 2008). The disease conditions related to alcohol consumption fall into three categories that reflect the nature of the conditions and the nature of the aetiologic influence of alcohol on the conditions (Rehm et al 2003): wholly alcohol-attributable conditions which include alcoholic psychoses, alcohol-dependence syndrome, alcoholic polyneuropathy, alcoholic cardiomyopathy, alcoholic gastritis, alcoholic liver cirrhosis, and ethanol toxicity; chronic conditions where alcohol is deemed a contributory cause which include lip, oral, pharyngeal, oesophageal, liver, laryngeal, and breast cancer (see Figure 1.1), epilepsy, hypertension, cardiac arrhythmias, stroke, oesophageal varices, gastro-oesophageal haemorrhage, liver cirrhosis, acute and chronic pancreatitis, spontaneous abortion, low birth weight, and psoriasis; acute conditions where alcohol is a contributory cause, which include road injuries, injuries from falls, fires, drowning, occupational and machine injuries, other accidents, suicide, assault, and child abuse.

Figure 1.1 Alcohol related cancers



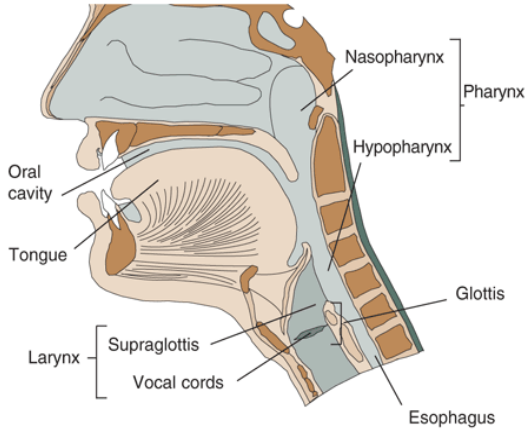
1.4 Alcohol and cancer outcomes

Alcohol has long been implicated as a risk factor for cancer (Blot 1992). Reports early in the last century described smoking and drinking as unusually common among cancer patients This link between alcohol and cancer was first observed over a hundred years ago in a study of 85000 persons insured with the United Kingdom Temperance and General Provident Institution between 1841 and 1901 (Newsholme 1903). In this study, it was found that the cumulative death-rate from malignant disease was 0.95 among abstainers and 1.32 per 1,000 among non-abstainers. Cancer site analysis did not indicate any 'special irritating effects' of alcohol on the oesophagus or stomach. Newsholme (1903) observed of his findings that if alcohol was to influence cancer development, it must be an indirect effect and only one of a number of conditions favouring cancer. Newsholme, however, did not totally reject the notion that alcohol 'cannot be elevated to the position of a primary cause, concluding that 'this is at present unknown'. These sentiments would not be out of place in modern day epidemiological studies of the association between alcohol consumption and cancer. Pearce (1910) subsequently updated Newsholme's analysis and showed a widening gap in mortality experience between abstainers and non-abstainers and delivered a prophetic message when concluding that "The influence of alcohol on the incidence of cancer is really important". Several case series studies followed those by Newsholme and Pearce; in a French study, Lamu (1910) noticed an increased incidence of oesophageal cancer in absinth drinkers; Abbe (1913) described drinking (and smoking) as unusually common among oral cancer patients; Craver (1932) investigated a variety of factors in patients with cancer of the oesophagus and found alcohol to the second most important factor, after tobacco, in the development of oesophageal cancer.

It was not until the late 1950s and early 1960s, however, that epidemiological studies began to depict the association in quantitative terms. Case-control studies in the United States (Wynder and Bross 1957, Wynder et al 1961, Vogler et al 1962, Vincent and Marchetta 1963, Keller and Terris 1965) and France (Schwartz et al 1957) documented an elevated risk of oral cancer associated with alcohol consumption, as well as smoking, although adjustment for one factor by the other was generally not made in these early studies. Wynder and Bross (1957), in a detailed history of 36 patients, found that alcohol consumption, particularly whisky, was an important factor in the development of oral cancer; whereas this risk increased in moderate drinkers, it rose very sharply among heavy drinkers (i.e. those who drank 7 or more ounces of whiskey a day). Schwartz et al (1957) recorded the average daily alcohol consumption in a large range of cancer patients and calculated the average consumption for each type of cancer. The result was a scale showing that these averages were highest among patients with cancer of the mouth, tongue, pharynx, hypopharynx, larynx and oesophagus (upper aero digestive tract, see Figure 1.2). Vogler et al (1962) reported an excess of drinkers among male mouth cancer patients though acknowledged that the association with other factors was minor compared to

that with tobacco. Keller and Terris (1965), in an American case control study involving 600 cases and 600 controls, further observed that both heavy alcohol consumption and heavy smoking were independently and significantly related to cancer of the mouth and pharynx.

Figure 1.2 Upper aero digestive tract



In one of the first critical reviews of the association between alcohol and cancer (Lowenfels 1975), several mechanisms were hypothesised whereby heavy drinking might predispose to subsequent formation of cancer, including;

- Alcohol itself might be carcinogenic, though Lowenfels observed that this was unlikely in view of the simple uncomplicated molecular structure of ethanol and experimental evidence which suggested that prolonged exposure of mice to 20% alcohol in their drinking water, did not induce tumours
- Contamination of alcoholic beverages during or after production by carcinogens
- Damage to mucus membranes from alcohol might increase susceptibility to another carcinogen
- Alcohol might enhance the carcinogenic effect of smoking. Heavy drinkers are nearly always heavy smokers
- An associated nutritional defect in the alcoholic might predispose to cancer

Lowenfels acknowledged that the precise mechanism was not known, but concluded that the association between alcohol and risk of cancer seemed strongest where there is direct contact of tissues with alcohol (oral cavity, pharynx, larynx, and oesophagus) or where there is serious organ damage (liver). Lowenfels also observed that the current evidence available would suggest that 'alcoholism' was not influential on the major forms of cancer in Westernized countries, namely cancer of the breast, colon, lung, or cervix.

Some fifteen years on from the Lowenfels' review, a large group of experts met in Lyon, France, at the invitation of the International Agency for Research on Cancer (IARC), in order to review thoroughly the literature on the association between alcohol consumption and cancer and to make a judgement concerning the strength of evidence that alcohol is carcinogenic to humans. In making their judgement, the experts were guided by several criteria for causality first suggested by Hill (1965), which provided a background framework to assess the causal nature of an observed association in epidemiological studies (Lucas and McMichael 2005). These criteria lay particular emphasis upon the temporality of the relationship between exposure and outcome, its strength of association, the presence of a plausible biological mechanism, evidence of a dose-response relationship, the consistency of findings in diverse studies, and coherence with other disciplinary findings and biomedical theory (Table 1.1).

Table 1.1 Criteria for judgment of causal associations in observational studies

Temporality: For a relationship to be causal, the cause must precede the effect. Considerations of temporality are especially noteworthy for diseases that take a long time to develop, such as cancer.
Strength of association: Strong associations argue for causation. Whereas weak associations in observational studies can easily be due to bias, large amounts of bias would be necessary to produce strong associations. Some suggest that relative risks (a measure used in cohort studies that compares the risk of a disease or other event in a group of people exposed to a particular substance or condition to that in a comparison group (typically an unexposed group or one with a low level of exposure)) more than 3 in cohort studies, or odds ratios (a similar though not identical measure to the relative risk that is frequently used in case-control studies. It compares the odds of an event occurring in one group of people to the odds of it occurring in another group) greater than 4 in case-control studies, provide strong support for causation (Sackett et al 1991, Grimes and Schulz 2002).
Biological gradient (dose-response relation): The likelihood or intensity of a biological effect is greater in people or animals with greater exposures to an agent than in those with lesser exposures. The presence of a dose-response relationship tends to support causality
Consistency: An association is more likely to be causal if it is observed by different researchers, in different places, circumstances, and times.
Coherence with existing knowledge: Is the association consistent with available evidence?
Biological plausibility: An association is more likely to be causal if it makes sense in terms of scientific understanding of the biology of the disease or health effect under investigation.

Source: IARC 1988a, Grimes and Schulz 2002

The subsequent report of the IARC meeting (IARC 1988b), generally regarded as one of the most significant reviews of the alcohol cancer association undertaken (Blot 1992, Single et al 2000), assessed the epidemiological evidence for an association between alcohol consumption and twenty-seven cancers. The review confirmed Lowenfels' (1975) earlier hypothesis by concluding that the 'occurrence of malignant tumours of the oral cavity, pharynx, larynx and oesophagus and liver was

causally related to the consumption of alcoholic beverages' (IARC 1988b). Of greater significance, however, and in contrast to Lowenfels' earlier findings were the expert group's conclusions on the association between alcohol consumption and breast, and colorectal cancer. Although the report observed that no 'firm conclusions' could be drawn about a causal relationship between alcohol and breast, and colorectal cancer, the expert group concluded that 'the available epidemiological evidence indicated a positive association between alcohol consumption and breast cancer in women' and for colorectal cancer concluded that the evidence of an increased risk of colorectal cancer was 'suggestive but inconclusive' (IARC 1988b). As the report noted, 'the modest elevation in relative risk that has been observed is potentially important because of the high incidence of breast and colorectal cancer in many countries' (IARC 1988b). For the remaining cancers under investigation, the expert group concluded there was 'little evidence that alcohol had a causal role in lung, stomach and pancreatic cancer, or the evidence was too inconclusive or inconsistent to allow for a judgement of causality to be made for cancers of the urinary bladder, kidney, ovary, prostate, brain, skin and cervix.

In the decade after the publication of the IARC (1988b) report, a substantial body of evidence has emerged from epidemiological studies reporting on the alcohol-cancer association. Epidemiologists also began to make use of meta-analysis and pooled analysis. Meta-analysis is a formal quantitative method for evaluating a potential health effect across a body of epidemiologic literature. In a meta-analysis, researchers assess heterogeneity across studies, examine subgroups of studies to determine if selected subsets of the research data provide similar or different results, and calculate summary relative risk estimates. A meta-analysis provides a more statistically precise risk estimate, as well as a better understanding of the consistency of findings (or lack of) in the research literature. A meta-analysis is distinct from a qualitative or narrative review in that a meta-analysis involves a systematic review of the literature, relevant data extraction, and quantitative analyses of data across multiple studies. A pooled analysis is similar to a traditional meta-analysis, except that exposure and outcome data are combined (or pooled) from multiple studies and are analysed as a single dataset (Egger et al 1997a, Egger 1997b, Shapiro 1997). Systematic literature reviews, and meta- and pooled analyses of studies published up until the end of the last century further developed the findings of the 1988b IARC report. Evidence strengthened regarding an association between alcohol consumption, even at low to moderate levels of drinking and cancer of mouth, pharynx, larynx, oesophagus and liver (English et al 1995, WCRF/AICR 1997, Corrao et al 1999, Gutjahr et al 2001), reinforcing the causal relationship between alcohol and these cancers observed in the IARC report (1988b). One of the first meta-analyses of published non-experimental research was an evaluation of breast cancer risk in relation to alcohol consumption which provided further evidence of a small increased risk of breast cancer from alcohol consumption (Longnecker 1988). A meta-analysis of 34 cohort studies (Ellison et al 2001) and a pooled analysis of 53 cohort and case control studies (Collaborative Group on Hormonal Factors in Breast Cancer 2002) provided further evidence of a modest increase in risk of

breast cancer, even at moderate levels of consumption, with a dose response trend. A meta-analysis also observed an increased risk of colorectal cancer (Bagnardi et al 2001) though the evidence here of an association was less convincing leading cancer experts to conclude in a comprehensive systematic review that alcohol 'probably' increases the risk of colorectal cancer (WCRF/AICR 1997). Evidence of an association between alcohol consumption and lung, stomach, prostate, bladder, endometrial and ovarian cancer remained either inconsistent or inconclusive based on findings from systematic reviews (WCRF/AICR 1997, Gutjahr et al 2001) and meta-analyses (Longnecker 1995, Bagnardi et al 2001). During the writing of this present thesis, IARC and WCRF/AICR published findings from an update of their earlier international reviews published in 1988 and 1997 respectively. The most significant changes from these earlier reviews were the conclusions that that there is now sufficient epidemiological evidence to regard alcohol as a causal factor in the development of breast, colon and rectal cancer (Baan et al 2007, WCRF/AICR 2007).

Alcohol is one of the very few examples of a chemical which has never been shown to cause cancer in experimental animals, but which is nevertheless implicated in the causation of certain cancers in humans (Turyns 1990, Blot 1992). Alongside the increasing epidemiological evidence on associations between alcohol consumption and cancer, researchers, therefore developed and investigated hypotheses regarding possible mechanistic pathways through which alcohol drinking may cause cancer. Although the mechanisms by which alcoholic beverages exert their carcinogenic effect are still not fully understood and are likely to differ depending on anatomical site (Poschl and Seitz 2004), strong evidence has emerged of plausible mechanisms whereby alcohol may cause cancers of oral cavity, oropharynx, larynx, oesophagus and liver. In humans and experimental animals, ethanol (i.e. alcohol) metabolism generates acetaldehyde, a known animal carcinogen, predominantly in the liver, and low concentrations of acetaldehyde are found in the blood. Among heavy drinkers, the rate of ethanol oxidation is likely to be enhanced, resulting in increased levels of acetaldehyde in the liver and blood leading to DNA damage to tissues that come into direct contact with alcohol (IARC 1988b, Poschl and Seitz 2004, Bofetta and Hashibe 2006). An increase in sex hormone concentrations (i.e. oestrogen) is seen as the most important explanation of a biological mechanism of the alcohol and breast cancer association, and is supported by randomized controlled alcohol feeding trials (Terry et al 2001, Lin et al 2005, Stolzenberg-Solomon et al 2006). The possible mechanisms of carcinogenicity of alcoholic drinks are concisely summarised in a recent IARC review (Boffetta and Hashibe 2006), together with a subjective assessment of the strength of the evidence available (Table 1.2).

Table 1.2 Possible mechanisms of carcinogenicity of alcoholic beverages.

Mechanism	**Potential target organs**
STRONG EVIDENCE	
DNA damage by acetaldehyde	Head & neck, oesophagus, and liver
Increased oestrogen concentration	Breast
MODERATE EVIDENCE	
Solvent for other carcinogens	Head & neck, and oesophagus
Production of reactive-oxygen species and nitrogen species	Liver, colon & rectum and others
Changes in folate metabolism	Colon & rectum, breast, gastric, kidney
WEAK EVIDENCE	
Nutritional deficiencies (e.g., in vitamin A)	Head & neck, breast prostate and others
Reduced immune surveillance	Liver, breast and others
Carcinogenicity of constituents other than ethanol	Head & neck, oesophagus, liver, and others
DNA damage by ethanol	Head & neck, oesophagus, and liver

Adapted from Boffetta & Hashibe (2006)

1.5 Research to policy: the burden of cancer attributable to alcohol consumption

Epidemiology as a scientific method provides evidence that bears directly on the health of the population. As a consequence, epidemiological findings generally have immediate relevance to the debate on and the formation of policies affecting health (Samet 2000). The application of quantitative methods, such as the meta-analysis and pooled analyses of individual level data from multiple studies has allowed epidemiologists greater power to explore weak associations observed in epidemiological studies of alcohol consumption and breast, colorectal and other cancers (Longnecker 1988, Samet et al 1998). Such approaches are not without their critics (Charlton 1995, Feinstein 1995, Shapiro 1997), but nevertheless, results from meta and pooled analyses have increasingly been used to quantify the risk in the whole population and to produce population level estimates of alcohol-caused cancer mortality and morbidity to inform policy making and planning (Boniol and Autier 2010); in Australia (English et al 1995, Ridolfo and Stevenson 2001), Canada (Single at al 1999), the United States (Rothman 1980, Schultz 1990, Tseng et al 1999), Italy (Cipirani et al 1999, Corrao et al 2000), Denmark (Britton et al 2003), Germany (Nolte et al 2003, John & Hanke 2003), England and Wales (Britton & McPherson 2001, White et al 2004, Jones et al 2008) and Scotland (Grant et al 2009). In the majority of these studies, 40% to 50% of overall alcohol related cancer mortality is attributable to deaths from breast and colorectal cancer.

The use of meta-analysis and pooled analysis to draw conclusions about the association between alcohol consumption and the risk of certain cancers e.g. breast and colorectal merits further consideration. In in any reasonably well conducted study, a weak association may be due to

confounding or bias, but it is unlikely that a strong association can be completely explained away by defects in study design (Shapiro 1997). That point is critical to the topic of meta-analysis: when associations are strong (as, say, with alcohol and oral cancer), there is no need to resort to it. It is when associations are weak (e.g. breast and colorectal) that meta-analysts are tempted to combine studies. Consideration of confounding and bias becomes of paramount importance, particularly when associations between individual risk factors or interventions and disease outcomes are not strong, e.g., those characterized by relative risks of less than 2.0 (Szklo 2001). The argument that in the meta-analysis of a large number of reasonably well conducted studies, bias and confounding should, in the aggregate, tend to "cancel each other out" may hold true for randomised controlled trials, but for the argument to hold true in observational research 'some very large and dubious assumptions must be made that the right studies, with the right weights, in the right directions, are present' (Feinstein 1995, Charlton 1996, Shapiro 1997). If this is not the case, the "cancelling out" will not occur. Even if it is assumed that there is no bias, and that uncontrolled confounding is the only issue, there can be no reassurance that the "cancelling out" will occur, since the same confounder may be shared by more than one study (Shapiro 1997).

Measurement bias in meta-analysis is inevitable since so many of the individual studies included in this approach are likely to vary in the definition of alcohol consumption, timing of intake and of the quantity consumed with multiple sources of confounding present in most studies. Dawson (2003) observed that, as the one important goal of alcohol epidemiology is to understand the association between alcohol consumption and alcohol-related problems, alcohol consumption first must be determined as accurately as possible. Yet many of the results for alcohol consumption and cancer outcomes are based on epidemiological work, which have numerous shortcomings with respect to the measurement of alcohol consumption (Rehm et al 1997, Room et al 2005, Turner and McLellan 2009). For example, in cohort studies, measures of alcohol consumption are usually assessed only once, at the beginning of the observation interval. In relating such a measure to an endpoint, e.g. incident cancer, it is assumed that (a) individual alcohol consumption is stable between the beginning and the end of the study, or (b) changes in consumption are the same for all members of the cohort, or (c) at least rank order between people with regard to consumption is preserved or (d) any changes in consumption are irrelevant for the outcome (Room 1977). It may be argued that none of the assumptions hold true for most studies (Lemmens et al 1997). Moreover, measures of alcohol consumption are usually limited in scope, often failing to capture theoretically relevant aspects of the alcohol-cancer association such as drinking pattern, drinking frequency and lifetime exposure. Other relevant methodological limitations include definitions of drinkers and non-drinkers, choice of reference period, beverage strength and beverage specific serving size (WHO 2000, Greenfield and Kerr 2008, Turner and McLellan 2009).

More recently concerns have arisen about the variation contributed by measurement of ethanol content of "drinks" which Greenfield and Kerr (2008) argue may be of equal importance to all the other influences discussed above from the perspective of accuracy of consumption and drinking pattern measurement. Most measures of alcohol consumption are phrased in terms of "drinks", meaning standard drinks of the respective country or area surveyed. In some cases, these drinks are defined for the respondents in terms of millilitres or typical container sizes of beer, wine or spirits suggested to constitute a 'standard drink', but in many cases they are not (Greenfield and Kerr 2008). Regardless, it appears that respondents are likely to report in terms of the drink sizes they actually consume (Kaskutas and Graves 2000). These differences can therefore affect the precision and statistical significance of risk estimates, as a factor of the accuracy of the assumptions made about the ethanol content of self-reported drinks (Greenfield and Kerr 2008). The 'standard' drink concept also suggests that there is a serving size of alcohol that is typical of a particular country, however, the concept is complicated by different standards across countries (Miller 1991, ICAP 1998, WHO 2000, WCRF/AICR 2007). In practice, one standard will be taken by researchers to apply to all beverage types while in reality the typical serving sizes and ethanol contents tend to differ by beverage type, leading to non-equivalence (Greenfield and Kerr 2008). The end result can be difficulties in the interpretation of the epidemiological evidence and confusion about the clear "bottom line" messages to policy makers (Samet 2000).

As Seabrook (2007) observed, this 'confusion' was perfectly illustrated in a BMJ editorial (Key 2007) discussing the recommendations of the WCRF/AICR (2007) report 'Food, nutrition, physical activity, and the prevention of cancer: a global perspective'. In the WCRF/AICR report, the expert panel concluded that men drinking more than two 'standard' drinks per day and women drinking more than one 'standard' drink per day were at increased risk of cancer. The 'standard' drink in the WCRF/AICR report contains 10-15 grams of ethanol (the range reflecting the variation in standard drink size definition used in international studies). Key (2007), however, assumed that the standard drink in the WCRF/AICR report was equivalent to the UK 'unit' measure and observed that the "the report's recommendation that men should drink no more than two units of alcohol a day and women no more than one unit a day" were much lower than government advice on safe daily drinking limits in Britain (<3 units for men and <2 units for women) and would require "a substantial shift in drinking habits would be needed to achieve these goals" (Key 2007). This highlights a widespread confusion regarding units of alcohol and "standard" drinks - WCRF "standard drinks" contain 10-15 grams of ethanol and British units contain 8 grams (Seabrook 2007).

Although the need to measure alcohol consumption accurately and consistently is crucial to understanding the associations between alcohol consumption and cancer outcomes, the measurement bias inherent in many approaches to measuring alcohol consumption suggests the need for caution when interpreting such studies. It can be hypothesised that there will be differences in not only the

exposure prevalence in different countries, but also in drinking patterns which may affect the slope of alcohol related risk (Poikolainen 1998). Therefore, both quantitative measures (how many light, moderate and heavy drinkers in population) and qualitative measures (drinking patterns e.g. daily, 'binge' drinking) of alcohol exposure present some methodological barriers to generalising the data derived from a single population. Given the importance of alcohol as a risk factor and the rising incidence of many cancers in Scotland attributable to alcohol consumption (ISD Scotland 2010a), it is important that measures of alcohol consumption are reliable and valid and that estimates of risk are based on the relationship between alcohol and a range of cancers in the context of a Scottish population.

1.6 Hypotheses

The overall aim of this body of work is to test the following hypotheses:

1. Alcohol consumption is a risk factor for a number of cancers

2. Alcohol consumption is associated with an increased risk of cancer, in the Scottish general population

3. People admitted to hospital in Scotland with an alcohol related condition are at more risk of developing an alcohol related cancer than the general population

1.7 Objectives

These hypotheses will be tested through the following objectives, each of which will comprise a chapter:

1. To systematically review the literature on alcohol related cancers to determine the strength of evidence of an association between alcohol and each cancer type, and if it varies by drink type, amount drunk, and drinking pattern and frequency (Chapter 2).

2. To describe the epidemiology of alcohol consumption in Scotland, reviewing sources of data on alcohol consumption in Scotland to determine trends in drinking over time, and variation by gender and age (Chapter 3).

3. To review trends in the incidence of alcohol related cancers in Scotland (Chapter 4).

4. To investigate the cancer risk associated with alcohol consumption in a sample of the Scottish population using a record linkage between the Scottish Health Surveys, hospital discharge data, cancer and death registrations (Chapter 6).

5. To explore whether people admitted to hospital in Scotland with an alcohol related diagnosis are at increased risk of an alcohol related cancer using a record linkage between hospital discharge data, cancer and death registrations (Chapter 7).

Chapter 2 Systematic review of literature on alcohol consumption and cancer risk by cancer site

In Chapter 1, the origins of epidemiological research into the association between alcohol consumption and cancer were traced. A summary of the current evidence, from international reviews (including meta-analyses) based on published research up to 1999, was provided. This evidence shows a strong association between alcohol consumption and an increased risk of oral and pharyngeal, laryngeal, oesophageal and liver cancer. An increased risk of breast and colorectal cancer has also been observed. The evidence of an association between alcohol consumption and other types of cancer e.g. stomach, pancreatic, lung prostate, endometrial, ovarian and bladder, remains inconclusive. Chapter 1 concluded with a summary of some issues related to collection of alcohol data in epidemiological studies. Since the above reviews, many further studies have been published which can be used, in some cases, to further refine estimates of risk and in others, to support (or refute) a significant association between alcohol consumption and specific cancer types. The inconsistency of findings in this area and the on-going publication of new research underline, from a public health perspective, the need to continuously evaluate the risk of alcohol as an exposure factor for cancer by updating and reviewing, systematically, the literature around alcohol and cancer risk.

In this chapter, the published literature between 1999 and 2009 on the association between alcohol consumption and cancer will be systematically reviewed[2]. The cancers most commonly hypothesized to be associated with alcohol consumption are included in the review (i.e. oral, oesophageal, laryngeal, gastric (stomach), breast, liver, lung, colon, rectal, kidney, pancreatic, prostate, bladder, endometrial and ovarian). Specifically, the review will assess the strength of evidence provided by the epidemiological literature, between three dimensions of alcohol exposure and the risk of cancer;

1. total alcohol consumption ('recent' and lifetime)
2. drinking patterns (e.g. daily/weekly drinking, 'binge' drinking)
3. alcohol beverage type (e.g. wine, beer, spirits)

2.1 Methods

To address the inherent biases (i.e. selection and information bias) in conducting systematic reviews and in accordance with recommended practice in systematic reviews of observational studies, a

[2] During the course of the present study, IARC (Baan et al 2007) and WCRF/AICR (2007) updated their earlier reviews of the association between alcohol consumption and cancer, published in 1988 and 1997 respectively. These updated reviews covered the published literature between 1966 and 2005. Although they could not be included in the systematic literature review, the recommendations from the IARC and WCRF/AICR reviews are discussed, in the context of the findings from the present study, in the concluding section of each cancer type.

review search protocol was developed (Blettner et al 1999, Stroup et al 2000, Dickersin 2002, Von Elm et al 2007). The protocol was based on the Cochrane Collaboration's set of policies and guidance on how a systematic review of the literature should be conducted and reported (Higgins and Green 2009). The protocol includes details on study inclusion and exclusion criteria, outcomes, the search identification strategy, quality criteria for assessing studies, data extraction and data synthesis, and data presentation:

2.1.1 Study inclusion and exclusion

The following inclusion criteria were applied (i.e. studies had to meet all these criteria):

1. Human studies only: adult population aged 16 years and over

2. Cohort, Case-control or cross sectional (prevalence) studies

3. Studies published between January 1999 and 30 September 2009 in the English language in a peer reviewed journal

4. Studies reporting a measure of association between the risk of cancer and alcohol consumption

5. Data on any of the outcomes listed in section 2.1.2

Studies were excluded for any of the following reasons:

1. The paper did not deal with alcohol related health effects; it dealt, rather, with natural history, prognosis, treatment or complications of disease

2. Sample size was too small (less than 50 people with the cancer of interest)

4. Study design was one of the following, (non) randomized controlled trials, case reports, ecological (correlation) studies, literature review and meta-analyses (though relevant reviews and meta analyses were identified and retained for cross reference with bibliographies and findings)

5. There was a duplication of the study - when the results of a study were published more than once, only the most recent and complete article was included in the review

6. Study available in abstract form only or not available in English

7. Findings were reported in letters, news items and editorials

2.1.2 Outcomes

- Oesophageal cancer
- Pharyngeal cancer
- Laryngeal cancer

- Gastric (stomach) cancer
- Breast cancer
- Hepato-cellular (liver) cancer
- Lung cancer
- Colon cancer
- Rectal cancer
- Kidney (renal cell) cancer
- Pancreatic cancer
- Prostate cancer
- Bladder cancer
- Endometrial cancer
- Ovarian cancer

2.1.3 Search strategy for identification of studies

Electronic Searches

A computerised literature search of peer reviewed papers was undertaken using the OVID platform (Ovid Technologies, 2000-2009 Inc. <http://www.ovid.com> Version: rel10.5.1) and the following databases:

- Ovid MEDLINE (R) (1999 to 30 September 2009)
- PSYCINFO (1989 to 30 September 2009)
- EMBASE (1999 to 30 September 2009)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1999 to 2006[3])

In addition, the following online library databases were also searched:

- Alcohol and Alcohol Problems Science Database, commonly referred to as ETOH (1972-2003)[4]
- Dissertation Abstracts Online

The search strategy combined alcohol and cancer related MeSH headings and free text words as follows:

- alcohol drinking, drinking behaviour, alcoholism, alcohol abuse, alcoholic beverages, alcohol consumption
- neoplasms/cancer: pharyn$, laryn$, colonic, rectal, colorectal, colon$, colorec$, stomach, gastric, esophag$, oesophag$, liver, hepatic, mouth, oral, breast, pancreatic, pancreas, bladder, kidney, renal, prostrate, ovarian, ovary, endometrial, endometrium
- carcinoma or cancer or tumour or tumour or malignan$.

[3] The CINAHL database was withdrawn from the OVID platform in 2006 and became a subscription service
[4] ETOH is a database of historic alcohol-related research information. Produced by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), ETOH contains over 130,000 records and covers the period from 1972 to 2003.

Initially, a broad search strategy was compiled for each database searched, but revised appropriately for each database to take account of differences in controlled vocabulary and syntax rules (see Appendix A for search terms used in each bibliographic database). The results were then limited to human studies, published in the English language and in peer reviewed journals from January 1999 to September 2009. No attempt was made to contact study authors for additional information due to time constraints.

All located records with available abstracts were downloaded to a Reference Manager (version 13: Researchsoft Thomson - ISI Reference Manager 2004) database and stored with the search strategies for each database. References retrieved from other sources (e.g. hand searching, reference lists) were also entered into a Reference Manager database. Duplicate records were then identified and deleted.

Grey Literature

Electronic searching of bibliographic databases, described above, can, however, only retrieve articles that are present in the database being searched (e.g. conference proceedings and non-indexed journals would not typically be included), and only if they are indexed under the 'key words' selected by the searcher (Dickersin 2002). The term 'grey literature' a commonly used term which refers to publications issued by government, academia, business, and industry, in both print and electronic formats, but not controlled by commercial publishing interests, and where publishing is not the primary business activity of the organization. Scientific grey literature comprises newsletters, reports, working papers, theses, government documents, bulletins, fact sheets, conference proceedings and other publications distributed free, available by subscription, or for sale (Alberani 1990, Luxembourg Convention 1997, Last 2001). A number of electronic databases and bibliographic sources were, therefore, searched for relevant research reports (completed and uncompleted), references and abstracts from scientific meetings, conferences, and theses and dissertations (Calabria et al 2008). These included the following:

- World Health Organisation (WHO) www.who.int
- International Agency for Research on Cancer (IARC): http://www.iarc.fr/
- World Cancer Research Fund International: http://www.wcrf.org/
- National Institute on Alcohol Abuse and Alcoholism database: (available at: http://etoh.niaaa.nih.gov/ncadidatabases.htm)
- National Institutes of Health Research Portfolio Online Reporting Tools (RePORT): (available at: http://projectreporter.nih.gov/reporter.cfm)
- The National Research Register Archive (2000-2007): (available at http://www.nihr.ac.uk/Pages/NRRArchive.aspx)
- ProQuest Dissertations & Theses database (available at: http://www.proquest.co.uk/en-UK/catalogs/databases/detail/pqdt.shtml)
- Networked Digital Library of Theses and Dissertations: (available at: http://www.ndltd.org/)

Additional hand searching of the peer reviewed journals list below was also carried out. The table of contents was reviewed over a two year period for each journal and relevant papers were identified and matched against those retrieved from the electronic search:

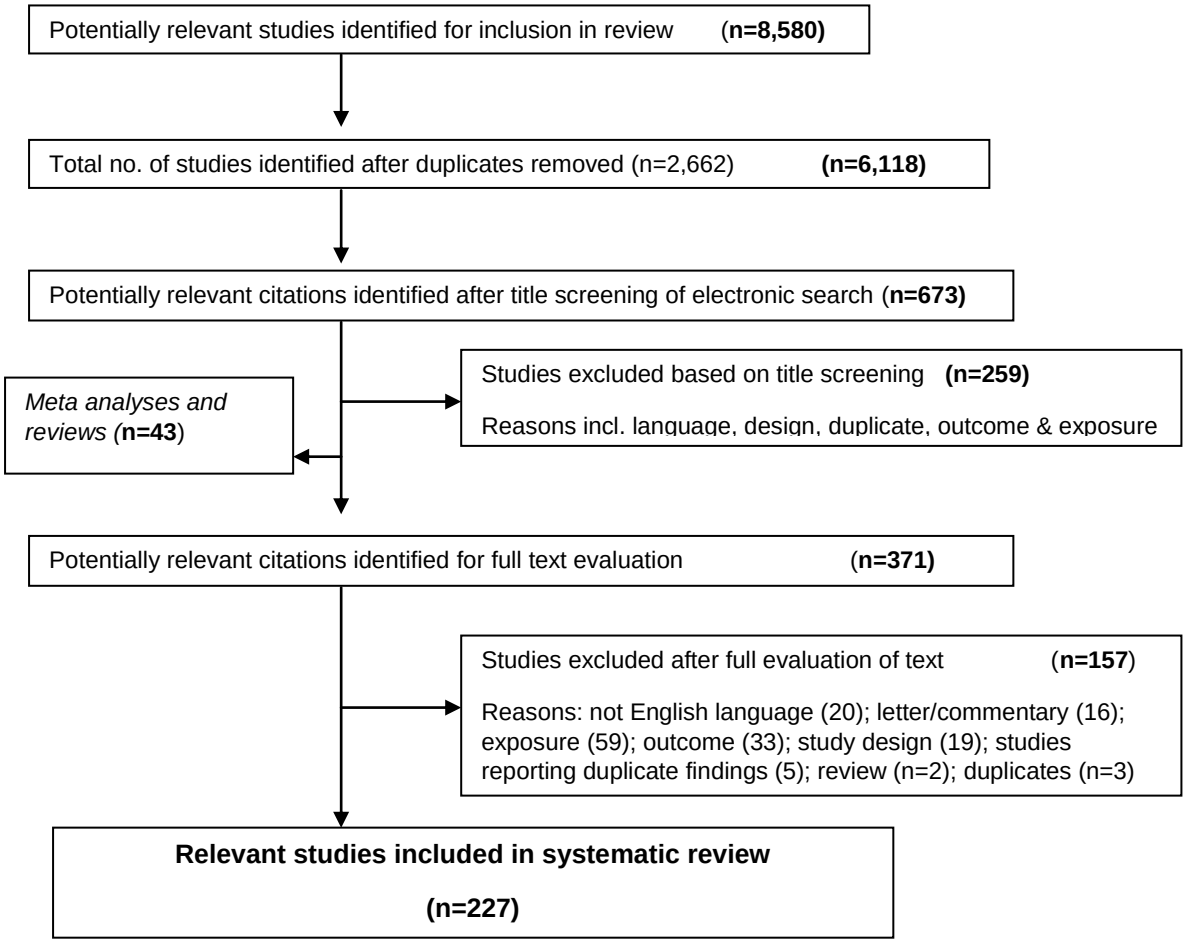
- Cancer Epidemiology Biomarkers and Prevention (1999-2000)
- International Journal of Cancer (2001-2002)
- Cancer Causes and Controls (2003-2004
- British Journal of Cancer (2005-2006)
- American Journal of Epidemiology (2007-2008)

2.1.4 Study selection criteria and procedures

All titles and abstracts identified by the computerised literature search were reviewed to identify potentially relevant papers. Publications not obviously addressing the relationship between alcohol consumption and the risk of cancer in humans were eliminated. Papers deemed relevant or of uncertain relevance were obtained and read in full. All selected papers were then reviewed against inclusion and exclusion criteria. Those deemed irrelevant were excluded and reasons for exclusion noted. Where there was an element of uncertainty, assistance was sought from academic supervisors and/or relevant experts in the area.

Progress was quantified at all stages of study selection using a flow diagram (Figure 2.1) based on the QUOROM guidelines for reporting of meta analyses of randomized controlled trials (Moher et al 1999).

Figure 2.1 Flowchart of the process of identifying and including references for the systematic review



2.1.5 Assessment of methodological quality

Quality assessment does not routinely occur in systematic reviews of observational studies (cohort, case-control, cross-sectional) and where it does occur, there is no clear consensus about the methods to be used (Mallen et al 2006). Assessment of quality of observational studies is often more difficult than assessment of quality for randomized controlled trials and other experimental studies because of inherent biases and differences in study design (Stroup et al 2000, IARC 2006). Careful consideration therefore is required of both the internal validity (e.g. study design, conduct and analyses) and the external validity (i.e. the extent to which the results observed in a study are applicable outside of the study) of individual studies included in a systematic review. Quality assessment methods for observational studies have not been adequately developed and, although several assessment scales and checklists have been proposed (Stroup et al 2000, Hayden et al 2006, von Elm et al 2007), none of them have been fully validated and there are no widely agreed quality criteria for assessing studies (Altman 2001).

The Cochrane Non-Randomized Studies Methods Working Group currently recommends the use of the partly validated Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses (Wells et al 2005, Higgins and Green 2009). The NOS allocates stars, with a maximum of nine stars available for studies appraised on three areas: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. Studies that score between 6-8 stars are generally considered to be of the highest quality, 4-5 of medium quality and 2-3 of low quality (Leonardi-Bee et al 2006, Ellen et al 2006, Henderson et al 2007a and 2007b, Park et al 2010). The face/content validity of the NOS has been established based on a critical review of the items by several experts in the field who evaluated its clarity and completeness for the specific task of assessing the quality of studies to be used in a meta-analysis. Also, the NOS has been refined based on experience of using it in several projects, in particular, a project assessing the association of CHD with hormone replacement therapy in postmenopausal women and a project assessing the association of connective tissue disease with silicone breast implants (Wells et al 2005). Deeks et al (2003) evaluated a range of quality assessment scales and NOS was found to be the most sensitive for observational studies compared to other scales for measuring the quality of observational studies. The NOS was, therefore, adapted for the purposes of this study and is reproduced in Appendix B.

There are a number of issues related to collection of alcohol data in epidemiological studies including; quality of self-reported alcohol data (Feunekes et al 1999); difficulties in quantifying prior long term alcohol intake (Schottenfeld 1979); and measurement error which is likely to occur with summarization across different types of alcoholic beverages (Fraumeni 1979). The NOS only provides for the measurement of the 'exposure' in a single fashion and does not allow for consideration of the myriad of ways an exposure can be measured, and over what time period and by what frequency. All of these are important considerations when measuring the impact of alcohol consumption (i.e. the exposure) as a risk factor for an outcome. The consumption of alcohol takes place in a number of ways and depending on frequency, quantity consumed and time period during which consumption occurred, may affect the measurement of the association with cancer (Room 1979). To assess how these aspects of drinking were addressed in the papers included in the systematic review, several alcohol consumption indicators were included in the data extraction sheet (see section 2.6) and are summarised in Table 2.1.

Table 2.1 Alcohol consumption measurement indicators.

A	B	C
Assessment of alcohol consumption	**Alcohol analytical strategy**	**Drinking dimensions reported**
Questionnaire type	Measure (e.g. grams, drinks)	Average intake per day, week
Reference period	Frequency (e.g. per day, week)	Frequency (daily, weekly, monthly)
Frequency (e.g. per week, day)	Reference group	'Binge' drinking
Beverage type	No. of drinking categories	Heavy/excessive consumption
Alcohol content of drink measures	Maximum intake level	Duration of drinking (years)
Gram equivalency of alcohol measure		Age started drinking

2.1.6 Data Extraction

A specifically designed data extraction spreadsheet was completed for each full-text evaluated report. This spreadsheet includes 40 variables distributed into five modules. Modules were designed to collect information on (i) the general characteristics of the study such as design, population, setting, size and response rate, (ii) the measurement of alcohol consumption (see Table 2.1 column A and C), (iii) the measurement of the cancer outcome e.g. case identification and verification, (iv) statistical methods used to obtain effect estimates and to adjust for confounding and (v) the presentation of the study findings (e.g. see Table 2.1 column B).

2.1.7 Presentation and Synthesis of Extracted Data

Data from each full text evaluated report were synthesised into summary tables, giving descriptive information for each study included. This was performed separately for each of the cancer outcomes [see section 2.1.2]. A meta-analysis was not carried out as part of the systematic review due to the heterogeneity of included studies. Separate tables were prepared providing:

1. A summary of study characteristics and design (e.g. author, country, sample base and selection of study population, and study size), presented in the individual cancer chapters (chapter 2.3 to 2.16).

2. Quality assessment scores for each full text evaluated report by individual items in the NOS. From this, summary tables of the scores by individual paper and cancer type were derived, and presented in the individual cancer chapters (chapter 2.3 to 2.16).

3. Full descriptive information, for each evaluated paper, describing; study aims, study sample and characteristics (including population, exclusion criteria, observation time), and exposure measurement and main results (including questionnaire type, reference period, reference group and full study results). Descriptive tables by cancer type are provided in Appendix D.

4. A summary of alcohol measurement and reporting methods (based on indicators listed in Table 2.1).

2.2 Results

Searches of Medline, Embase, Cinahl, PsychInfo, ETOH and DOI resulted in 8,580 papers being identified (see Fig 2.1). Exact duplicates were deleted on merging which left 6,118 papers. After screening of title and abstract (where available), 371 papers were identified as either relevant (187) or of uncertain relevance (184). Where an abstract was not available, the paper was included in the category of 'uncertain' relevance. Full text of these 371 papers were obtained and measured in full against the inclusion and exclusion criteria [see section 2.1.1]. After removing papers (n=157) because they were either (a) duplicate studies, (b) not published in the English language, (c) an inappropriate study design and (d) irrelevant exposure and/or outcome measure, 214 relevant papers remained for measurement against quality assessment criteria. Reasons why individual papers, were excluded at the full text evaluation stage, are shown in Appendix E. From the excluded list, 43 reviews (including meta and pooled analyses} were identified and retained for cross reference with bibliographies and findings. A further 13 relevant papers, from bibliographies of reviews and from the grey literature, were identified and added to the list for quality assessment. This left 227 papers, from 149 studies, for appraisal in the systematic review (Table 2.2). Bibliographic references and descriptive tables for these references are provided in Appendix C and D respectively.

Table 2.2 Number of studies and papers for full text evaluation, by study type

	Papers	**Studies**
Overall	227	149
Cohort	93	46
Case-control	129	95
Cross-sectional	1	1
Meta or Pooled analysis	4	-

Multiple papers were provided by individual cohort and case control studies. One case control study carried out in Italy and Switzerland was the basis for nineteen papers (14.7% of all case control studies). Over a third of the papers (34.4%) describing cohort studies were based on five cohort studies; the European Prospective Investigation into Cancer and Nutrition (EPIC); the Swedish Mammography Cohort (SMC); the Copenhagen Centre for Prospective Population Studies; the Netherlands Cohort Study on diet and cancer (NCS); the Health Professionals Follow-up Study and Nurses' Health Study. As all these cohort studies contributed papers on two or more cancer types, further details of these studies are provided in Box 2.1 to avoid repetition of study characteristics in each cancer section. There were two pooled cohort studies which were retained in the review as they

included unpublished data from cohort studies on the alcohol-cancer association. Two meta-analyses were also retained in the review despite this being an exclusion criterion; both studies reported on an aspect of the alcohol-cancer association (e.g. breast cancer by oestrogen status, lung cancer by drink type), where study findings are inconsistent and imprecise as a result of the small number of cases identified in individual studies.

A breakdown of the cancers under investigation by individual studies is provided in Table 2.3. The most common cancers investigated for an association with alcohol consumption were breast (17.4%) oesophagus (10.9%), colorectal (10.4%) and prostate (9.5%). Only a small number of studies were identified that reported on the association between alcohol and cancer of the kidney (3.0%) and endometrium (3.5%).

Table 2.3 Cancer type by individual studies

	Cohort	Case-control	Other	Total[1]
Bladder	3	5	-	8
Breast	20	14	1	35
Colorectal	13	7	1	21
Endometrial	4	3	-	7
Gastric (stomach)	6	7	-	13
Kidney	3	3	-	6
Laryngeal	-	9	-	9
Liver	1	8	-	9
Lung	8	5	2	15
Oesophagus	5	17	-	22
Oral	-	13	-	13
Ovarian	6	7	-	13
Pancreas	9	9	1	19
Prostate	8	3	-	11

[1] Totals do not match those in Table 2.2 since some papers reported on more than one cancer

In the following sections, and for each cancer type a summary of the evidence from previous reviews covered the published literature up to approximately 2000 is provided at the start of each cancer section. For each cancer type a description of individual study characteristics and assessment of overall study quality is provided. Results are presented for the association between cancer and; total alcohol consumption, other drinking dimensions (e.g. drinking frequency, drinking duration, age at which first started drinking, drinking pattern); drink type (wine, beer, spirits) and effect modification by other risk factors. For the sections describing results by total alcohol consumption and by drink type, forest plots comparing the highest versus the lowest alcohol exposure category are presented. Measures of alcohol consumption are commonly expressed in terms of ‘grams’, ‘standard drinks’, ‘units’ or millilitres. Standard "drinks" or "units" generally contain between 8 and 14 grams of pure

ethanol, although the measure varies among countries (Table 2.4). One gram is approximately equivalent to 1.25 millilitres (ICAP 2010). Each section then concludes with a discussion of the quality of the evidence, the strengths and weaknesses of the findings and an assessment of the strength of evidence for an association with alcohol consumption for each cancer type.

Table 2.4 Grams of ethanol in standard drinks and alcohol units, by country

Standard drink / unit size (grams of ethanol)	**Country**
8	United Kingdom
9.9	Netherlands
10	Australia, Austria, France, Ireland, New Zealand, Poland, Spain
11	Finland
12	Denmark, Italy, South Africa
13.6	Canada
14	Portugal, United States

Source: ICAP 2003

Box 2.1 Details of selected cohort studies that form basis of several papers

Copenhagen Centre for Prospective Population Studies (CCPS): The Copenhagen Centre for Prospective Population Studies is based on three comprehensive Danish programmes of prospective population studies: the Copenhagen City Heart Study, the Copenhagen County Centre of Preventive Medicine (formerly, the Glostrup Population Studies) which includes six cohorts, and the Copenhagen Male Study. In the former two, initiated in 1976 and 1964, respectively, subjects were randomly selected within age strata in defined areas in greater Copenhagen. In the Copenhagen Male Study, initiated in 1970, employees of 14 large companies in Copenhagen were invited to participate. The mean participation rate in all studies was 80% (range 69-88%).

Swedish Mammography Cohort (SMC): From 1987 to 1990 a population-based mammography screening program was introduced in two counties in central Sweden. In Västmanland County all women born between 1917 and 1948 received a mailed invitation to be screened by mammography between March 1987 and March 1989 (n=41,786) together with a 6-page questionnaire; 31,735 women (76%) returned the completed questionnaires. In Uppsala County all women born between 1914 and 1948 were invited to the screening and received the same questionnaire between January 1988 and December 1990 (n=48,517); 34,916 women (72%) returned the completed questionnaires. Questionnaires completed before undergoing mammography were obtained from 66,651 women (74%) in the source population. At enrolment, women were 30-74 years old.*(URL: http://www.imm.ki.se/smc/history/index.html)*

The Netherlands Cohort Study on diet and cancer, (NLCS): The NLCS is an ongoing cohort study that was initiated in 1986. The study consists of 58,279 men (48.2%) and 62,573 (51.8%) women who were 55-69 years old at the beginning of the study and were identified from 204 Dutch computerized municipal population registries. Studies reporting on the NLCS in this review all followed the case–cohort approach in which data are processed and analyzed only for a random sample of the cohort and all incident cancer cases arising each year. Cases were identified for the entire cohort, whereas a random sample of the cohort, i.e., the sub-cohort, was used to estimate person years at risk accumulating in the cohort (from the date of entry into the cohort until the date of a cancer diagnosis, death from any cause.

European Prospective Investigation into Cancer and Nutrition (EPIC): The EPIC study is a Europe-wide prospective cohort study of the relationships between diet and cancer, as well as other chronic diseases, such as cardiovascular disease. EPIC is coordinated by the International Agency for Research on Cancer (IARC), part of the World Health Organization. Study population consists of 521,457 healthy adults, mostly aged 35-70 years, who were enrolled in 23 centres in ten European countries: Denmark (11%), France (14%), Germany (10%), Greece (5%), Italy (9%), The Netherlands (8%), Norway (7%), Spain (8%), Sweden (10%) and the United Kingdom (17%). One UK centre (Oxford) recruited 27,000 vegetarians and vegans; this subgroup forms the largest study of this dietary group. Recruitment to the study took place between 1993 and 1999, and follow up is planned for at least ten years, with repeat interview/questionnaires every three to five years. *(URL: http://epic.iarc.fr/*

Health Professionals Follow-up Study and Nurses Health Study, (HPFS and NHS): The HPFS is an ongoing cohort study that was initiated in 1986 and consists of 51,529 male dentists, pharmacists, optometrists, osteopaths, podiatrists, and veterinarians aged 40-75 years at the beginning of the study. Fifty-eight percent of the men in the HPFS cohort are dentists, and the other professions include optometrists, osteopaths, podiatrists, pharmacists, and veterinarians. *(URL: http://www.hsph.harvard.edu/hpfs/).*

The NHS is an ongoing cohort study of 121,700 U.S. female nurses who were residents in 11 large U.S. states and were 30-55 years old at enrolment in 1976. The nutritional component of the NHS began in 1980; 89,538 women form the diet cohort. *(URL: http://www.channing.harvard.edu/nhs/)*

2.3 Bladder cancer

Bladder cancer: summary of evidence from previous reviews
Earlier systematic reviews covering the published literature up to the early 1990s concluded that overall studies on cancer of the bladder showed no association with alcohol consumption (IARC 1988b, WCRF/AICR 1997). Bagnardi et al (2001), in a meta-analysis of four cohort and seven case-control studies published between 1966 to 2000, observed a small increase in risk at the highest alcohol intake level (100 g/d; RR 1.17, 95% CI 0.97-1.41), compared to non-drinkers. Zeegers et al (1999, 2004) reviewed three cohort and thirteen case control studies, published between 1966 and 2003, and concluded, that although there was convincing evidence for a positive association between alcohol consumption and bladder cancer risk in men (but not in women), the risk was "small and not clinically relevant".

The literature search identified eight studies, published between 1 January 1999 and September 2009, which examined the relationship between alcohol consumption and bladder cancer. There were three prospective cohort studies and five case control studies. Tables for each paper, describing the study aims, population, alcohol measurement methods and main results are provided in Appendix D.

2.3.1 Study characteristics

A summary of the general characteristics of the studies is provided in Table 2.3.1 below.

Table 2.3.1 Alcohol and bladder cancer: general characteristics of studies reviewed

Authors	Year	Country	Outcome/No outcome Case/Control	Age range (M/Mdn)	Sample base	Sample selection
Cohort studies						
Allen	2009	UK (women)	928/1,180,368	>55	nationwide breast screening clinics	random selection
Djoussé	2004	USA	126/10,000	5-70 (M=40)	town	volunteers
Zeegers	2001	Netherlands	674/2,826	55-69	municipal population registries	random sample
Case control studies			***cases/controls***			
Benedetti	2009	Canada (men)	425/507	35-70 (M=59.1)	city hospital/local population	consecutive/random sample
Demirel	2008	Turkey	164/324	40-88 (M=64/61)	city hospital	consecutive/selected sequentially
Jiang	2007	USA	1,586/1,586	25-64, (M=58)	state cancer registry /local neighbourhood	consecutive/ random sample
Pelucchi	2002	Italy	727/1,067	25-79 (Mdn=60/63)	hospital	consecutive/selected sequentially
Pohlabeln	1999	Germany	300/209	M=65	4 state hospitals	consecutive/selected sequentially

Abb: n/s not specified; M=mean; Mdn= median

One paper was based on an established prospective cohort study described in Chapter 2.2 Box 2.1; Netherlands Cohort Study on diet and cancer (Zeegers et al 2001). In the largest cohort study (Allen et al 2009), approximately 1.2 million women, attending breast cancer screening clinics in the UK, were recruited to the Million Women Study. The study reported on the association between moderate alcohol intake and risk of fourteen cancers and identified 928 incident cases of bladder cancer, over a

mean follow up period 7.2 years. Djoussé et al (2004) derived their cohort from the Framingham Study which began in 1948 and included 873 women, aged 28-62 years, in Framingham, Massachusetts, at the first examination. In 1971, examination was begun on many of the children of the original cohort and their spouses and 5,124 subjects aged 12-60 years joined the study. The combined cohort was followed up for 27.3 years. In the largest case control study, Jiang et al (2007) identified cases through the Los Angeles County Cancer Surveillance Program and controls from a random sample of a 'neighbourhood' population which was not defined in the paper.

2.3.2 Study quality

The quality scores assessed, according to the NOS (in which higher scores reflect higher quality, see table footnote), varied between studies with cohort studies generally of a higher quality than the case control studies (Table 2.3.2).

Table 2.3.2 Bladder cancer: assessment of study quality

	Selection* (out of 4)	**Comparability* (out of 2)**	**Outcome/Exposure[1]* (out of 3)**	**Total**
Cohort				
Allen 2009	4	2	3	9
Djoussé 2004	4	2	2	8
Zeegers 2001	4	2	3	9
Case-control				
Benedetti 2009	3	2	1	6
Demirel 2008	2	0	1	3
Jiang 2007	3	2	2	7
Pelucchi 2002	3	2	3	8
Pohlabeln 1999	2	2	1	5

* High quality characteristics within each of these items were awarded a star, up to a maximum of four stars for selection, two stars for comparability and three stars for assessment. [1] Outcome for cohort, exposure for case-control studies

Of the cohort studies, all three scored highly across all three items: sample selection, comparability and outcome measurement. Only the paper by Djoussé et al (2004) did not achieve maximum ratings by not reporting any loss to follow-up that may have occurred in their study. For comparability, smoking was robustly adjusted for in all three studies, using measures of amount, frequency and duration smoked based on self-reported data. To further address the bias that may be caused by the residual effects of smoking, Djoussé et al (2004) used a risk set method that matched each bladder cancer case to control subjects on current smoking status and age. Two studies controlled for the effects of socio-economic status by either using the using the median family income of the census tract of residence in two Canadian cities from which study cases and controls were recruited (Benedetti et al 2009) or by using quintiles of the Townsend deprivation index[5] (Allen et al 2009)

[5] Townsend deprivation index includes measures of unemployment, overcrowding, owner - occupier status, and car ownership for the postcode area of each participant, based on the 1991 United Kingdom National Census, (Townsend et al 1988)

To address misclassification bias caused by measurement error from changes in alcohol consumption from baseline measurement, Allen et al (2009) categorized women into five levels of alcohol intake, based on consumption reported at recruitment, but used the average intake of alcohol (expressed as grams per day) in each category reported in the follow-up survey three years later. Djoussé et al (2004) collected alcohol consumption data every 4 years over a 27 year follow-up period and used a weighted average of repeated measures of alcohol consumption over time. Zeegers et al (2001) did not collect follow up information though with a mean follow up period of only 6 years and a study population aged more than 55 years, it is unlikely that changes in drinking levels would have markedly influenced the positive associations reported in this study. There was considerable variation in the recall period over which the amount of alcohol consumed was measured, from within the last week (Allen et al 2009), the last month (Djoussé et al 2004) and within the last year (Zeegers et al 2001).

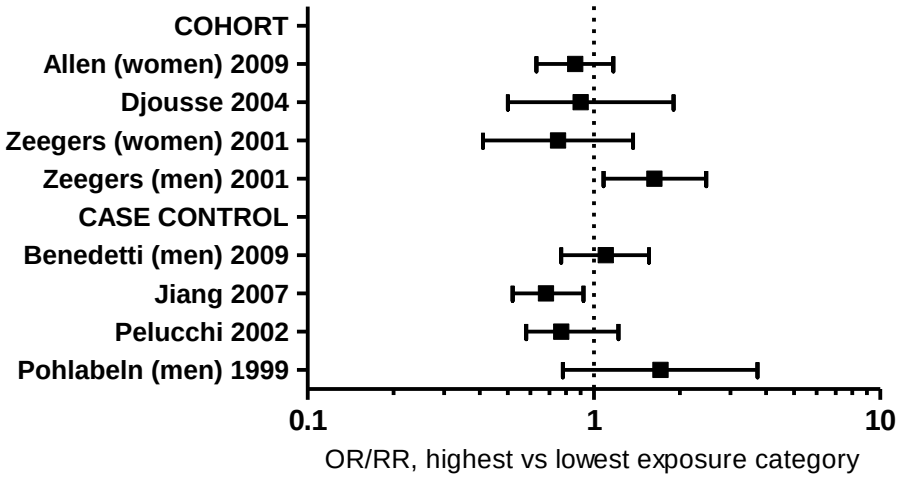
Case control study quality varied between a low rating of three stars out of possible nine (Demirel et al 2008), a moderate rating of five stars (Pohlabeln et al 1999) and a high rating of eight stars (Pelucchi et al 2002). For sample selection, all case control studies scored either two or three stars. Of those that only scored two, most were not awarded the third because of the use of controls recruited from a hospital setting. Only Pelucchi et al (2002) addressed concerns that use of hospital controls may under estimate the effect of alcohol on bladder cancer by excluding from their comparison group patients admitted for smoking and alcohol chronic conditions and alcohol related traumas. Two population case control studies failed to confirm that bladder cancer (or any other cancer that may be related to alcohol consumption) was absent in the control group at recruitment (Jiang et al 2007, Benedetti et al 2009). The study by Demirel et al (2008) was the only paper not to control for the effects of smoking (and age) and this may partly explain the increased risk of bladder cancer associated with lifetime alcohol daily consumption reported in this study. Residual confounding from smoking is still likely in the remaining studies, but will vary from study to study due to the range of smoking variables used in adjusting analyses.

Case control studies did not perform well in exposure assessment - only one study managed three stars, failing on not specifying the blinding status of interviewers (Pelucchi et al 2002). Three studies did not report response rates for cases and controls ((Pohlabeln et al 1999, Demirel et al 2008, Benedetti et al 2009) or reported variation in response rates between cases (83%) and controls (69%) (Jiang et al 2007). The low response rate in controls reported in the Jiang paper may explain the inverse association between alcohol consumption and bladder cancer reported in this paper if non-responders among controls were more likely to be drinkers.

2.3.3 Results: total alcohol intake and risk of bladder cancer[6]

Three studies reported on the association between bladder cancer and 'recent' alcohol intake defined as habitual alcohol consumption during the year before the study (Zeegers et al 2001), in the previous month (Djousse et al 2004) and within the last two years (Jiang et al 2007). Two studies reported on the association between bladder cancer with lifetime alcohol intake defined as any period when alcohol was drunk at least once a week or nearly every day (Benedetti et al 2009) and amount drunk 10 to 15 years prior to prior to survey baseline (Pohlabeln et al 1999). The remaining three studies did not specify a reference period (Pelucchi et al 2002, Demirel et al 2008, Allen et al 2009). A summary of bladder cancer risk estimates, comparing the highest versus the lowest alcohol exposure category, is presented in Figure 2.3.1. Risk estimates reported by Demirel et al (2008) are not included in Figure 2.3.1, as they only reported on current drinking status (yes/no) and risk of bladder cancer.

Figure 2.3.1 Alcohol consumption and bladder cancer, highest versus lowest exposure category by study type, (relative risk/odds ratio and 95% confidence intervals)



Zeegers et al (2001), observed an increased risk of bladder cancer in men, but not women, across all categories of alcohol intake, compared to those drinking less than once a month, though the relative risk (RR) was only statistically significant at the highest intake level (>30 grams per day [g/d]) and there was no evidence of dose response relationship (*p value for trend* =0.13). Zeegers et al (2001) also observed, a weak inverse association (RR 0.75, 95% CI 0.41-1.37) with bladder cancer and women drinking at the highest alcohol exposure category (5 to <15 g/d). There was an insufficient number of female drinkers in this study to explore whether risk of bladder cancers increased with the amount drunk. Allen et al (2009), in a large prospective cohort study of approximately 1.2 million women in the UK, did not find any association with bladder cancer across all categories alcohol intake (15 drinks per week [d/w] RR 0.96, 95% CI 0.63-1.17, *p value for trend* =0.2). In the remaining cohort study, Djoussé et al (2004) observed a 50% reduction in the risk of bladder cancer for those

[6] Multivariate relative risks/odds ratios are presented unless otherwise stated

drinking >48 g/d, compared to never drinkers, but this estimate was based on only eight cases. Risk estimates for all other categories of alcohol intake, in the Djoussé paper, were not associated with an increased risk of bladder cancer.

In the largest case control study of alcohol and bladder cancer included in the present review, Jiang et al (2007), reported a weak statistically significant inverse association between alcohol and bladder cancer for those drinking >1 drink per day [d/d], with strong evidence of a dose response relationship (*p value for trend* =0.003) up to >4 d/d. Pelucchi et al (2002) also observed a small, but statistically non-significant, reduced risk (OR 0.77, 95% CI 0.58-1.22) of bladder cancer at the highest alcohol intake level (up to ≥6 d/d), but there was no evidence of a dose response relationship (*p value for trend* =0.52). Demirel et al (2008) reported an unadjusted odds ratio of 1.85 (95% CI 1.15-2.96) for 'drinkers' (undefined in the paper), compared to never drinkers

Two case control studies reported on the association between bladder cancer and measures of 'lifetime' alcohol consumption. Benedetti et al (2009) found little evidence of an association in men regularly drinking >7 d/w (OR 1.10, 95% CI 0.77-1.56), compared to men who had not drank weekly over their lifetime. Pohlabeln et al (1999) observed an increased risk (OR 1.71, 95% CI 0.78-3.73) of bladder cancer for those reporting drinking, on average >41 g/d, over ten to fifteen years prior to entry into the study, compared to those who reported no daily alcohol intake.

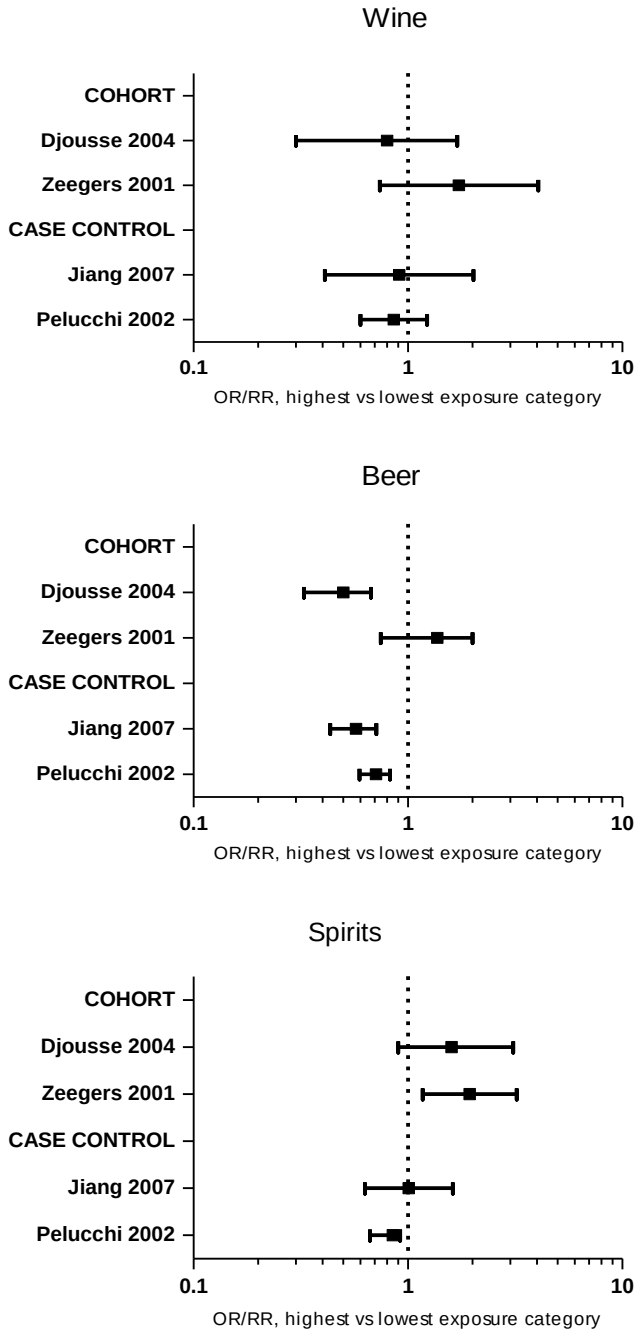
2.3.4 Results: drinking dimensions and risk of bladder cancer

Two case control studies reported on the association between drinking duration (i.e. number of years) and bladder cancer. Pelucchi et al (2002) did not find any association between the length of time their study population had been drinking and bladder cancer. A statistically significant inverse association between bladder cancer and drinking alcohol for >41 years (OR 0.66, 95% CI 0.48-0.89) was reported by Jiang et al (2007), with strong evidence of a linear increase in risk with years of drinking (*p value for trend* =0.017). In addition, Jiang et al (2007) also reported a statistically significant inverse association with bladder cancer for those who first started drinking at aged 18 years and younger and this association increased with increasing age of first use (*p value for trend* =0.005).

2.3.5 Results: drink type and risk of bladder cancer

A summary of bladder cancer risk estimates by drink type, comparing the highest versus the lowest alcohol exposure category as described in the four studies that investigated the risk of bladder by alcohol beverage type (wine, beer and spirits), is presented in Figure 2.3.2.

Figure 2.3.2 Alcohol consumption and risk of bladder cancer, highest versus lowest exposure; by drink type (relative risk and 95% confidence intervals)



Cohort studies

Zeegers et al (2001) observed an increased risk of bladder cancer at the highest alcohol intake level (>30 g/d) for beer (*p value for trend* =0.12), wine (*p value for trend* =0.48) and spirit drinkers, but this increased risk only reached statistical significance for spirit drinkers (RR 1.94, 95% CI 1.17-3.22, *p value for trend* =0.03). Djousse et al (2004) also reported a statistically non-significant 60% increased risk of bladder cancer among spirit drinkers drinking ≥4 d/w (*p value for trend* =0.2) compared to non-drinkers. In same study, wine drinkers did not have an increased risk of bladder cancer, but low

levels of beer drinking (>4 d/w) was associated with a statistically significant reduced risk of bladder cancer, with weak evidence of a dose response relationship (*p value for trend* =0.03).

Case control studies

In a large American case control study, Jiang et al (2007) reported similar protective effects of drinking beer, even for heavy beer drinkers (>4 d/d; OR 0.54, 95% CI 0.35-0.83) with strong evidence of a dose response trend (*p value for trend* =0.002) whereas spirit and wine consumption was not associated with bladder cancer. Pelucchi et al (2002) reported a small, but statistically significant, decreased risk of bladder cancer for 'current' beer drinkers compared to non-drinkers, though an insufficient number of beer drinkers in this study prevented further analysis of risk associated with specific drinking categories.

2.3.6 Results: effect modification

The effect modification of other risk factors for bladder cancer was reported in two studies Pelucchi et al (2002), in a hospital based case control study, reported that the association between alcohol consumption and bladder cancer did not differ within strata of smoking status; current smokers who drank ≥6 d/d had an OR of 0.81 (95% CI 0.46-1.44), compared to non-drinkers, and never smokers who drank ≥6 d/d (OR 0.99, 95% CI 0.42-2.33). In addition, odds ratios according to average drinks per day, in separate strata of age, gender, smoking habit, occupation at risk, coffee and tea, and green vegetable intake, were below unity in most subgroups though only statistically significant for coffee drinking. In the paper, it was stated that none of the interaction terms were statistically significant, but these terms were not presented in main text (Pelucchi et al 2002). Zeegers et al (2001) reported that the association between alcohol consumption and bladder cancer risk did not differ within strata of smoking status, amount, or duration; but no data were presented in the paper to demonstrate this.

2.3.7 Summary and conclusions

Eight studies, three cohort and five case-control, were appraised which considered the association between alcohol and bladder cancer. Study quality varied by design; cohort studies were generally of high quality, whilst case control studies were of low to moderate quality subject to considerable selection bias (Demirel et al 2008, Benedetti et al 2009) and, response bias (Pohlabeln et al 1999, Jiang et al 2007). Key confounders, in particular smoking, were controlled for, except in the study by Demirel et al (2008).

Overall, the findings from these studies provide inconsistent evidence of an association between bladder cancer and total alcohol consumption. Only one cohort study (Zeegers et al 2001) reported a

small (RR<2) positive association at the highest alcohol exposure level, with little evidence of significant dose response relationship. Although a small inverse association between bladder cancer and alcohol consumption was reported in a large case control study (Jiang et al 2007), with a significant dose response relationship, results in this study may be subject to bias due to a high non-response rate among controls (approximately 30%). Residual confounding from smoking is likely to explain all these small associations, but this will vary from study to study due to the range of smoking variables used in adjusting analyses. The findings of previous systematic reviews of the association between bladder cancer and alcohol consumption have also been inconsistent. Zeegers et al (2004) reviewed papers published between 1966 and 2003 and concluded, on the basis of a meta-analysis (of three cohort and thirteen case control studies (SOR[7] 1.3, 95% CI 0.9-2.0) carried out by the same authors (Zeegers et al 1999), that although there was convincing evidence for a positive association between alcohol consumption and bladder cancer risk in men (but not in women), the risk is small and not 'clinically' relevant. Bagnardi et al (2001), in a meta-analysis of four cohort and seven case-control studies published between 1966 to 2000, observed a small increase in risk at the highest alcohol intake level (pooled RR for 100 g/d; 1.17, 95% CI 0.97-1.41, compared to non-drinkers) with no evidence of risk increasing with amount of alcohol drunk. Pelucchi and La Vecchia (2009) concluded that the existing epidemiological data, based on thirty four papers published between 1970 and 2007, on alcohol drinking and bladder cancer suggests no association although the findings were not always consistent. Recent international reviews have also concluded that the evidence of an association between bladder cancer and alcohol consumption is inconclusive or limited (Baan et al 2007, WCRF/AICR 2007).

Interestingly, an association between bladder cancer and alcohol in the present review was more evident when examined by drink type, with a statistically significant protective effect from beer drinking reported in three (including one cohort study) of the four studies investigating the risk of bladder cancer by alcohol beverage type. Previous systematic reviews have not reported on this aspect of the alcohol-bladder cancer association. There are some plausible mechanisms that may explain the beer-mediated bladder cancer protection. Beer is consumed in greater volume than other types of alcoholic beverages and previous reports document the diuretic properties of alcohol in both experimental animals and humans, with acute alcohol consumption increasing urine flow, possibly by inhibiting anti-diuretic hormones (Jiang et al 2007). Increased fluid intake and frequency of urination may, therefore, play a role in the alcohol-mediated bladder cancer protection by decreasing the time the bladder is exposed to carcinogens in the urine (Oyasu & Hopp 1974, Melicow 1974). These hypothesised mechanisms, however, still remain controversial (Zeegers et al 2004). Residual confounding from smoking and limitations of sub-group analyses (e.g. small sample sizes in each of

[7] SOR = Summary Odds Ratio

the study's alcohol intake categories) and recall bias could equally explain the inverse association reported for beer drinking and bladder cancer.

In summary, the evidence from this review does not provide convincing evidence of an association between alcohol consumption and an increased risk of bladder cancer. However, given the small number of studies identified in the review, a lack of consistency in findings, the possible residual effect of smoking and the variation in approaches to the measurement of alcohol consumption, an association between alcohol consumption and bladder cancer risk cannot be ruled out.

2.4 Breast cancer

Breast cancer: summary of evidence from previous reviews
Earlier systematic reviews covering the published literature up to the early 1990s concluded that although the available data indicate a positive association between alcohol consumption and breast cancer in women, a firm conclusion about a causal relationship could not be made IARC 1988b, WCRF/ICR). Several pooled analyses, based on studies published up to and including 2000, have suggested a positive association between alcohol consumption and breast cancer with a modest dose-response relationship, such that consumption of 25-40 g/d is associated with a 30-40% increase in risk, (Longnecker 1994, Smith-Warner et al 1998, Ellison et al 2001, Collaborative Group 2002). These analyses have also suggested a linear effect of alcohol on breast cancer risk, whereby the risk of breast cancer increases by each daily amount of alcohol drunk: Ellison et al (2001), in a meta-analysis of 15 cohort and 27 case control studies, reported a 10% increase in breast cancer risk per 12 g/d of alcohol drank. Similar results were reported in a pooled analysis of six cohort studies (RR 1.9, 95% CI 4%-13%, Smith-Warner et al 1998) and a pooled analysis of 53 cohort and case control studies (RR 1.7, 95% CI 5%-8%, Collaborative Group 2002).

This literature review identified 41 papers from 34 studies, published between 1999 and 2009, examining the association between alcohol consumption and breast cancer. Of the 41 papers, 26 papers were based on 21 cohort studies and 15 were based on 13 case control studies. Tables for each paper, describing the study aims, population, alcohol measurement methods and main results are provided in Appendix D.

2.4.1 Study characteristics

Cohort studies

Of the 21 cohort studies, 20 were prospective in design with the remaining study, a retrospective linkage cohort study (Kuper et al 2000). Four prospective cohort studies contributed two or more papers to the review and all were retained since each study reported on a different aspect of the association between alcohol consumption and breast cancer; by lifetime (Tjønneland et al 2003) and 'recent' (Tjønneland et al 2004) alcohol consumption in the Netherlands Diet, Cancer and Health Cohort; in women of all ages (Thygesen et al 2008) and by post- (Nielsen et al 2008) and pre- (Petri et al 2004) menopausal status in the Copenhagen City Heart study; by post-menopausal (Chen et al 2002) and pre-menopausal status (Garland et al 1999) in the US Nurses Health Study and by incidence and mortality in the US Cancer Society Cancer Prevention Study (CPS-II) Nutrition Cohort (Feigelson et al 2001, 2003).

A summary of the general characteristics of the cohort studies is provided in Table 2.4.1 below. Nine papers were provided by five of the established prospective cohort studies described in more detail in Section 2.2, Box 2.1; CCPS (Petri et al 2004, Nielsen et al 2008, Thygesen et al 2008); NLCS (Tjønneland et al 2003, 2004), NHS (Garland et al 1999, Chen et al 2002), SMC (Suzuki et al 2005) and EPIC (Tjønneland et al 2007). The largest cohort study identified in the present review included

approximately 28,000 incident cases of breast cancer (Allen et al 2009) and has been previously described in section 2.3.1. Other large cohort studies by Tjønneland et al (2007) and Lew et al (2009) identified 4000 and 5500 breast cancer cases respectively. The majority of cohort studies were of reasonable size identifying over 1000 breast cancer cases. Three studies identified less than 250 cases (Jain et al 2000, Petri et al 2004, Lin et al 2005).

Table 2.4.1 Alcohol and breast cancer: general characteristics of cohort studies

Authors	Year	Country	Outcome/No outcome	Age range (M/Mdn)	Sample base	Sample selection
Allen	2009	UK	28,380/1,251,916	>55	breast screening clinics	volunteers
Baglietto	2005	Australia	537/16,910	40-69	electoral rolls, community notices	volunteers
Chen	2002	USA	1,722/119,978	30-55	*Nurses' Health Study* registered nurses in 14 states	volunteers
Garland	1999		445/116,226	25-42		
Chlebowski	2007	USA	3,236/144,680	50-79 (M=63)	clinical centres	volunteers
Dumeaux	2004	Norway	1,130/85,818	30-70	general population	random sample
Feigelson[1]	2001	USA	1,422/240,588	>29	*CPS-II Nutrition Cohort* general population (50 states)	random selection
Feigelson	2003		1,303/65,258	40-87 (M=63)		
Horn-Ross	2004	USA	1,742/101,718	<85	active/retired female teachers/administrators in one state	volunteers
Jain[1]	2000	Canada	241/58,685	40-59	nationwide breast screening programme	volunteers
Kuper	2000	Sweden	514/36,342	(M=42.7)	all hospitals	consecutive
Lew	2009	USA	5,461/178,957	50-71	six US states	volunteers
Lin	2005	Japan	151/35,693	40-79	general population	random selection
Mattison	2004	Sweden	342/11,384	>50	city population	volunteers
Nielsen	2008	Denmark	267/4,768	39-91, (M=62)	*CCPS* general population registry (see Section 2.2 Box 2.1)	random sample
Petri	2004		76/12,998	20-91		
Thygesen	2008		476/8,842	not specified		
Rohan	2000	Canada	1,469/4,212	40-59	nationwide screening trial	volunteers
Sellers	2002	USA	1,875/32,518	55-69	state list of licensed drivers	random sample
Stolzenberg -Solomon	2006	USA	500/24,900	55-74	nationwide screening trial	random selection
Suzuki	2005	Sweden	1,284/50,563	not specified	regional population	random sample
Tjønneland	2003	Denmark	425/23,353	50-64 (Mdn=57)	*Diet cancer health study* regional population	random selection
Tjønneland	2004		423/23,260			
Tjønneland	2007	Europe	4,285/270,403	35-75	general population	random selection
Zhang	1999	USA	287/4,761	28-62	city population	volunteers
Zhang	2007	USA	1,484/37,377	>45	nationwide female health professionals	volunteers

Abb: n/s not specified; M=mean; Mdn= median [1] Outcome is breast cancer mortality

Case-control studies

There were 15 case control papers from 13 case control studies reporting on the association between alcohol consumption and breast cancer (Table 2.4.2). Two case control studies contributed two papers each to the review. All papers were retained in the review because each paper reported on a different aspect of the relationship between alcohol and breast cancer; by drinking in 'adolescence' (Kinny et al 2000) and by lifetime alcohol consumption (Marcus et al 2000) in the US Carolina Breast Cancer Study; and by the modifying effect of menopausal status (McDonald et al 2004) and hormone receptor status (Li et al 2006) in the US Women's Contraceptive and Reproductive Experiences Study (CARE).

A summary of the general characteristics of the case control studies is provided in Table 2.4.2 below. The majority of studies were based in the USA. The largest case control study identified 6,327 cases (Newcomb et al 2009). Five studies identified over 1000 breast cancer cases (Althuis et al 2003, McDonald et al 2004, Li et al 2006, Terry et al 2006, Berstad et al 2008). Only two case control studies included less than 500 cases (Wrensch et al 2004, Bessaoud et al 2008).

Table 2.4.2 Alcohol and breast cancer: general characteristics of case control studies

Authors	Year	Country	Case/Control)	Age range (M/Mdn)	Sample base	Sample selection Cases/Controls
Althuis	2003	USA	1,750/1,557	20-54	regional population (5 US states)	consecutive/random sample
Berstad	2008	USA	1,728/435	20-49, (M=43)	regional population	not specified
Bessaoud	2008	France	437/922	25-85 (M=58)	regional hospitals/electoral lists	consecutive/random sample
Deandrea	2008	Italy	989/1,350	23-74, (Mdn=55)	hospitals in 6 regional areas	consecutive/non-random selection
Enger	1999	USA	744/2,623	21-64	state population	consecutive/random selection
Kinny	2000	USA	890/841	20-74	*Carolina Breast Cancer Study* state cancer registry/ driver licence lists	consecutive/random sample
Marcus			864/790			
Kropp	2001	Germany	706/1,381	<51 (M=42)	regional population	consecutive/random sample
Lenz	2002	Canada	556/577	50-75	city hospitals	consecutive/non-random selection
Li	2003	USA	975/1,007	65-79	state cancer registry /health insurance lists	consecutive/non-random selection
Li	2006	USA	3,463/4,682	35-64	*CARE* regional population	consecutive/random selection
McDonald	2004		4,575/4,682			
Newcomb	2009	USA	6,327/7,558	20-69	cancer registries/ driver licence lists or medi-care in 3 states	consecutive/non-random selection
Terry	2006	USA	1,508/1,506	20-98	state population	consecutive/random sample
Wrensch	2003	USA	285/286	>18	state cancer registry/	consecutive/random selection

Abb: n/s not specified; M=mean; Mdn= median

2.4.2 Study quality

The quality scores for cohort and case controls studies, according to the NOS, are presented in Tables 2.4.3 and 2.4.4, respectively. Cohort studies were generally of high quality scoring an average 7.5 stars on the NOS (Table 2.6.3) and case control studies of moderate quality scoring an average 6.7 stars (Table 2.6.4).

Table 2.4.3 Breast cancer: assessment of study quality in cohort studies

	Selection* (out of 4)	**Comparability* (out of 2)**	**Outcome* (out of 3)**	**Total**
Cohort				
Allen 2008	4	2	3	9
Baglietto 2005	4	2	3	9
Chlebowski	4	2	3	9
Chen 2002	3	2	2	7
Dumeaux 2004	4	2	2	8
Feigelson 2001 Feigelson 2003	4	2	2	8
Garland 1999	3	2	2	7
Horn-Ross 2004	3	2	2	7
Jain 2000	3	2	2	7
Kuper 2000	3	2	3	8
Lew 2009	4	2	3	9
Lin 2005	4	2	3	9
Mattison 2004	4	2	3	9
Nielsen 2008 Petri 2004 Thygesen 2009	4	2	2	8
Rohan 2000	4	2	3	9
Sellers 2002	4	2	2	8
Stolzenberg 2006	4	2	2	8
Suzuki 2005	4	2	3	9
Tjønneland 2003 Tjønneland 2004	4	2	2	8
Tjønneland 2007	4	2	1	7
Zhang 1999	4	2	2	8
Zhang 2007	3	2	2	7

*High quality characteristics within each of these items were awarded a star, up to a maximum of four stars for selection, two stars for comparability and three stars for assessment

Table 2.4.4 Breast cancer: assessment of study quality in case control studies

	Selection* (out of 4)	Comparability* (out of 2)	Exposure (out of 3)	Total
Case-control				
Althuis 2003	4	2	1	7
Berstad 2008	4	2	1	7
Bessaoud 2008	3	2	1	6
Deandrea 2008	3	2	1	6
Enger 1999	3	2	1	6
Kinny 2000 Marcus 2000	4	2	2	8
Kropp 2001	4	2	2	8
Lenz 2002	3	2	3	8
Li 2003	3	2	3	8
Li 2006 McDonald 2004	4	2	3	9
Newcomb 2009	3	2	3	8
Terry 2006	2	2	1	5
Wrensch 2003	3	2	1	6

*High quality characteristics within each of these items were awarded a star, up to a maximum of four stars for selection, two stars for comparability and three stars for assessment

On the basis of sample selection, cohort and case control studies scored highly on the NOS, with either three or four stars out of four. All studies that scored three failed on the selection of sub-groups of the general population in cohort studies (e.g. teachers, nurses, health professionals) or through the selection of hospital based controls in case-control studies. For outcome assessment in cohort studies, all studies scored either two or three stars. Of those that only scored two, most were not awarded the third because diagnosis of breast cancer was identified through self-reports via mailed questionnaires. However, in five of these studies, the majority of self-reported cases (>90%) were subsequently verified by a pathologist (Garland et al 1999, Zhang et al 1999, Chen et al 2002), or verified by reviewing medical records (Feigelson et al 2003, Stolzenberg and Solomon et al 2006).

For exposure assessment in case control studies, there was more variation, with four papers scoring three stars, seven papers scoring two stars and seven papers scoring one star. Most papers scoring one failed because they did not specify the blinding status of the interviewers. Of more concern was the number of case control studies with low and contrasting response rates among cases and controls. Results could be biased if the women who were not interviewed differed from those who did participate, with regard to their use of alcohol. Kinny et al (2000) observed that some characteristics of their non-responders (i.e. older, less educated, black race) were associated with lower levels of alcohol consumption, suggesting that their results may underestimate the true association between alcohol consumption and breast cancer. Selection bias could, however, influence results in either direction and none of the case control studies were able to determine the net effect of non-responders on their risk estimates.

In the 'comparability' category, one star was awarded if a study controlled for age and one star awarded if a study controlled for either one of the following; weight, hormone replacement therapy use, socio-economic status, reproductive factors, oral contraceptive use or diet and/or measures of 'energy intake'. All prospective cohort and case control studies achieved a maximum of two stars, but the studies ranged from adjusting for only two, to all of the afore-mentioned potential confounders. Weight (measured by body mass index) and reproductive factors (age at menarche, age at first full-term pregnancy, parity) were the most common possible confounders controlled for; only one prospective cohort study (Stolzenberg and Solomon) and three case control studies did not control for the effects of weight in their analysis (Enger et al 1999, Kropp et al 2001, Wrensch et al 2003). Hormone replacement therapy (HRT) use was the next most common variable controlled for. This was more common in cohort studies than in case control studies; three of the 14 case control studies adjusted their analysis for HRT use (Lenz et al 2002, Li et al 2006, Newcomb et al 2009), whilst only three of the 21 cohort studies did not control for HRT use (Garland et al 1999, Jain et al 2000, Zhang et al 2007).

Education was the most common measure of socio-economic status (SES) controlled for in studies included in present review and varied across studies, from type of education, length of education to number of qualifications. This was more common in case control studies where 9 of the 14 studies controlled for education, compared to 7 of the 21 cohort studies. Two additional SES measures were controlled for; by Enger et al (1999) based on five categories derived from census tract of residence and by Wrensch et al (2003) for self assessed socio-economic status defined as 'poor', 'lower', 'middle' and 'upper class'. Allen et al (2009) controlled for the effects of socio-economic status by using quintiles of the UK Townsend deprivation index which includes measures of unemployment, overcrowding, owner-occupier status, and car ownership for the postcode area of each participant, based on the 1991 National Census.

Smoking terms including smoking status, number of packs per day and length of time smoked, were included in the models of eight studies and six studies also controlled for oral contraceptive use. Other more controversial risk factors and possible confounders of the alcohol breast cancer association such as nutritional factors, particularly folate intake were only controlled for in a small number of studies (Baglietto et al 2006, Feigelson et al 2003, Mattison et al 2004, Suzuki et al 2005).

2.4.3 Results: total alcohol intake and risk of breast cancer[8]

Twelve, nine cohort and three case control, studies reported on the association between 'recent' total alcohol consumption (i.e. amount consumed in the previous year) and the risk of incident breast

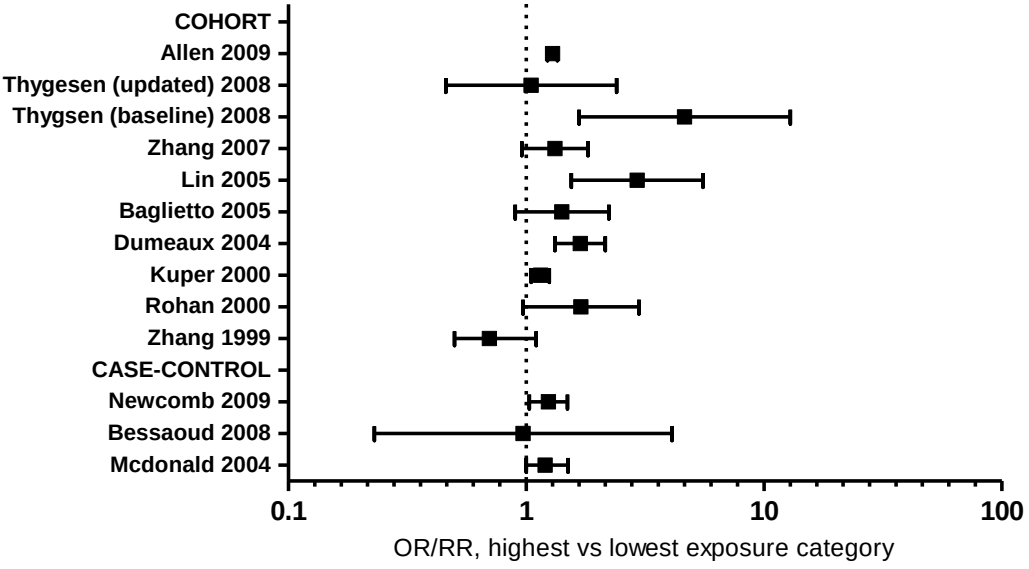
[8] Multivariate relative risks/odds ratios are presented unless otherwise stated

cancer. A summary of breast cancer risk estimates, comparing the highest versus the lowest alcohol exposure category, is presented in Figure 2.4.1.

Allen et al (2009), in a large UK prospective cohort study with over 28,000 incident cases of breast cancer, reported that women drinking >15 drinks per week [d/w] had a statistically significant increased risk (RR 1.29, 95% CI 1.23-1.35) of breast cancer, compared to women drinking <2 d/w, with strong evidence of a statistically significant dose response trend (*p value for trend* <0.001). Non-drinkers, in the same study, were not at an increased risk of breast cancer (RR 1.00, 95% CI 0.97 to 1.03).

Three cohort studies, with approximately 1,500 incident cases of breast cancer, produced mixed results. Rohan et al (2000) and Zhang et al (2007) observed a statistically non-significant increased risk (ranging from 10% to 70%) of breast cancer across all alcohol intake categories (maximum of >30 grams per day [g/d]). Zhang et al (2007) provided stronger evidence then Rohan et al (2000) of the risk of breast cancer increasing with amount of alcohol drunk; *p value for trend* <0.001 and =0.35 respectively. Dumeaux et al (2004) reported statistically significant estimates for all alcohol intake levels (up to >10 g/d, compared to 0 g/d, *p value for trend* <0.0001), compared to non-drinkers.

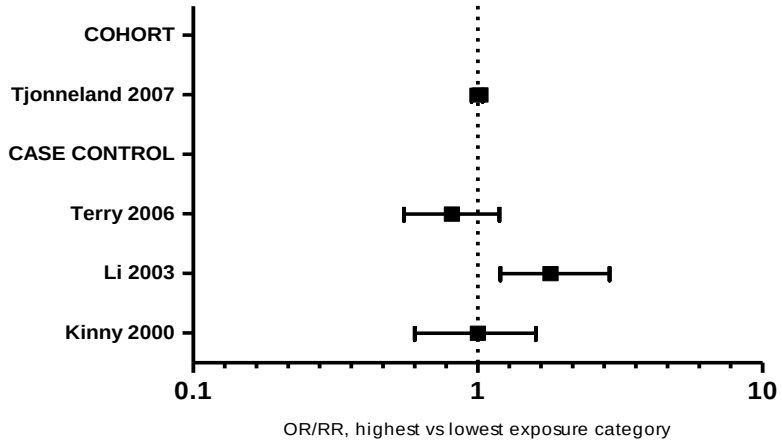
Figure 2.4.1 Recent alcohol consumption and risk of breast cancer, highest versus lowest exposure category, by study type (relative risk/odds ratio and 95% confidence intervals)



The remaining cohort studies were small to moderate in size (≤750 cases) and reported mixed results on the association between alcohol consumption and breast cancer. Baglietto et al (2005) observed a non-significant 40% increase in risk (HR 1.41, 95% CI 0.90-2.23) of breast cancer among women drinking ≥40 g/d, compared to abstainers. In this study, women who drank between 1-19 g/d (representing 80% of all drinkers in the cohort) had a small, and statistically non-significant, increased risk of breast cancer (HR 1.12, 95% CI 0.93-1.36). In the Copenhagen City Heart Study, increased risks were observed for women with baseline alcohol intakes of 13-24 g/d (HR 1.36, 95% CI 1.01-1.81) and >48 g/d (HR 4.64, 95% CI 1.67-12.9), compared to women drinking <1.71 g/d (Thygesen et al 2008), with strong evidence of a statistically significant dose response association (*p value for trend* <0.001), between alcohol intake and breast cancer. However, in the alcohol exposure category with the largest number of drinkers (1.71-12 g/d), there was no association (RR 1.00, 95% CI 0.80-1.24) with breast cancer. When the analysis was updated to take into account current drinking behaviour over the period of follow-up (27 years) in the study, there was no significant association (*p value for trend* =0.13) between breast cancer and alcohol consumption across all alcohol intake categories (Thygesen et al 2008). Two studies reported on the association between low level drinking only, and breast cancer. In a Japanese cohort study (Linn et al 2005), average alcohol intake of <15 g/d did not significantly increase the risk of breast cancer. However, risk was significantly increased for women who drank ≥15 g/d (RR 2.93, 95% CI 1.55-5.54), compared to non-drinkers. Zhang et al (1999) did not find any association at any level of drinking and increased risk of breast cancer. In this study women drinking >15 g/d, compared to non-drinkers had a 30% (RR 0.7, 95% CI 0.5-1.1) reduced risk of breast cancer.

Of the case control studies, Newcomb et al (2009) observed a statistically significant increased risk of breast cancer at the highest alcohol exposure category (≥14 d/w). Drinking below this level was not, however, associated with an increased risk of breast cancer and the OR for an increment of 1 drink per day and risk of breast cancer was 1.01 (95% CI 1.00-1.02). McDonald et al (2004), based on reported alcohol intake within the previous two years, reported a weak, statistically significant, increased risk of breast cancer, but no obvious linear trend with amount drunk (up to >14 d/w). Bessaoud et al (2008), in a French case control study, found no association between breast cancer and drinking >20 g/d, and with an increment of 10 g/d (OR 0.94, 95% CI 0.75-1.17).

Figure 2.4.2 Lifetime alcohol consumption and risk of breast cancer, highest versus lowest exposure category by study type (relative risk/odds ratio and 95% confidence intervals)



Four studies reported on the association between lifetime alcohol consumption and risk of breast cancer. A summary of breast cancer risk estimates comparing the highest versus the lowest alcohol exposure category are presented in Figure 2.4.2. Lifetime drinking of approximately 20-30 grams per week (g/w) was not associated with an increased risk of breast cancer in a prospective cohort study (Tjonneland et al 2007) and in two case control studies (Kinny et al 2000, Terry et al 2006). Li et al (2003) did, however, report raised point estimates across all levels of alcohol intake, based on consumption over the last twenty years, but only intake at the highest exposure level (≥30 g/d) was statistically significant (*p value for trend* =0.419).

2.4.3.1 Results: total alcohol intake and risk of breast cancer by histological types

Three studies reported on association between alcohol consumption and breast cancer, by histological type. In a large cohort study, Lew et al (2009) reported a strong, statistically significant, dose response association between alcohol consumption and increased risk of ductal tumours (>35 g/d, RR 1.46 (95% CI 1.22-1.75, *p value for trend* >0.001), compared to non-drinkers, and slightly weaker evidence of an increased risk of lobular tumours (>35 g/d; RR 1.52 95% CI 0.95-2.44, *p value for trend* =0.04). In the same study, there was no increased risk of ductal-lobular tumours at any alcohol intake level, compared to non-drinkers.

In a case control study, Li et al (2003) also reported a positive association for both ductal and lobular tumours across all alcohol exposure categories, compared to never drinkers. However, this increased risk only reached statistical significance for lobular tumours among women drinking >30 g/d (OR 3.3, 95% CI 1.7-6.4, *p value for trend* =0.453). The corresponding figures for ductal tumours were OR 1.5 (95% CI 0.9-2.6, *p value for trend* =0.638). Li et al (2006) reported a similar non-significant increased risk (range 10-90%) of ductal, lobular, medullary and ductal lobular tumours in women

drinking >7 d/w, compared to never drinkers. Less common tumours identified in the cohort, tubular, comedo and mucinous, were not associated with alcohol consumption (Li et al 2006).

2.4.3.2 Results: total alcohol intake and risk of breast cancer mortality

Two prospective cohort studies reported on the association between alcohol consumption and breast cancer mortality. In an American cohort study, Feigelson et al (2001) reported an increased risk of breast cancer mortality across all alcohol consumption categories, compared to non-drinkers, with weak evidence of a statistically significant dose response trend (>3 d/d; RR 1.2, 95% CI 1.0-1.5, *p value for trend* =0.08). Women drinking >20g, compared to non-drinkers were not at increased risk of death from breast cancer in a Canadian cohort study (Jain et al 2000). In the same study, the authors reported a '1% increase' in risk of breast cancer mortality per 10 gram increase in alcohol intake (HR 1.012, 95 CI 1.005-1.019).

2.4.4 Results: drinking dimensions and risk of breast cancer

Overall, six studies reported on the risk of breast cancer by a number of drinking dimensions, including drinking frequency, duration of drinking and age at which participants first started drinking.

Two cohort and two case-control studies reported on the association between breast cancer and measures of drinking frequency. In a cohort of American teachers, post-menopausal women who were 'daily heavy' drinkers (i.e. drinking a weekly average of >20 g/d and regularly drinking alcohol on ≥5 days in a week) had a statistically significant increased risk of breast cancer (RR 1.34, 95% CI 1.07-1.67), compared to non-drinkers (Horn-Ross et al 2004). 'Daily heavy' drinkers drinking <20 g/d on ≥5 days per week (RR 1.07, 95% CI 0.86-1.32) and 'sporadic' drinkers (i.e. those drinking alcohol on <4 days in a week; RR 0.99, 95% CI 0.84-1.17) were not at an increased risk of breast cancer. In a Japanese cohort, the risk of breast cancer increased by 50% among both 'daily' and 'weekly' drinkers, compared to non-drinkers (Lin et al 2005). In a French case control study, frequent (>5 times per week, (OR 0.75, 95% CI 0.40-1.45) or sporadic drinkers (OR 1.03, 95% CI 0.62-1.71) were not an increased risk of breast cancer compared to never drinkers (Bessaoud et al 2008). Lenz et al (2002) observed a 50% (OR 1.5, 95% CI 1.0-2.2) increase in risk of breast cancer in current weekly and daily drinkers for post-menopausal women, compared to a 20% (OR 1.2, 95% CI 0.8-1.8) increase for infrequent drinkers, compared to never drinkers.

Four studies investigated the association between age at when first alcoholic beverage was drunk and risk of breast cancer. Drinking before the ages of twenty (Marcus et al 2000), and thirty five years (Lin et al 2005) was not associated with an increased risk of breast cancer. Horn-Ross et al (2004) observed that among both pre- and post-menopausal women in a cohort of American teachers, drinking >20 g/d at ages 18-22 and at 30-35yrs was not significantly associated with an increased risk

of breast cancer. Wrensch et al (2003), in a population based case control study, reported a three -fold increase (OR 2.8, 95% CI 1.9-5.0) in the odds of developing breast cancer for women who starting drinking alcohol aged ≥21yrs, compared to those who first drank <21 yrs.

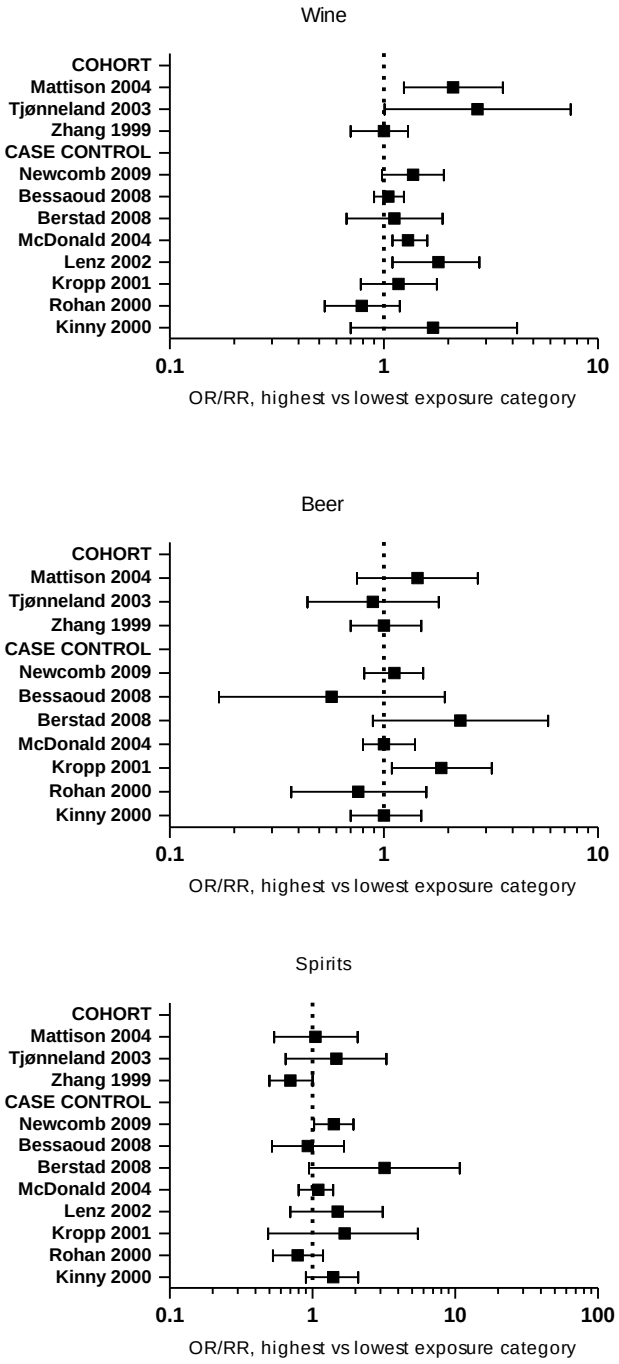
Tjonneland et al (2004) reported no association between lifetime intake (based on aggregated reports of drinking by cohort members in their twenties, thirties and forties) and increased risk of breast cancer, compared to abstainers.

2.4.5 Results: drink type and risk of breast cancer

Eleven studies reported on the association between breast cancer and alcohol consumption, by type of alcohol beverage (e.g. wine, beer, and spirits). A summary of risk estimates, comparing the highest versus the lowest alcohol exposure category, are presented in Figure 2.4.3. In general, a positive association was observed between the highest alcohol exposure category in each study and an increased risk of breast cancer, from drinking wine, but not for drinking beer or spirits.

In four studies reporting on the association between drink type and breast cancer in post-menopausal women only, intake of wine, but not beer or spirits, significantly increased the risk of breast cancer. Mattison et al (2004) observed a statistically significant two fold increase in breast cancer risk among post-menopausal women in a Swedish cohort, drinking >20 millilitres per day in the previous week. No association was observed at lower intake levels. In a study where wine was the preferred drink, Tjonneland et al (2003) also observed a twofold increase in breast cancer among post-menopausal wine drinkers, drinking >24g-≤60 g/day and >60 g/d in their Danish cohort, compared to those drinking between 0-6 g/d. In two case control studies, McDonald et al (2004) reported a small statistically significant increased risk of breast cancer among post-menopausal (but not pre-menopausal) women drinking >7 d/w in the previous two years, compared to non-drinkers and Lenz et al (2002) found a two-fold increased risk of breast cancer in current regular drinkers of wine compared to abstainers. Berstad et al (2008) found no association between drink type and risk of breast cancer in pre-menopausal women drinking approximately one drink per day.

Figure 2.4.3 Alcohol consumption and risk of incident breast cancer, highest versus lowest exposure category; by drink type (relative risk and 95% confidence intervals)



Spirit drinking, but not beer or wine, significantly increased the risk of breast cancer in an American study (Newcomb et al 2009), but only at the highest intake level (>14 d/w compared to non-drinkers). Three further studies reported a non-significant 50-80% increased risk of breast cancer from drinking of spirits (Kropp et al 1999, Kinny et al 2000, Tjonneland et al 2003). A statistically significant increased risk of breast cancer at the highest intake level only (>12 g/d) was also reported for beer

drinkers only in a German case control study (Kropp et al 1999). Mattison et al (2004) and Berstad et al (2008) also reported an 80% and two-fold increase in breast cancer risk from beer drinking, but neither estimate was of statistical significance.

In three studies, wine, beer or spirit drinking was not associated with an increased risk of breast cancer among women of any ages; for very low levels of drinking (>3 g/d), compared to non-drinkers in the Framingham cohort (Zhang et al 1999); for consumption up to >20 g/d, compared to non-drinkers in a nested case control study (Rohan et al 2000); for drinking up to >91 g/d in a population case control study, compared to abstainers (Kinny et al 2000).

2.4.6 Results: effect modification

Menopausal status

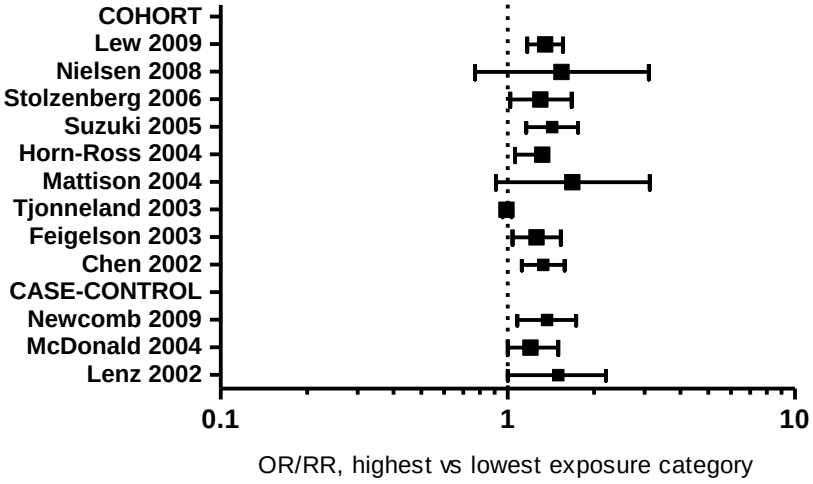
Fifteen studies, reported on the dose response association between breast cancer and alcohol consumption by menopausal status. Of these, three studies reported on the association between breast cancer and alcohol in both pre- and post-menopausal women (Horn-Ross et al 2004, McDonald et al 2004, Newcomb et al 2009). In the remaining studies, eight reported on the association between alcohol and breast cancer in post-menopausal women, and four studies in pre-menopausal women. A summary of findings comparing risk estimates for breast cancer between the highest and lowest alcohol exposure category, by menopausal status, are presented in Figures 2.4.4 and 2.4.5.

In the three studies reporting on both post- and pre-menopausal women, there was no strong evidence that the association between breast cancer and alcohol consumption was modified by menopausal status. In a cohort of American teachers, Horn-Ross et al (2004) reported a 32% statistically significant increased risk of breast cancer for post-menopausal women, drinking ≥20 g/d, compared to non-drinkers. The corresponding increase of 21% in pre-menopausal women was not statistically significant, but did not differ significantly from that of pre-menopausal women ($P_{interaction}$=0.54). McDonald et al (2004) reported a non-significant 10% and 30% increased risk of breast cancer in pre- and post-menopausal women respectively, drinking >168 g/w, compared to non-drinkers, but differences were not statistically significant ($P_{interaction}$<0.16). Menopausal status did not significantly modify the association ($P_{interaction}$=0.05) between alcohol and breast cancer risk in a cohort of American health professionals; Newcomb et al (2009), reported a statistically significant 37% increased risk of breast cancer in post-menopausal women drinking >168 g/w and a non-significant 10% increased risk in pre-menopausal women compared to non-drinkers.

Nine studies reported on risk of breast cancer from alcohol consumption in post-menopausal women (Figure 2.4.4). Overall, the majority of studies reported a statistically significant association between the highest alcohol exposure category and an increased risk of breast cancer. In one of the largest

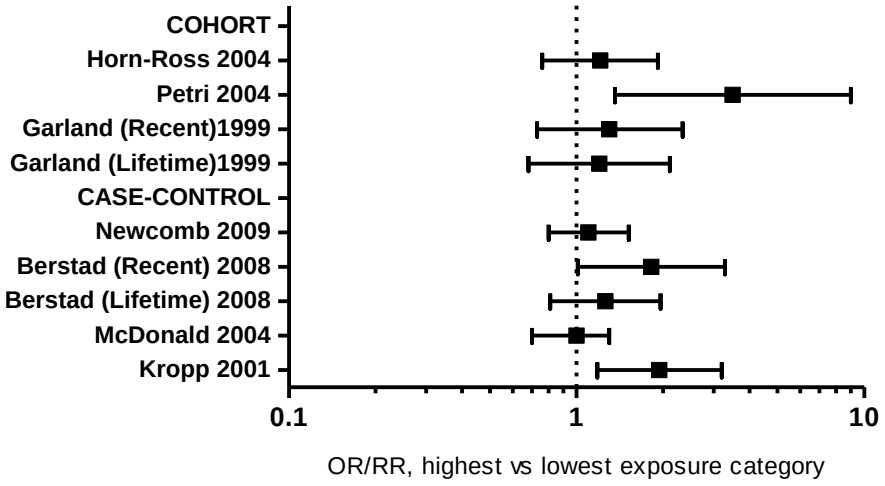
cohort studies of the alcohol-breast cancer association, included in the present review, Lew et al (2009) observed a statistically significant dose response relationship (*p value for trend* >0.001) for alcohol intake up to >35 g/d in post-menopausal women, though point estimates were not statistically significant below <10 g/d. Suzuki et al (2005) observed positive associations with breast cancer, at all alcohol intake levels, based on drinking reports within the previous six months, with strong evidence of statistically significant dose response relationship (≥10 g/d; RR 1.43, 955 CI 1.16-1.76, *p value for trend* =0.0012).

Figure 2.4.4 Alcohol consumption and breast cancer in post-menopausal women, highest versus lowest exposure category (relative risk/odds ratio and 95% confidence intervals)



Four studies reported on risk of breast cancer from alcohol consumption among pre-menopausal women (Figure 2.4.5). In a Danish cohort, Petri et al (2004) observed a threefold increase in risk among pre-menopausal women drinking >27 d/w, though no increased risk was observed at lower intake levels. Garland et al (1999) reported non-positive associations between breast cancer and both current and lifetime alcohol consumption. Berstad et al (2008) did observe a weak statistically significant dose response relationship (*p value for trend* =0.04), but only consumption at the highest intake level (>14 d/w) reached statistical significance. Kropp et al (1999) in a German case control study, observed a statistically significant increased risk of breast cancer among women drinking at the highest intake levels of ≥31 g/d, though this estimate was based on less than 50 cases and controls. Conversely, at low levels of alcohol consumption (between 1-11 g/d) and where there were ten times as many cases and controls, a mild statistically significant inverse association (OR 0.67, 95% CI 0.50-0.91) was observed between alcohol consumption and breast cancer.

Figure 2.4.5 Alcohol consumption and breast cancer in pre-menopausal women, highest versus lowest exposure category by study type (relative risk/odds ratio and 95% confidence intervals)



Hormone receptor status

Nine observational studies and one meta-analysis were identified that investigated alcohol intake and risk of breast cancer, defined by hormone receptor status; oestrogen (ER) and progesterone (PR) receptor status. Six of these studies were included in a meta-analysis (Suzuki et al 2008) which also included four studies not identified by the present review's search strategy. The results, therefore, of the meta-analysis are presented here and compared with the three studies identified in this review, but not included in the meta-analysis.

Suzuki et al (2008) reported that the dose response meta-analysis (based on 4 cohort and 16 case controls studies) showed that an increase in alcohol consumption of 10 g/d was statistically significantly associated with a 12% (95% CI 8%-15%; *p* heterogeneity among studies =0.24) increased risk of developing all ER+ (positive) tumours and a 7% (95% CI 0%-14%; *p* heterogeneity among studies =0.27) increased risk of all ER- (negative) tumours. Among joint ER/PR tumour subtypes, an increase in alcohol consumption of 10 g/d was associated with a 11% (95% CI 7%-14%) increase in risk of ER+/PR+ tumours, and a 15% (95% CI 2%-30%) increase in risk of ER+/PR- tumours. Alcohol consumption was not associated with an increased risk of ER-/PR+ tumours (RR 1.04, 95% CI 0.76-1.43) or ER-/PR- tumours (RR 1.04, 95% CI 0.98-1.09).

Of the three studies included in this review, but not in Suzuki's meta-analysis, Chlebowski et al (2007) observed that women drinking >1 d/d (approximately 12 grams), compared to those drinking ≤1 d/d, had a statistically significant increased risk of ER+ tumours (OR 1.17 95% CI 1.02-1.33) and a small, non-significant, increased risk of ER- tumours (OR 1.06 95% CI 0.75-1.49). Differences between risk estimates were, however, not statistically significant ($P_{interaction}$=0.60). An Italian case control study, (Deandrea et al 2007), reported a statistically significant two-fold increased risk (OR

2.16, 95% CI 1.68-2.76) of ER+ tumours in women drinking ≥13.8 g/d, compared to never drinkers. The odds of ER-tumours increased by 36% in women drinking >13.8 g/d, but was not statistically significant (OR 1.36, 95% CI 0.93-2.01). In a large cohort study, Lew et al (2009), reported a statistically significant dose response relationship for ER+/PR+ tumours (>35 g/d; RR 1.46, 95% CI 1.12-1.91, *p value for trend* =0.003), but not for ER+/PR- (>20g/d; RR 1.13, 95% CI 0.73-1.77, *p value for trend* =0.51) or ER-/PR- tumours (>20g/d; RR 1.21, 95% CI 0.79-1.84, *p value for trend* =0.25).

Hormone Replacement Therapy

Five cohort studies examined the interaction between alcohol and hormone replacement therapy (HRT) use on the risk of breast cancer.

In one of the largest studies included in the present review of the alcohol and breast cancer association, Lew et al (2009) observed a statistically significant increased risk in breast cancer for both current and never users of HRT, who drank >35 g/d (RR 1.40, 95% CI 1.14-1.71, and RR 1.31 95% CI 1.04-1.64, respectively, $P_{interaction}$=0.10). In the same study, only current users of HRT for >10 years, and who drank >35 g/d were at increased risk (RR 1.70, 95% CI 1.28-2.26) of breast cancer, though duration of HRT use overall did not significantly ($P_{interaction}$=0.26) modify the association between alcohol and breast cancer. In a cohort of American nurses, compared with non-drinkers who never used HRT, current HRT users for ≥5 years and who drank >20 g/d had a RR for breast cancer of 1.99 (95% CI 1.41-2.79). In contrast, the RR was 1.32 (95% CI 1.05-1.66) in women taking HRT for ≥5 years and who were non-drinkers and 1.28 (95% CI 0.97-1.69) in never-users of HRT who drank >20 g/d (Chen et al 2002). The authors reported that, although the RRs suggested a modifying effect of HRT on the alcohol-breast cancer association, the test for interaction was not statistically significant, though no results were presented in the paper (Chen et al 2002). Similar findings were reported by Horn-Ross et al (2004) in a cohort of American teachers.

Zhang et al (2007) reported that for an increment of 10 grams of alcohol per day, there was a statistically significant increased risk of breast cancer among women who were current (RR 1.15, 95% CI 1.05-1.26) users of HRT, but not past (RR 0.91, 95% CI 0.72-1.16) or never (RR 0.99, 95% CI 0.86-1.15) users of HRT, although the test for interaction was not statistically significant ($P_{interaction}$=0.07). The same results for current and never users ($P_{interaction}$=0.11) of HRT among drinkers, were reported in a Danish cohort study (Neilsen and Gronbaek 2008).

Body weight

Four studies examined the interaction between alcohol and body weight (as measured by body mass index (BMI: kg/m^2) on the risk of breast cancer.

In a large cohort study, women who weighed <25 kg/m^2 or who were overweight (≥25-<30 kg/m^2) or obese (≥30 kg/m^2), had an increased risk of breast cancer across all alcohol intake levels (up to a maximum of >35g/d) and there was no evidence of a statistically significant ($P_{interaction}$=0.27) effect of weight on the alcohol and breast cancer association (Lew et al 2009). Zhang et al (2007) reported similar results for an increment of 10 grams of alcohol per day in women weighing <25 kg/m^2 or ≥25 kg/m^2 ($P_{interaction}$=0.68). In a cohort of teachers, Horn-Ross et al (2004) observed an increased risk of breast cancer of similar magnitude in stratum of women weighing <27.3 kg/m^2 or ≥27.3 kg/m^2 and drinking either <20g/d or ≥20 g/d, compared to non-drinkers weighing <27.3 kg/m^2 .

In an American case control study, women with a BMI of <25 kg/m2and who drank 15-30 g/d over their lifetime, had a two-fold increased risk (OR 2.13, 95% CI 1.29-3.54) of breast cancer, compared to non-drinkers. In contrast, women with a BMI of ≥25 kg/m2and lifetime drinking of 15-30g/d, compared to non-drinkers, were not at increased risk (OR 0.95, 95% CI 0.58-1.54) of breast cancer (Terry et al 2006). No formal test for interaction was reported in the paper.

Folate

Five studies examined the possible interaction between alcohol and folate consumption on risk of breast cancer. Three studies found no evidence that the association between alcohol and breast cancer was significantly modified by total folate intake. Zhang et al (2007) reported positive associations across all folate intake levels (highest category of ≥600 µg/day) with an increment of 10 grams of alcohol per day, but no evidence of a statistically significant interaction ($P_{interaction}$=0.96). In a further two cohort studies, Feigelson et al (2003) and Lew et al (2009) did not find an increased risk of breast cancer in any stratum of total folate and total alcohol intake. There was no evidence of a significant modifying effect of folate on the alcohol and breast cancer association in either study; $P_{interaction}$=0.61 and $P_{interaction}$=0.13, respectively.

Two studies, however, did provide some weak evidence of a significant interaction between folate intake and alcohol consumption on the risk of breast cancer. Baglietto et al (2005) reported a statistically significant two-fold increase in risk in women with a low folate intake (200 µg/day) and who drank >40 g/d, compared to abstainers (HR 2.00, 95% CI 1.14-3.49). Women with a daily intake of 330 µg/day or 400 µg/day and who drank >40 g/d, did not have an increased risk of breast cancer ($P_{interaction}$=0.04). Stolzenberg-Solomon et al (2006) also observed that low levels of drinking (>7.62 g/d) and a folate intake of ≤335.5 µg/day, increased the risk of breast cancer in women two-fold (RR 2.10, 95% CI 1.08 4.07), compared to non-drinkers, but in women drinking >7.62 g/d and a folate intake of ≥335.5 µg/day, the RR was 1.23 (95% CI 0.93-1.62, $P_{interaction}$=0.05).

Other effect modifiers

Dumeaux et al (2004) observed a two fold increase in risk of breast cancer from women who were long term users (>10 years) of oral contraceptives (OC) and drinking >10 g/d, compared to non-drinkers and non-users of OC. No significant interaction between alcohol consumption and duration of OC use was observed after stratification by menopausal status; pre-menopausal ($P_{interaction}$=0.14) and post-menopausal women ($P_{interaction}$=0.21). The results for the interaction of alcohol intake with history of breast cancer in first-degree relatives were not statistically significant in three studies that tested for this interaction, though in each study no data was presented in the paper (Horn-Ross et al 2004, Suzuki et al 2005, Terry et al 2006).

2.4.7 Summary and conclusions

This review identified 41 papers from 34 studies, published between 1999 and 2009, which examined the relationship between alcohol consumption and the risk of breast cancer. Overall, the majority of the larger prospective studies included in the present review reported a statistically significant dose response association between 'current' alcohol consumption and an increased risk of breast cancer. These findings were consistent in studies of the association between breast cancer and alcohol consumption in post-menopausal and pre-menopausal women. Positive associations between 'current' alcohol consumption and an increased risk of breast cancer were in general only associated with alcohol consumption of approximately >15 g/d (i.e. approximately >1 'standard' drink or >2 UK 'units per day). The evidence from the present review that current drinking of <15g/d increases the risk of breast cancer was less conclusive; results from the larger cohort studies in the present review were mixed ranging from no association, to small, statistically non-significant, positive associations. When analysed as a continuous variable, however, an increment of 10 grams of alcohol per day was consistently associated with a statistically significant 5-10% increased risk of breast cancer.

The results for 'current' alcohol consumption are broadly consistent with those published previously. Several pooled analyses, based on studies published up to and including 2000, have suggested a positive association between alcohol consumption and breast cancer with a modest dose-response relationship, such that consumption of two to three drinks (between 25-40 g/d) is associated with a 30-40% increase in risk, (Longnecker 1994, Smith-Warner et al 1998, Ellison et al 2001, Collaborative Group 2002, Key et al 2006). These analyses have also suggested a linear effect of alcohol on breast cancer risk, whereby the risk of breast cancer increases by each daily amount of alcohol drunk: Ellison et al (2001), in a meta-analysis of 15 cohort and 27 case control studies, reported a 10% increase in breast cancer risk per 12 g/d of alcohol drank. Similar results were reported in a pooled analysis of six cohort studies (RR 1.9, 95% CI 4%-13%, Smith-Warner et al 1998) and a pooled analysis of 53 cohort and case control studies (RR 1.7, 95% CI 5%-8%, Collaborative Group 2002). A recent international systematic review has concluded that the evidence is now convincing that alcohol

consumption is a cause of pre-menopausal and post-menopausal breast cancer and that there is a strong dose response pattern without a threshold effect (WCRF/AICR 2007).

Lifetime alcohol consumption was not associated with an increased risk of breast cancer in the present review, though only four studies reported on this aspect of the alcohol-breast cancer association. Recall bias, leading to an underreporting of alcohol intake in the distant past, may, however, have resulted in attenuation of risk estimates for lifetime consumption. Four studies reported on the association between drinking frequency and increased risk of breast cancer. Measures of 'daily' drinking were consistently associated with a statistically significant increased risk of breast cancer. This is not an unexpected finding since 'daily' drinkers often account for the majority of total alcohol consumed in surveys of drinking habits. Of more interest is the finding by Horn-Ross et al (2004) that only 'daily' drinkers drinking >20 g/d, compared to non-drinkers, had a statistically significant increased risk of breast cancer. This suggests that a more valid and interesting comparison in relation to risk of breast cancer by drinking frequency, is one that takes into account both quantity and frequency.

The results of analyses by drink type, in the present review, were inconsistent. There was some evidence that wine, but not beer or spirits, increased the risk of breast cancer in post-menopausal women, but in many of these studies it was moderate drinkers who consumed wine more often than beer or spirits. This pattern of increased risk may, therefore, implicate wine, when, in fact, risk may be associated with moderate consumption of any alcoholic beverage. Higher estimates for wine may also be due to residual confounding by social class, which strongly affects beverage preference; in a number of studies, women of high socio-economic status drank more wine, while drinking beer was associated with lower educational level (Tjonneland et al 2003, 2004, McDonald et al 2004). The previous literature has not consistently linked one beverage type to breast cancer risk (Smith-Warner et al 1998). A meta-analysis (Ellison et al 2001) and a pooled analysis (Smith-Warner et al 1998) concluded that their analyses did not support the hypothesis that alcoholic components of wine modify the alcohol-breast cancer relation.

The evidence from the present review and that from large international reviews and meta-pooled analyses would therefore suggest that current alcohol consumption of approximately 12-16 grams per day is associated with an increased risk of breast cancer. Lifetime consumption, drinking patterns and drink type associations with breast cancer are less conclusive: some caution needs to be taken, however, regarding the association between alcohol intake and breast cancer observed in the present review. Risk estimates, when comparing the highest with the lowest alcohol exposure category and for an increment of 10 15 grams of alcohol per day, were modest in size in both cohort and case control studies, ranging from a 10% to 70% increased risk of breast cancer. Small associations could be explained by imprecise control for what Mattison et al (2004) termed the 'web of confounding

factors' of the alcohol-breast cancer association. Although many of the studies in this review controlled for some, but not all of the possible confounding factors e.g. body weight, HRT use, sexual reproductive factors, socio-economic status and smoking, too little detail was provided in most papers on measurement of these terms to rule out the effects of residual confounding.

In the present review, the association between an increased risk of breast cancer and alcohol consumption did not vary by menopausal status. This is consistent with the evidence in the published literature; in a meta-analysis (Ellison et al 2001) and two large pooled analyses (Smith and Warner et al 1998, Colloborative Group 2002), no significant differences in the relation between alcohol intake and relative risk of breast cancer before and after menopause were observed. Hormone replacement therapy use and obesity were also not significant modifiers of the association between alcohol consumption and breast cancer in the five studies in the present review reporting on this aspect. Body weight was adjusted for in 30 of the 34 studies in the review, and adjustment for weight did not appreciably change the relation between alcohol intake and breast cancer risk. Although folate intake did not significantly modify the alcohol and breast cancer association in three studies, there was some evidence from two cohort studies that 'heavy' drinkers with low folate intake levels had a statistically significant greater risk of breast cancer than drinkers with a high folate intake. No firm conclusions can be made concerning the effect of folate since only a small number of studies, with small numbers in each stratum of alcohol and folate intake, reported on this aspect. Incomplete assessment of folate consumption from food frequency questionnaires may have led to measurement error contributing to the inconsistencies reported on the modifying effect of the alcohol consumption and breast cancer association.

There was some evidence from the present review that **a**lcohol use may selectively increase a woman's risk of hormonally responsive breast cancers, i.e. hormonally related breast cancer risk factors are associated with ER/PR positive breast tumours, but not with ER+/PR- or ER-/PR- tumours. The finding that alcohol may be more strongly associated with ER+/PR+ risk of breast cancer lends support to the theory that hormone receptor status defines distinct diseases, rather than different stages of the same disease (Enger et al 1999). However, missing receptor status of study participants' was a problem for all studies, leading to potential misclassification bias and possible attenuation of risk estimates. Low numbers of hormone receptor subtypes in all studies could reduce the statistical power to detect a true association and although a meta-analysis concluded that receptor status was a modifier of the alcohol-breast cancer relationship, no figures on the number of cases involved in the analysis were provided (Suzuki et al 2008). Epidemiological data from previous studies investigating the relationship between alcohol use and risk of breast tumours with different hormone receptor profiles has been inconsistent with some observing positive associations across all receptor subtypes (Li et al 2003, Suzuki et al 2005). The fact that alcohol use is but a moderate risk factor for breast cancer may account for these inconsistencies, although additional investigation of these relationships is warranted.

Interestingly, a large prospective cohort study included in the present review, reported that the strong positive dose response relation between baseline alcohol intake and breast cancer observed in their study was markedly attenuated by inclusion of the most recent alcohol intake levels (Thygesen et al 2008). When the authors examined this association by latency period, their findings suggested a pronounced increase of effect with latency. Effect estimates of updated alcohol intake on the risk for breast cancer increased almost monotonically; for an alcohol intake of 12-23 g/d, the risk estimates increased markedly from RR=1.18 for a 0-year time window to RR=2.48 for a 20 year window, while for alcohol intake of >48 g/d, the estimates increased from RR=1.05 for 0 years to RR=110.5 for a 20 year window. There is some biological evidence indicating a long latency between alcohol intake and breast cancer, as alcohol influences an early stage of carcinogenesis (Poschl and Seitz 2004). One proposed mechanism is that alcohol increases the breast area occupied by mammographically dense tissue, which is associated with breast cancer. Another hypothesis is that cumulative lifetime exposure to oestrogens increases the risk for breast cancer, and studies of both pre- and post-menopausal women support the hypothesis that alcohol intake increases oestrogen concentrations. Singletary and Gapstur (2001) also concluded that the biological evidence for a longer latency between alcohol intake and breast cancer is stronger than that for a short latency. In a study of long-term lifestyle factors like alcohol intake, however, the time of exposure is often not clear (Rothman 1981), and the effect of latency may be difficult to separate from the effect of cumulative exposure (product of duration and intensity) and this information was not available in the Thygesen et al (2008) study.

In summary, despite the overall consistency in the association between alcohol and an increased risk of breast cancer, several important questions remain concerning the nature of the dose response association including whether the association between alcohol intake and breast cancer risk is affected by the timing of alcohol exposure (e.g. current or lifetime), modified by other risk factors and potential confounders or effect modifiers of the relationship such as, reproductive factors, deprivation, folate intake, use of hormone replacement therapy or is more pronounced among women diagnosed with hormone receptor positive tumours or in certain histologic subtypes. Given that the magnitude of the association between alcohol consumption and breast cancer risk appears to be relatively modest, resolution of the nature of the dose-response relationship may require further pooling of data, particularly from prospective studies. This would also assist with clarification of whether the association between alcohol consumption and breast cancer risk is modified by other factors, and of whether there are beverage-specific effects. Furthermore, to better understand the biological mechanisms involved, more studies on alcohol intake and studies on interactions between alcohol intake and other lifestyle habits (such as use of hormone replacement therapy), nutritional factors (such as low folate intake) and or biological characteristics (such as tumor hormone receptor status) with adjustment for potential confounding factors are needed**.**

2.5 Colorectal cancer

Colorectal cancer: summary of evidence from previous reviews
Systematic reviews of the literature published up until the early 1990s concluded that in view of the inconsistent findings from epidemiological studies and the probability of uncontrolled confounding by dietary factors, no conclusion could be drawn about the role of alcohol consumption of alcoholic beverages in the causation of colorectal cancer (IARC 1988b, WCRF/AICR 1997, Doll 1999). A pooled analysis of 8 cohort studies, reported that the increased risk for colorectal cancer was limited to persons with an alcohol intake of ≥30 g/d; compared with non-drinkers, the pooled multivariate relative risks for 30 to <45 g/d 1.16 (95% CI 0.99-1.36) and ≥45 g/d 1.41 (95% CI 1.16-1.72) (Cho et al 2004).

The literature search identified 22 studies, published between 1999 and 2009, which examined the association between alcohol consumption and colorectal cancer. Tables for each paper, describing the study aims, population, alcohol measurement methods and main results are provided in Appendix D.

Of the 22 studies, 15 were cohort (14 prospective and 1 retrospective) studies and seven were case control studies. Five studies assessed the effect of alcohol on colorectal cancer as a single entity (Flood et al 2002, Ye et al 2002, Hong et al 2005, Thygesen et al 2008, Toriola et al 2008). A further nine studies reported on the association between alcohol consumption and colon and rectal cancer separately (Murata et al 1999, Ji et al 2002, Sharpe et al 2002, Otani et al 2003, Pedersen et al 2003, Shimizu et al 2003, Wei et al 2004, Akhter et al 2007). Murtaugh et al (2004) investigated the association between alcohol consumption and rectal cancer and Su and Arab (2004) the association between alcohol consumption and colon cancer. The remaining studies reported estimates for all of colorectal, colon and rectal cancer.

2.5.1 Study characteristics

A summary of the general characteristics of the studies is provided in Table 2.5.1 below. Of the individual cohort studies, four papers were based on established prospective cohort studies described in section 2.4; Netherlands Cohort Study on diet and cancer (Bongaerts et al 2008); European Prospective Investigation into Cancer and Nutrition (Ferrari et al 2007); Health Professional follow up study (Thygesen et al 2008) and Copenhagen Centre for Prospective Population Studies (Pedersen et al 2003). In a Swedish record linkage cohort study, patients with a diagnosis of 'alcoholism' based on ICD-9 coding of hospital admissions outpatient data were identified and retrospectively followed up for an average of 10 years (Ye et al 2003).

Table 2.5.1 Alcohol and colorectal cancer: general characteristics of studies reviewed

Authors	Year	Country	Outcome/No outcome Case/Control	Age range (M/Mdn)	Sample base	Sample selection
Cohort studies						
Akhter	2007	Japan (men)	307/24,972	40-64	regional population	random sample
Allen	2009	UK (women)	6,298/1,273,998	>55	breast screening clinics	volunteers
Bongaerts	2008	Netherlands	2,323/118,677	55–69	general population	random sample
Chen	2005	China	242/64,363	≥30	regional population	volunteers
Ferrari	2007	Europe	1,833/476,899	35-70	various	random selection
Flood*	2002	USA	490/44,774	40-93 (M=61.9)	national breast screening programme	random selecton
Otani	2003	Japan	716/89,288	40-59	regional population	volunteers
Pedersen	2003	Denmark	623/32,377	23-95	general population	random sample
Shimizu	2003	Japan	295/29,051	≥35	regional population	volunteers
Su	2004	USA	111/10,418	25-74	general population	representative sample
Thygesen	2008	USA	868/46,564	40-75	male health professionals	volunteers
Toriola	2008	Finland	59/2,623	(M=53)	regional population	representative sample
Tsong	2007	Singapore	845/62,412	45-74	regional population	non-random selection
Wei	2004	USA	1,478/134,365	30-55	nurses and health professionals, nationwide	random sample
Ye	2003	Sweden	929/178,469	(M=45)	all hospitals	consecutive
Case control studies						***cases/controls***
Ho	2004	Hong Kong	822/926	(M=66.8)	3 hospitals serving 30% of HK pop.	consecutive/non-random selection
Hong	2005	S.Korea	209/209	(M=59)	city hospital	consecutive/random sample
Ji	2002	China	1805/1552	30-74	regional population	consecutive/random sample
Kim	2002	S.Korea	243/245	30-79	city hospital	consecutive/non-random selection
Murata	1999	Japan (men)	429/794	30-79	university hospital	consecutive/non-random selection
Murtaugh	2004	USA	952/1205	30-79	regional population	consecutive/random sample
Sharpe	2002	Canada	585/500	35-70	city hospital/electoral lists	consecutive/random sample

* included in meta-analysis by Moskai et al (2008). Abb: n/s not specified; M=mean; Mdn= median

Cohort and cases control studies varied in size. The largest cohort study identified in the present review included approximately 6,300 incident cases of colorectal cancer in women (Allen et al 2009). Other large cohort studies by Bongaerts et al (2008), Ferrari et al (2007) and Wei et al (2004) identified 2,323, 1,833 and 1478 colorectal cancer cases respectively. A third of the cohort studies identified less than 500 incident cases. The smallest cohort study, recruited only 59 colorectal cancer cases from a cohort of middle-aged Finnish men (Toriola et al 2009). The largest case control study identified approximately 1800 cases and controls (Ji et al 2002). Two of the seven case control

studies, identified in the present review, recruited less than 250 cases and controls to their study population (Kim et al 2002, Hong et al 2005).

2.5.2 Study quality

The quality scores assessed according to the NOS are presented in Table 2.5.2. Overall cohort studies were of a high quality, scoring between 8-9 stars. Case control study quality was of a moderate to high quality scoring between 5-8 stars.

Table 2.5.2 Colorectal cancer: assessment of study quality

	Selection* (out of 4)	Comparability* (out of 2)	Outcome/Exposure[1]* (out of 3)	Total
Cohort				
Akhter 2007	4	2	3	9
Allen 2009	4	2	3	9
Bongaerts 2008	4	2	3	9
Chen 2005	3	2	3	8
Ferrari 2007	4	2	3	9
Flood 2002	4	2	2	8
Otani 2003	4	2	3	9
Pedersen 2003	4	2	3	9
Shimizu 2003	4	2	2	8
Su 2004	4	2	3	9
Thygesen 2008	3	2	2	7
Toriola 2008	4	2	3	9
Tsong 2007	4	2	3	9
Wei 2004	4	2	1	7
Ye 2003	4	0	3	7
Case control				
Ho 2004	3	2	1	6
Hong 2005	2	2	2	6
Ji 2002	2	2	3	7
Kim 2004	2	2	1	5
Murata 1999	2	2	2	6
Murtaugh 2004	3	2	3	8
Sharpe 2002	3	2	2	7

* High quality characteristics within each of these items were awarded a star, up to a maximum of four stars for selection, two stars for comparability and three stars for assessment; [1] Outcome for cohort, exposure for case-control studies

Only three of the cohort studies did not achieve maximum ratings in each of the criteria on the NOS. Flood et al (2002) only achieved two out of three stars for outcome measurement because identification of colorectal cancer cases in their study was based on self-reports. Eighty per cent of self-reported cases were, however, subsequently verified by pathology reports and on this basis the authors accepted the remaining 20% self-reports, without pathology confirmation, as colorectal cancer cases. Thygesen et al (2008) did not achieve four stars in sample selection, as the study population was selected from a sub-group of the general population i.e. health professionals and only two stars for outcome measurement because they did not provide information on completeness of follow-up in their study cohort. Ye et al (2003) did not control for any of the established confounding risk factors

of the alcohol and colorectal cancer association as this information was not available in their hospital based record linkage cohort study.

For sample selection in case control studies, the majority of studies secured two stars out of four because either they used cases and controls from a hospital or clinical setting, or failed to confirm that cases of colorectal cancer were not present in their study controls. In general, case control studies performed poorly in exposure assessment. The extent of interviewer bias was not clear as the majority of case control studies did not specify blinding status. Among the hospital based case control studies, two reported high response rates (>90%) among cases and controls with two studies not reporting response rates in their paper (Murata et al 1999, Kim et al 2004). Of the population case control studies, response rates varied from over 90% (Ji et al 2002) to 73% and 69% amongst cases and controls respectively (Murtaugh et al 2004).

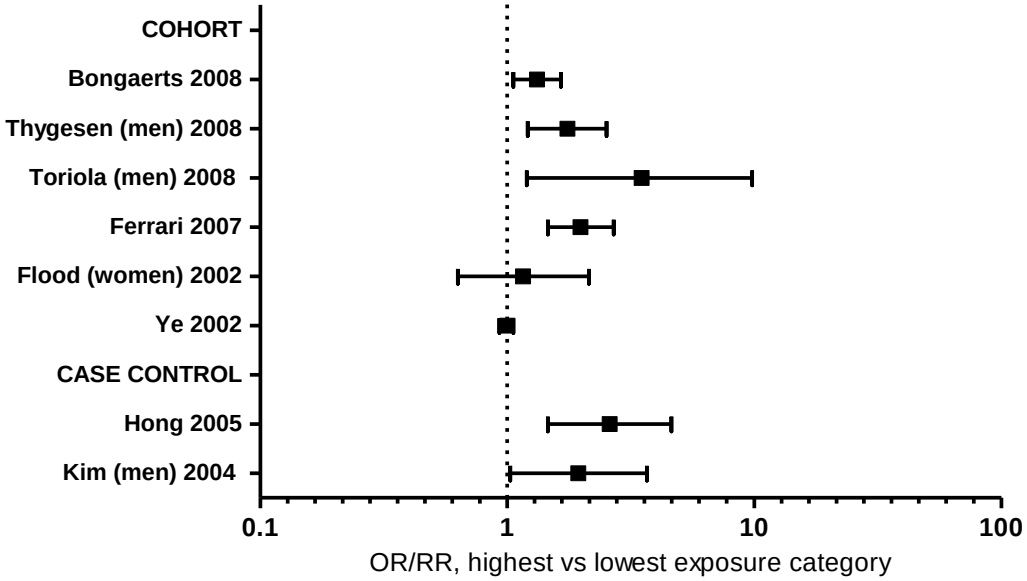
In the 'comparability' category, one star was awarded if a study controlled for age and one star awarded if a study controlled for either one of the following; weight, smoking, diet and or nutritional status and physical activity. All prospective cohort and case control studies achieved a maximum of two stars, but the studies ranged from adjusting for only two to all of the afore-mentioned potential confounders of the alcohol and colorectal cancer association. Weight (measured by BMI) was the most often used measure across studies and smoking terms included amount and duration smoked. Diet and or nutritional terms used in studies varied considerably; energy from non-alcohol sources (Ferrari et al 2007), folate, methionine, processed meat and calcium intake (Pedersen et al 2003, Thygesen et al 2008), fruit and vegetable intake (Akhter et al 2007), total energy intake, intakes of fat, dietary fibre and calcium (Bongaerts et al 2008).

2.5.3 Results: total alcohol intake and risk of colorectal cancer[9]

Eight studies reported on the dose response association between alcohol consumption and colorectal cancer. Of these, five studies reported on the association between colorectal cancer and 'recent' alcohol consumption; defined as intake in the previous year (Flood et al 2002, Ferrari et al 2007, Bongaerts et al 2008, Thygesen et al 2008, Toriola et al 2008). One study reported on the association between colorectal cancer with lifetime alcohol intake (Kim et al 2004). Hong et al (2005) did not specify a reference period. In the remaining study Ye et al (2002) did not collect alcohol consumption data. A summary of colorectal cancer risk estimates, comparing the highest versus the lowest alcohol exposure category, is presented in Figure 2.5.1.

[9] Multivariate relative risks/odds ratios are presented unless otherwise stated

Figure 2.5.1 Alcohol consumption and colorectal cancer, highest versus lowest exposure category, by study type (relative risk/odds ratio and 95% confidence intervals)



In general, individual cohort and cases control studies also consistently reported a statistically significant increased risk of colorectal cancer at the highest alcohol exposure category, compared to the lowest (Figure 2.5.1.) In a large Dutch cohort, drinking >30 grams per day [g/d], increased the risk (RR 1.32, 95% CI 1.06-1.65) of colorectal cancer, compared to abstainers (Bongaerts et al 2008). In the same study, drinking <30 g/d was, however, not associated with an increased risk of colorectal cancer. In a large multi-centre European cohort (Ferrari et al 2007), no association with colorectal cancer was reported for those drinking <30 g/d (e.g. 15-29g/d; OR 1.03, 95% CI 0.88-1.20), compared to those drinking <5 g/d. In contrast the risk of colorectal cancer increased by 26% (95% CI 6%-49%) and 64% (95% CI 29%-108%) in those drinking 30-59.9 g/d and >60 g/d, respectively. There was strong evidence of a statistically significant dose response association (*p value for trend* =0.001). Non-drinkers were not increased risk of colorectal cancer (RR 0.98, 95% CI 0.72-1.22). A similar pattern was observed for the association between average lifetime intake and risk of colorectal cancer (Bongaerts et al 2008). Thygesen et al (2008) reported that baseline, updated and cumulative average alcohol intakes were positively associated with colorectal cancer, with only minor differences among the approaches (baseline intake >45g/d; RR 1.75, 95% CI 1.21–2.52, *p value for trend* =0.0006). Point estimates for baseline and cumulative alcohol intake indicate a threshold effect, with a statistically significant increased risk only for alcohol intake of >30 g/d. The hazard ratio for baseline alcohol intake was 1.07 (95% CI 1.02-1.11) per 10 g/d increase (Thygesen et al 2008). Flood et al (20020 observed a non-significant increase in risk among women who drank >2 drinks per day (RR 1.16), compared to non-drinkers. With only 11 cases in the top category of consumption, the confidence intervals were wide (95% CI 0.63-1.24) and the test for tend was not significant (*p*=0.84)

In a small Finnish cohort study, Toriola et al (2008) reported a 3.5-fold (95% CI 1.2-9.9 *P* value 0.02) increased risk among people who drank >115 grams per week [g/w] compared with the lowest quintile (<3.3 g/w) of alcohol consumption. Although men drinking ≤115 g/w also showed a two-fold increase in risk, none of the estimates were of statistical significance and confidence intervals were wide. Similar patterns of a statistically significant increased risk of colorectal cancer at the highest alcohol exposure category only, were reported in two hospital based case control studies; >30 g/d compared to <5 g/d (Kim et al 2004) and >80 g/w, compared to ≤ 80 g/w (Hong et al 2005). Ye et al (2002), in a study based on record linkage to inpatient registers in Sweden, reported that the incidence rate (SIR 1.00, 95% CI 0.93-1.06) of colorectal cancer cases in a cohort of people admitted to hospital with a diagnosis of 'alcoholism,' was comparable to that found in the general population in Sweden.

2.5.3.1 Results: total alcohol intake and risk of colon and rectal cancer

Fourteen studies reported on the dose response association between alcohol consumption and colon and rectal cancer. Of these three studies reported on the association between colon and/or rectal cancer with lifetime alcohol intake; Murtagh et al (2004) defined lifetime intake as average weekly alcohol consumption 10 and 20 years ago; Ji et al (2002) defined lifetime drinkers as those with at least one drink per week for 6 months and Kim et al (2004) did not specify did not specify a measure for their 'lifetime' drinkers. Three studies did not specify a reference period (Murata et al 1999, Akhter et al 2007, Tsong et al 2007). The remaining studies reported on the association between colon and/or rectal cancer and 'recent' alcohol consumption defined as intake in the previous year with the exception of the study by Ho et al (2004) who reported 'drinking habits immediately prior to diagnosis.A summary of colon and rectal cancer estimates, comparing the highest versus the lowest alcohol exposure category, are presented in Figure 2.5.2 and Figure 2.5.3, respectively.

Overall, individual prospective cohort studies were also consistent in reporting an increased risk of colon and rectal cancer in the highest alcohol exposure category. In three cohort studies, however, an increased risk of colon or rectal cancer was only reported in those drinking >30g/d, compared to non-drinkers (Akhter et al 2007, Bongaerts et al 2008) or those drinking between 0.1-<5 g/d (Ferrari et al 2007). Ferrari et al (2007) also reported that an

Figure 2.5.2 Alcohol consumption and colon cancer, highest versus lowest exposure category by study type (relative risk and 95% confidence intervals)

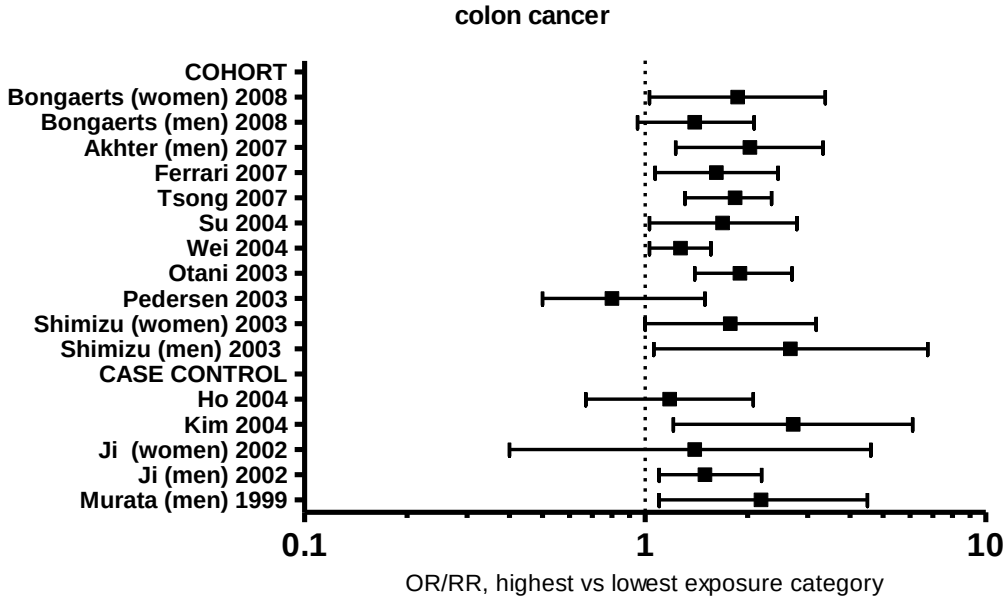
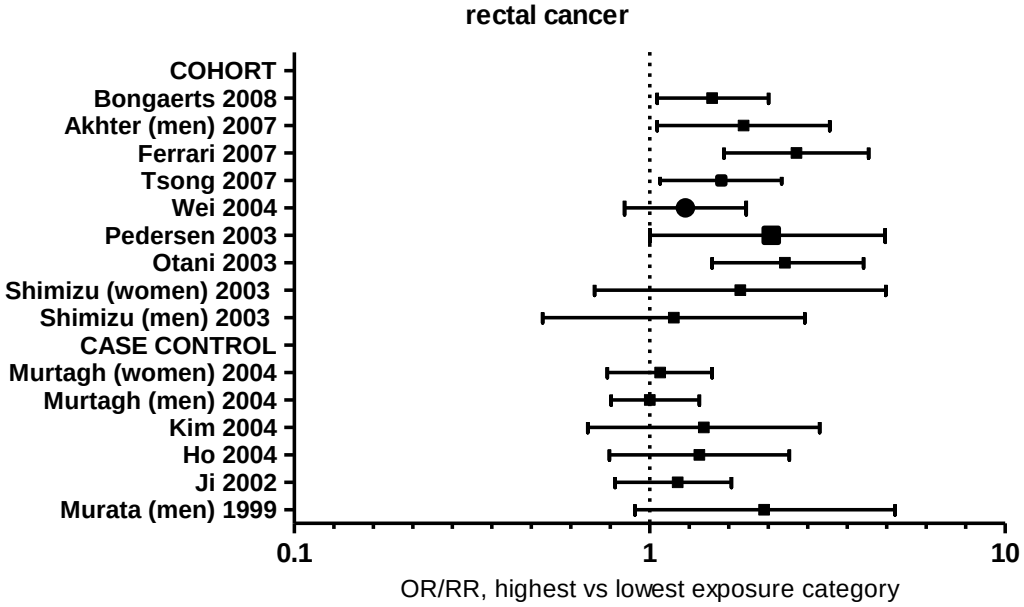


Figure 2.5.3 Alcohol consumption and rectal cancer, highest versus lowest exposure category by study type (relative risk and 95% confidence intervals)



increment of 10 grams of alcohol per day significantly increased the risk of both colon (RR 1.07, 95% CI 1.02-1.12, *P* value =0.004), and rectal (RR 1.11, 95% CI 1.05-1.17, *P* value <0.001) cancer. Allen et al (2009), in a large UK prospective cohort study with over 6,000 incident cases of colon cancer and 2000 cases of rectal cancer, reported that women drinking >15 drinks (approximately 150 grams) per week [d/w] did not have an increased risk (RR 1.00, 95% FCI 0.87-1.15, *p value for trend* =0.8) of colon cancer, compared to women drinking <2 d/w. Non-drinkers, in the same study, were also not

at an increased risk of colon cancer (RR 1.00, 95% CI 0.94-1.07). In contrast, there was a statistically significant increased risk of rectal cancer in women drinking >15 d/w (RR 1.25, 95% FCI 1.06-1.49, *p value for trend* =0.02), though drinking <15 d/w was not associated with an increased risk of rectal cancer (Allen et al 2009).

Ji et al (2002) observed an increased risk of colon cancer only in men drinking ≥560 g/w, (OR 1.5, 95% CI 1.1-2.2, *p value for trend* =0.16) and in women drinking ≥262.5 g/w (OR 1.4, 95% CI 0.4-4.6, *p value for trend* =0.60). Murtaugh et al (2004) found little evidence that alcohol consumption significantly increased risk of rectal cancer in men (>114 g/w; OR 1.0, 95% CI 0.78-1.38) and women (>114 g/w; OR 1.07, 95% CI 0.76-1.50). Four hospital based case control studies observed statistically significant associations between an increased risk of colon cancer, and positive associations for an increased risk of rectal cancer, at the highest alcohol intake level (Ho et al 2004, ≥40 g/w compared to <40 g/w; Kim et al 2004, >30 g/d compared to <3.5 g/d; Murata et al 1999, 56ml[10] of alcohol per day compared to non-drinkers).

2.5.3.2 Results: total alcohol intake and risk of colon cancer by tumour site

Four studies, three cohort and one case control, analysed the effect of alcohol intake on increased risk of distal and proximal colon cancer. In all four studies, alcohol consumption was more closely associated with an increased risk of distal colon cancer. Of the three cohort studies, Ferrari et al (2007) observed that for both measures of average lifetime drinking and baseline drinking, heavy drinkers only (>60 g/d; baseline *p value for trend* =0.018, average lifetime *p value for trend* =0.025) had a statistically significant increased risk of distal, but not proximal colon cancer (baseline *p value for trend* =0.442; average lifetime *p value for trend*=0.708). Bongaerts et al (2008) reported that daily alcohol consumption of >30 g/d, compared to abstainers, was associated with an increased risk of distal (RR 1.32, 95% CI 0.95-1.83), but not proximal (RR 1.05, 95% CI 0.75-1.46) colon cancer. In a Japanese cohort, Akhter et al (2007) reported that the volume of alcohol drunk per day among current drinkers only showed a strong dose-dependent significant linear association for distal (*p value for trend*= 0.0002) colon cancer and not proximal (*p value for trend* =0.04) colon current alcohol drinkers though only 'moderate' (22.8-45.5 g/d) and 'heavy' drinkers (≥45.6 g/d) had a statistically significant increased risk of distal colon cancer.

2.5.4 Results: drinking dimensions and risk of colorectal cancer

Four studies reported on other aspects of drinking behaviour and the association with colorectal cancer. Chen et al (2005), in a Chinese prospective cohort study, reported no significant association

[10] one gram = approximately 1.25 milliliters (ml)

between alcohol consumption and the risk of colorectal in men taking alcohol occasionally (RR 0.99 95% CI 0.61-1.63) and daily (RR 1.03 95% CI 0.65–1.64). Among daily female drinkers, the risk of colon cancer increased 2.7-fold compared to non-drinking females (RR ¼ 2.70, 95% CI, 0.80–9.14), but this association was no significant. In a Canadian case control study, 'daily' drinkers and 'weekly' drinkers were at higher risk of distal and rectal cancer, compared to those who did not drink weekly, but there was no increase in the risk of proximal cancer (Sharpe et al 2002). Among 'daily drinkers', however, only those drinking >5 drinks per day [d/d] had a statistically significant increased risk of distal (OR 3.0, 95% CI 1.6-5.6) and rectal (OR 2.0, 95% CI 1.1-3.6) cancer. 'Daily' drinkers drinking >5 d/d were also at an increased risk of proximal colon cancer (OR 1.6, 95% CI 0.9-2.9).

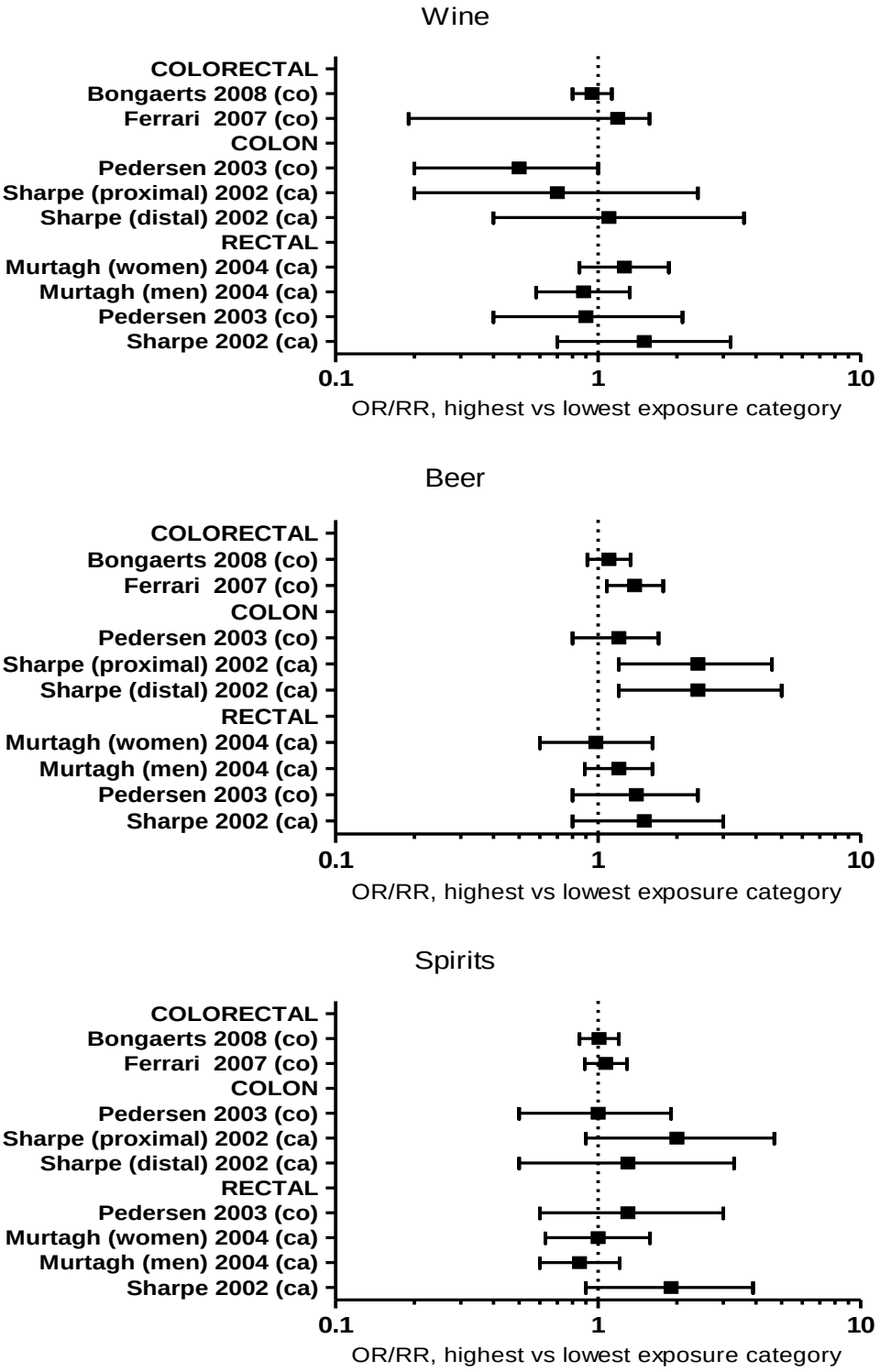
Two case control studies reported conflicting results on the association between duration of drinking habit and risk of colorectal cancer. Ho et al (2004) reported that among current drinkers, drinking duration was not associated with an increased risk of colorectal cancer (>39 years; OR 0.75 95% CI (0.38–1.49 *p value for trend* =0.52, compared to <20 years). On the other hand, Ji et al (2002) observed that among current drinkers, increased risks of colon and rectal were associated with long-term alcohol consumption. The ORs for colon cancer among men were 1.3 (95% CI 0.9-1.8) and 1.4 (95% CI 0.9-2.2) for current drinkers of 30-44 years and ≥45 years, respectively, compared to non-drinkers *(p value for trend* =0.10). Similar patterns were reported for the association between drinking duration and rectal cancer (*p value for trend* =0.10).

2.5.5 Results: drink type and risk of colorectal cancer

Five studies examined whether risk of colorectal cancer (including separate studies on colon and rectal cancer) varied by type of alcoholic beverage. A summary of risk estimates, comparing the highest versus the lowest alcohol exposure category, is presented in Figure 2.5.4.

In a large European cohort study, moderately higher colon cancer hazard ratios were observed for baseline beer intake (>40 g/d; 1.62, 95% CI 1.21-2.17 vs. 0.1-2.9 g/d), than wine (>40 g/d, 1.19, 95% CI 0.90-1.57 vs. 0.1-2.9 g/d) or spirits (>5 g/d 1.07 95% CI 0.89-1.29 vs. 0.1-1.9 g/day) (Ferrari et al 2007). The authors reported that these associations were not significantly different by cancer subtypes or alcoholic beverages, but results were not reported in the paper. In a Danish cohort study, Pedersen et al (2003) reported that beer and spirits were associated with a non-significant increased risk of colon and rectal cancer at the highest alcohol exposure category. Drinking wine on the other hand, was associated with a decreased risk of colon (>14 d/w; RR 0.5, 95% CI 0.2-1.0, *p value for trend* =0.07) and rectal cancer (>14 d/w; RR 0.9, 95% CI 0.4-2.1, *p value for trend*= 0.87). Bongaerts et al (2008), in a large Dutch cohort study, reported that wine, beer and spirit drinkers, compared to non-drinkers, did not have an increased risk of colorectal cancer overall and by sub-site (colon, including proximal and distal, and rectal cancer),

Figure 2.5.4 Alcohol consumption and risk of colorectal cancer, highest versus lowest exposure category, by drink type (relative risk and 95% confidence intervals (co=cohort, ca=case-control)



Of the case control studies, Murtaugh et al (2004) reported that the risk of rectal cancer increased non-significantly among men drinking >2.7 ‘servings’ of beer per week (OR 1.20, 95% CI 0.89-1.61), but not among men drinking red or white wine or spirits. Among women, the risk of rectal cancer increased non-significantly among those drinking >3.4 ‘servings of white wine per week (OR 1.26,

95% CI 0.85-1.86), but there was no association with red wine, beer or spirits. Sharpe et al (2002) reported that 'daily' drinkers of ≥5 'drinks' of beer or spirits per day, compared to non-weekly drinkers, had an increased risk of distal and proximal, and rectal cancer. Wine was not associated with increased risks at any sub-site.

2.5.6 Effect modification

Four studies assessed the joint effect on the alcohol and colorectal cancer association from one or more of the following risk factors for colorectal cancer; smoking, folate intake and weight (measured by Body Mass Index (BMI)).

Two studies assessed the joint effect of alcohol consumption and folate intake on colorectal cancer risk. Ferrari et al (2007), from the EPIC study, reported that the association between an increment of 15 grams of alcohol per day and an increased risk of colorectal cancer was stronger in individuals with 'low' folate intake (RR 1.13, 95% CI 1.06-1.20) than in those with 'high' folate intake (RR1.03, 95% CI 0.98-1.09 with a borderline significant interaction ($P_{interaction=}$0.06). No definition of low and high folate categories was provided in the paper. In a small American cohort study, Flood et al (2002) reported that for women who drank >1 d/d, with a low level of folate intake (<167 µg/1000 Kcal per day), did not have a significantly increased risk (OR 1.10 95% CI 0.67-1.80) of colorectal cancer compared to non-drinkers with a high folate intake (>232 µg/1000 Kcal per day of folate). In a similar analysis examining total folate, no combination of folate and alcohol consumption showed any significant increase in risk compared to the reference category. For both dietary and total folate, there was no greater risk among women in the low folate vs. high folate category, within the highest alcohol category.

All four studies assessed the joint effect of alcohol consumption and smoking on colorectal cancer risk. Ferrari et al (2007) reported that alcohol consumption was more strongly associated to colorectal cancer in current smokers (RR 1.23, 95% CI 1.12-1.36 for 15 g/d increase) than never smokers (RR 1.15, 95%CI 1.03-1.28) or former smokers (RR 1.11, 95% CI 0.97-1.28), but overall interaction was not statistically significant ($P_{interaction}$=0.41). Flood et al (2002) reported that the excess risk of colorectal cancers associated with alcohol was present only among non-smokers: the RR comparing women who drank >2d/d to non-drinkers was 1.78 95% CI 0.66-4.83. Among smokers (former and current) there was no association between alcohol consumption and colorectal cancer (>2d/d; RR=0.89 95% CI 0.41-1.93).

In a Japanese cohort study, colorectal cancer risk for drinkers of >300 g/w who smoked was estimated at RR 3.0 (95% CI, 1.8-5.1), compared with non-drinkers who never smoked (Otani et al 2003). Among those drinking >300 g/d and who had never smoked, the RR was 2.3 (0.7-7.1). The association did not differ between colon and rectum. Otani et al (2003) reported no significant

interaction between alcohol consumption and smoking status ($P_{interaction}$=0.88 in colorectal, and 0.75 in colon, and 0.44 in rectum). Tsong et al (2007) reported that the risk of colorectal cancer, at each level of cigarette smoking, increased with increasing alcohol intake. Similarly, at each level of alcohol intake, risk of rectal cancer increased with increasing level of smoking; compared with non-smokers and non-drinkers, heavy smokers who consumed seven or more drinks of alcoholic beverages per week had a HR of 2.03 (95% CI 1.03-3.97) for colorectal cancer. The interaction effects between alcohol and smoking on colorectal cancer risk ($P_{interaction}$=0.30), were not statistically significant.

2.5.7 Summary and conclusions

This literature review identified 22 studies and one meta-analysis, published between 1999 and 2009, which examined the association between alcohol consumption and risk of colorectal, colon or rectal cancer. Cohort studies were of a high quality and adjustment for most of the main confounders of the alcohol and colorectal cancer association took place in both cohort and case control studies. Overall, studies were consistent in only reporting a statistically significant increased risk of colorectal cancer associated with drinking ≥30 g/d. Drinking <30 g/d was not associated with an increased risk of colorectal cancer in many of the larger cohort and case controls studies though some smaller studies did observe a small, non-significant increased risk of colorectal cancer. These patterns were repeated in studies of the association between alcohol consumption and both colon and rectal cancer. Residual confounding, however, from imprecise measures of diet (e.g. fibre, folate, and methionine) is likely in many of the studies though the effect of this on the reported alcohol-colorectal association is difficult to determine. It is possible that the effect of alcohol consumption on the risk of colorectal cancer is modified by other factors and by intake level. High doses of alcohol combined with a low methionine, low folate diet have been shown in some studies to increase the risk of colon cancer in men (Pedersen et al 2003), but not in women (Flood et al 2002). In contrast, alcohol in combination with a high intake of vitamin B_6 among women has been shown to decrease the risk of colorectal cancer (Larsson et al 2005). Increasingly, studies are suggesting removing the concern from simple alcohol consumption to the interaction of folate and vitamin use, and enzyme genetic polymorphisms (Chen et al 2005, Larsson et al 2005).

The finding of the present review of a possible threshold effect of alcohol consumption on colorectal cancer risk, where only those drinking ≥30 g/d had a statistically significant increased risk, is consistent with previous published findings. Earlier systematic reviews covering the published literature between 1966 and 1999, have reported a possible direct relationship between alcohol drinking and risk of colorectal cancer, but that the relationship is quantitatively moderate with most studies reporting less than a twofold increase in risk, even at high levels of drinking (IARC 1988, Doll et al 1999). A pooled analysis of 8 cohort studies reported that the increased risk for colorectal cancer

was limited to persons with an alcohol intake of ≥30 g/d; compared with non-drinkers, the pooled multivariate relative risks for 30 to <45 g/d 1.16 (95% CI 0.99-1.36) and 1.41 (95% CI 1.16-1.72), for those who consumed ≥45 g/d (Cho et al 2004). A recent systematic review recently concluded that there was 'convincing evidence' that drinking >30 g/d is a cause of colorectal cancer in men and 'probably' in women'. The evidence of an effect at lower levels of drinking on colorectal cancer risk is currently inconclusive (WCRF/AICR 2007). In a meta-analysis of prospective cohort studies published between 1990 and June 2005 by Moskal et al (2008), the highest alcohol intake level, compared to the lowest, was positively, but not significantly associated with colorectal cancer (RR 1.34, 95% CI 0.92, 1.96). The results were heterogeneous across cohorts (p test for Heterogeneity (p Het) =0.002). High alcohol intake was significantly associated with colorectal cancer in men (RR 1.73, 95% CI 1.00-2.98, p Het=0.02), but not in women (RR 0.88, 95% CI 0.61-1.27, p Het=0.44). The paper did not define the amount drank at the highest level, however, in further dose response analysis, Moskal et al (2008) did observe a 21% increase, (95% CI 2%-43%) increase of colorectal cancer associated with an increment of 100g of alcohol per week, but not for women (RR 1.05, 95% CI 0.92-1.20). In the Moskal meta-analysis, results were combined from studies that varied in study populations, methods of assessment of alcohol intake, levels and type of alcohol consumed and adjustment for potential confounders varied across studies.

The evidence, from the present review, on the association between drink type and an increased risk of colorectal cancer, was inconclusive. Only five studies were identified that reported on this aspect of the alcohol and colorectal cancer association. Beer and spirits were consistently associated with an increased risk of colorectal cancer, whilst the evidence for wine included both inverse and positive associations with colorectal cancer. Many of the studies, however, had small numbers of drinkers of specific alcohol drink types and risk estimates lacked precision and prevented formal significance testing of interactions between wine, beer and spirits. The positive associations between beer and spirits and an increased risk of colorectal cancer correlated with these drink types being the most commonly consumed beverage in the studies' population, conversely the majority of inverse associations reported for wine drinking were reported by studies where wine was the least preferred beverage type. There has been, little consensus in the literature that there is an appreciable and consistent difference in risk of colorectal cancer among different types of alcoholic beverage (Doll et al 1999). In a pooled analysis of eight cohort studies (Cho et al 2004), beer or wine was significantly associated with an increased risk of colorectal cancer and spirits with a non-significant positive association of colorectal cancer, but the risk did not differ significantly by type of alcohol drink (for intake of ≥30 g/d, *P* Het >0.2).

It has been hypothesised that because of differences between men and women in alcohol metabolism and gut physiology, the risk of colorectal cancer from alcohol drinking may vary by gender, as a result of slower metabolism of alcohol in women than in men (Gapstur et al 1994, Corrao et al 1999). Few

studies in the present review reported on the association between alcohol consumption and colorectal cancer by gender. A statistically significant increased risk of colorectal cancer in both men and women drinking ≥30 g/d was reported in a meta-analysis of sixteen cohort studies (Moskal et al 2008) with higher risk estimates reported for men. Although there is was some evidence, in the meta-analysis, that gender differences were close to statistical significance (*P* Het =0.07), the authors reported that the relationship was 'attenuated' after the inclusion of alcohol level intake in their statistical model. Previous pooled and meta-analysis studies have not found a gender variation in risk of colorectal cancer. Bagnardi et al (2001) in a meta-analysis of 6 cohort studies and 16 case control studies, reported no significant effect of gender on modifying the effect of alcohol on the risk of colorectal cancer. Cho et al (2004) also found no significant heterogeneity by gender: for alcohol consumption of >45g, (*P* Het >0.2).

There was little evidence in the present review to suggest that the risk of colorectal cancer varied by tumour site. Previous meta- and pooled analyses have found no evidence of a significant difference in heterogeneity in estimates of the risk of colon and rectal cancer from alcohol consumption (Corrao et al 1999, Cho et al 2004, Wei et al 2004). To date, experimental research has not distinguished between colon and rectal cancer as most research has been performed on human colon cancer cells and can therefore offer no explanation as to potential differences, if any, in risk by sub-site (Pedersen et al 2002). A small number of studies from Europe and Asia in the present review did, however, report a consistently higher, and statistically significant, increased risk of distal colon, but not for proximal colon cancer from alcohol consumption. A recent review concluded that accumulating evidence suggests that the risk of colon cancer conferred by various environmental and genetic factors is different for proximal and distal tumours (Iacopetta 2002). The mechanisms for this relationship, however, are unclear. Administration of alcohol to experimental animals has been reported to influence carcinogenesis in the colon in different fashions depending on dose; lower doses have no effect on the proximal colon, but enhance carcinogenesis in the distal colon, while higher doses inhibit carcinogenesis in the proximal colon and have little effect on the distal colon (Seitz et al 1992). Evidence from this review, however, suggests that an increased risk of colorectal cancer and by tumour type (distal colon and rectal) from alcohol consumption was only apparent at higher doses of alcohol (≥30 g/d). The small number of studies reporting on the association between colon cancer and alcohol consumption by tumour type and the imprecision of risk estimates due to small sample sizes in many of the studies prevents any firm conclusions concerning the effect of alcohol on distal and proximal colon cancer. The existence of two broadly different groups of cancer, defined by site of origin in the colon (i.e. distal and proximal), should therefore be considered in the design of future epidemiologic studies on the association between alcohol consumption and colorectal cancer.

In summary, there is strong evidence of a threshold effect of alcohol consumption on colorectal cancer risk whereby approximately ≥30 g/d significantly increases the risk of colorectal cancer. The

positive association between total alcohol and colorectal cancer would appear to be attributable to ethanol itself rather than a specific beverage. There is little evidence to suggest a modifying effect of gender or by tumour type (colon and rectal) on the association between alcohol consumption and colorectal cancer risk. The association between alcohol consumption and distal colon cancer is worthy of further investigation. Future studies on the alcohol and colorectal cancer association should include well designed food frequency questionnaires to enable more accurate measurement of diet and nutritional status.

2.6 Endometrial cancer

Endometrial cancer: summary of evidence from previous reviews
Earlier systematic reviews covering the published literature between 1966 and 2001 concluded that studies did not offer much support for a positive association between alcohol intake and endometrial cancer, with results generally indicating no association or suggesting an inverse relationship with endometrial cancer (IARC 1988, Bandera et al 2003).

The literature search found nine studies, published between 1 January 1999 and 30 September 2009, which examined the relationship between alcohol consumption and endometrial cancer. There were six cohort studies (five prospective and one retrospective) and three case control studies. Tables for each paper, describing the study aims, population, alcohol measurement methods and main results are provided in Appendix D.

2.6.1 Study characteristics

A summary of the general characteristics of the studies is provided in Table 2.6.1 below.

Table 2.6.1 Alcohol and endometrial cancer: general characteristics of studies reviewed

Authors	**Year**	**Country**	**Outcome/No outcome Case/Control**	**Age range (M/Mdn))**	**Sample base**	**Sample selection**
Cohort studies						
Friberg	2009	Sweden	687/60,539	40-76	regional population	n/s
Jain	2000	Canada	221/5681	40-59	randomised controlled trial	volunteers
Loerbroks	2007	Netherlands	280/1,619	55-69	general population	random sample
Setiawan	2008	USA	324/41,250	45-75	state driver's license lists	n/s
Terry	1999	Sweden	133/11,526	>18	population register	census
Weiderpass	2001	Sweden	69/36,787	>18 (M=43)	national database of hospital patients	non-random selection
Case control studies			***cases/controls***			
Hosono	2008	Japan	148/11,814	23-80, (Mdn=56)	city cancer hospital	consecutive/random selection
McCann	2000	USA	523/865	(M=63/6 0)	state cancer registry/driver's license lists	consecutive/random sample
Weiderpass and Baron	2001	Sweden	1055/4216	50-74, (M=65/6 4)	regional cancer/population registries	consecutive/random selection

Abb: n/s not specified; M=mean; Mdn= median

Two papers were based on established prospective cohort studies described in box 2 section 2.4; the Netherlands Cohort Study on diet and cancer (Loerbroks et al 2007) and the Swedish Mammography Cohort (Friberg et al 2007). In the remaining cohort studies, Terry et al (1999) recruited their cohort from the Swedish Twin Registry and consisted of women from same-sexed twins born in Sweden over a forty year period around 1900. In a paper by Setiawan et al (2008), potential participants were identified through US state driver's license files, voter registration lists and Health Care Financing Administration data files and entered into the 'Multi Ethnic Cohort (MEC)' study. This cohort

consisted of over 200,000 men and women and comprised mainly five of self-reported racial/ethnic populations: African Americans, Japanese Americans, Latinos, Native Hawaiians and Whites. Eligible post-menopausal women (n= 41,574; 15.7% African Americans, 31.5% Japanese Americans, 21.5% Latinas, 6.7% Native Hawaiians, and 24.5% Whites) from the MEC study were then followed up for an average of 8.3 years. Post-menopausal status was not defined in the paper though the mean age of the post-menopausal cohort was approximately 60 years. Jain et al (2000) conducted their study as a case-cohort study within a cohort of approximately 57,000 women: the Canadian National Breast Screening Study, a randomized controlled trial primarily designed to assess mammographic screening for breast cancer in volunteer women aged 40-59 years. The sub-cohort was constructed by selecting a stratified (by recruitment centre) random sample of 5,681 women. In a record linkage cohort study, women who were hospitalised in any Swedish hospital, between 1965 and 1994 with a diagnosis of 'alcoholism' were identified and retrospectively followed up for an average of 10 years (Weiderpass et al 2001).

2.6.2 Study quality

The quality scores assessed, according to the NOS, are presented in Table 2.6.2. Overall, cohort and case control studies were of a moderate to high quality, scoring between 6-7 stars.

Table 2.6.2 Endometrial cancer: assessment of study quality

	Selection* (out of 4)	**Comparability* (out of 2)**	**Outcome/Exposure[1]* (out of 3)**	**Total**
Cohort				
Friberg 2009	3	2	2	7
Jain 2000	2	2	3	7
Loerbroks 2007	4	2	3	9
Setiawan 2008	4	2	3	9
Terry 1999	2	2	3	7
Weiderpass 2001	2	2	3	7
Case Control				
Hosono 2008	2	2	3	7
McCann 2000	3	2	2	7
Weiderpass 2001	3	0	2	5

* High quality characteristics within each of these items were awarded a star, up to a maximum of four stars for selection, two stars for comparability and three stars for assessment; [1] Outcome for cohort, exposure for case-control studies

The prospective cohort studies were generally of a high quality. The nearly complete end-point ascertainment across all cohort studies reduced the potential for bias from differential follow-up. The weakest area was in sample selection where only two studies by obtained a maximum rating (Loerbroks et al 2007, Setiawan et al 2008). Terry et al (1999), Jain et al (200) and Friberg et al (2009) failed to specify if endometrial cancer was absent from their study participants at baseline entry. In a cohort of people admitted to Swedish hospitals with 'alcoholism', it was not clear from the paper how 'alcoholic' patients were identified (Weiderpass et al 2001). Measurement error was an issue in one paper (Terry et al 1999) where over a long follow up period of approximately 20 years,

information on alcohol consumption was only collected at baseline. This may have lead to misclassification error since drinking habits, as well other lifestyle factors associated with endometrial cancer risk among the study population, will have changed over that period. What effect this would have on the point estimates is unclear though if we assume that drinking decreases with age, then risk estimates will be biased towards null.

For the case controls studies, non-response bias was a significant problem. Response rates for cases and controls were below 80% in the study by Weiderpass and Baron (2001) and only reached 50% for both cases and controls in a US population control study (McCann et al 2000). In both the afore-mentioned studies, physician and participant's refusal to take part in the study accounted for the majority of non-responders. Furthermore, in the study by McCann et al (2000), information on alcohol consumption was based in the first instance on usual intake over a 2 year period then for periods, 10 years, and 20 years before the interview and at age 16, increasing the potential for misclassification of alcohol drinking data as a result of recall bias.

The known risk factors for the endometrial cancer, which include oestrogen replacement therapy, obesity in middle age, diabetes mellitus and low parity, were controlled for in eight of the nine studies. In the record linkage cohort study by Weiderpass et al (2001), no adjustment for these risk factors took place since no lifestyle information was collected. The possibility of residual confounding may therefore account for the weak statistically significant inverse association observed in this study.

2.6.3 Results: total alcohol intake and endometrial cancer[11]

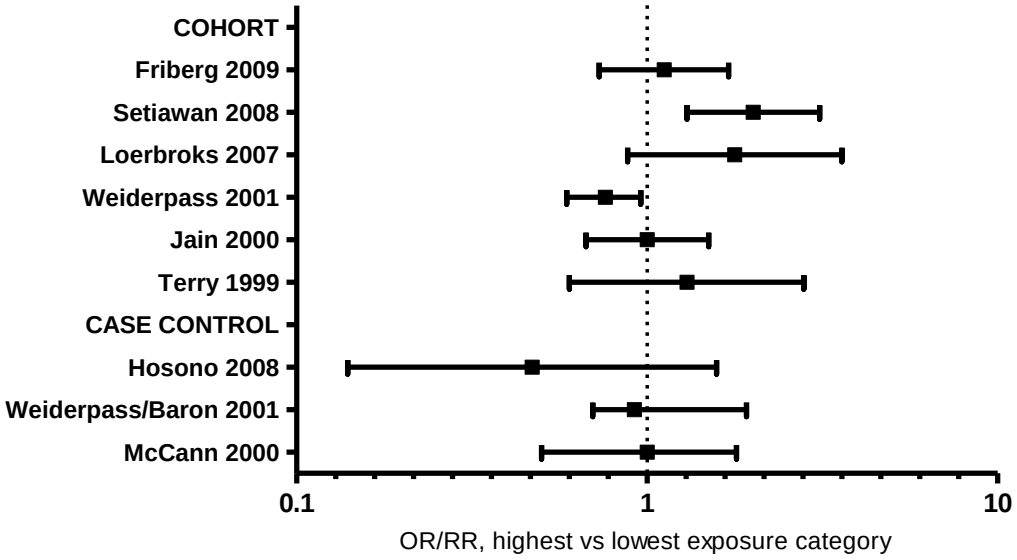
Seven of the eight studies reported on the association between endometrial cancer and 'recent' alcohol consumption; defined as intake in the previous year in four studies (Loerbroks et al 2007, Hosono et al 2008, Setiawan et al 2008, Weiderpass and Baron 2001), by McCann et al (2001) as usual consumption in the previous two years, with the remaining three studies not specifying a reference period. A summary of endometrial cancer risk estimates, comparing the highest versus the lowest alcohol exposure category is presented in Figure 2.6.1.

Setiawan et al (2008) reported a statistically significant increased risk (RR 2.01, 95% CI 1.30-3.11) of endometrial cancer in women drinking more than >24 grams per day [g/d], compared to non-drinkers. Women drinking <24 g/d did not have an increased risk of endometrial cancer and little evidence of a dose response relationship (*p value for trend* =0.19). Similar findings were reported by Loerbroks et al (2007) with a statistically non-significant, increased risk (RR 1.78, 95% CI 0.88-3.60) of endometrial cancer for women drinking >30 g/d, compared those drinking less than once a month. There was no

[11] Multivariate relative risks/odds ratios are presented unless otherwise stated

association with endometrial cancer below 30 g/d and no evidence of a dose response association (*p value for trend* =0.62).

Figure 2.6.1 Alcohol consumption and endometrial cancer: highest versus lowest exposure category, by study type (odds ratio/relative risk and 95% confidence intervals)



Friberg et al (2009) observed a small (12%), statistically non-significant, increased risk of endometrial cancer only in women drinking ≥10 g/d. There was no evidence of a dose response relationship and no significance test for trend was reported in the paper. Terry et al (1999) reported similar risk estimates for women drinking in the highest alcohol category (>7 g/d), but very few women (n=40) drank in this study and confidence intervals were large. Jain et al (2000) did not find an increased risk of endometrial cancer in women drinking across all quartiles (not defined in the paper) of alcohol consumption compared to non-drinkers. In the remaining cohort study, Weiderpass et al (2001) observed a statistically significant, lower risk of endometrial cancer in people admitted to hospitals in Sweden with a diagnosis of 'alcoholism', compared to that in the Swedish general population.

Two population based case control studies did not find an association between alcohol consumption and endometrial cancer at all intake levels, up to and including >4 g/d (Weiderpass & Baron 2001) and >9 grams per month (McCann et al 2000) compared to non-drinkers and those drinking less than monthly, respectively. In a hospital based case control study (Hosono et al 2008), consumption of >175 grams per week (approximately 2 'standard' drinks per day), compared to non-drinkers, was associated with a 50% reduced risk of endometrial cancer with convincing evidence of an increased protective effect with amount drunk (*p value for trend* =0.009)

2.6.4 Results: drinking dimensions and risk of endometrial cancer

Drinking frequency, and in particular daily drinking (5 times a week; OR 0.37, 0.17-0.82), was associated with an inverse association with endometrial cancer in a Japanese case control study (Hosono et al 2008), with strong evidence of a statistically significant dose response relationship (*p value for trend* =0.009). Weiderpass et al (2001), observed no substantial difference in endometrial cancer risk in their cohort of 'alcoholic' patients, according to duration of follow-up, calendar year at cohort enrolment or presence or absence of a hospital discharge diagnosis of obesity or liver cirrhosis compared to that expected in the general population in Sweden.

2.6.5 Results: drink type and risk of endometrial cancer

Two studies reported on the association between drink type and endometrial cancer (Table 2.6.3). No statistically significant association was observed for wine and current drinkers of beer and spirits in a Dutch cohort study- highest alcohol exposure category of >15 g/d (Loerbroks et al 2001). Similar finding were reported in a Swedish population based case control study for current drinks of wine, fortified wine, light and strong beer, and spirits (Weiderpass & Baron 2001).

Table 2.6.3 Alcohol intake and risk of endometrial cancer by drink type

Study	Ref. Group	Beer		Wine		Spirits	
Loerbroks	<1 per month	Yes	1.30 (0.82-2.07)	0.1–4g/d 5–14 ≥15	1.16 (0.84-1.59) 1.07 (0.68-1.67) 1.11 (0.64-1.93)	Yes	1.11 (0.73-1.68)
Weiderpass and Baron	non drinkers	Light beer Strong beer	0.94 (0.76-1.17) 0.80 (0.49-1.28)	Wine Fortified	0.96 (0.79-1.18) 1.10 (0.86-1.41)	Yes	1.06 (0.84-1.34)

2.6.6 Results: effect modification

No studies were identified.

2.6.7 Summary and conclusions

The present review identified nine papers, published between 1999 and 2009, which examined the association between alcohol consumption and endometrial cancer. Overall, the evidence provided by the majority of studies was not supportive of an association between alcohol consumption and endometrial cancer. Certain methodological limitations, such as small sample size, limited range of alcohol intake, and confounding may explain this finding. Bandera et al (2003), in a review of two cohort and thirteen case control studies published before 2001, also concluded that studies did not offer much support for a positive association between alcohol intake and endometrial cancer, with results generally indicating no association or suggesting an inverse relationship with endometrial cancer.

An effect of alcohol consumption on the risk of endometrial cancer, cannot, however, be ruled out. Many studies included in the present review, and that carried out by Bandera et al (2003), because of the limited range of alcohol intake in these studies, were effectively only measuring the association

between low level drinking (approximately ≤1 d/d) and endometrial cancer. It was, therefore, interesting to observe that in two prospective cohort studies in the present review (Loerbroks et al 2007, Setiawan et al 2008), both reported an approximate two-fold increased risk of endometrial cancer in women drinking ≥2 d/d (≥24 g/d). In both studies however, there was neither an association between endometrial cancer and women drinking <2 drinks per week or evidence of a dose response relationship. Two small case control studies identified in the Bandera et al (2003) review also reported an increased risk of endometrial cancer in women drinking ≥ 2 d/d. An effect of moderate alcohol consumption is biologically plausible. Alcohol has been shown to increase the levels of oestrogen, which in turn, have been shown to increase endometrial cancer risk by stimulating the proliferation of endometrial cells (Hill and Austin 1996, Purdie 2003). A recent study found significantly elevated blood oestrone levels in post-menopausal women who consumed >25 g/d, compared to non-drinkers (Rinaldi et al 2006).

Although a marked increase in oestrone concentrations, and ultimately in endometrial cancer risk, may be plausible in women who consume more than moderate amounts of alcohol, there are some unexplored aspects of the possible effect of moderate alcohol consumption on endometrial cancer risk such as the possible interaction with use of exogenous estrogens, that need clarification (Bandera et al 2003). Although many studies included in this review controlled for other known risk factors for endometrial cancer; weight, oral contraceptive use, cigarette smoking history and to a lesser degree hormone replacement therapy (HRT), residual confounding or an effect modification of these other risk factors cannot be ruled out. Even if alcohol is unrelated or weakly inversely related to endometrial cancer in all groups combined, it may be associated with increased risk in selected subgroups, such as women using HRT or those with low intake of folate.

Due to the small number of studies in this review, small sample sizes and inconsistent findings, the association of alcohol intake on the risk of endometrial cancer remains unclear. More studies are required that can report on the association between moderate and heavy alcohol consumption. Possible effect modification by menopausal status, weight, HRT, oral contraceptive use, and smoking status needs further evaluation. Moreover, information should be collected on frequency, quantity, and duration of use of wine, beer, and spirits, to ensure a better estimate of total alcohol intake as well as possible differences in risk by type of beverage.

2.7 Gastric (stomach) cancer

Gastric cancer: summary of evidence from previous reviews
Earlier systematic reviews concluded that in view of the overall lack of excess risk for stomach cancer in cohort studies, the inconsistent results of the case-control studies, and the inadequate control for dietary and socioeconomic factors, there was little in the aggregate data to suggest a causal role for alcohol consumption in stomach cancer (IARC 1988b, WCRF/AICR 1997). A meta-analysis of two cohort and fourteen case control studies, published between 1996 and 2000 (Bagnardi et al 2001), reported a positive (and statistically significant) association with gastric cancer; (25 g/d: RR 1.07, 95% CI 1.04-1.10; 50 g/d: RR 1.15, 95% CI 1.09-1.22; 100g/d: RR 1.32, 95% CI 1.18-1.49). Forman et al (2006), however, in a meta-analysis of five cohort and thirteen case control studies (published between 1980 and 2000) reported no significant linear increase in risk of gastric cancer with amount drunk; the RR from the cohort studies was 0.99 (95% CI 0.97-1.02) per 10 g/day and the PRR from the case-control studies was 1.02 (95% CI 1.00-1.04) per 10 g/day.

The literature search identified 21 studies, 10 cohort and 11 control studies, published between 1999 and 2009, which examined the association between alcohol consumption and the risk of gastric cancer. Tables for each paper, describing the study aims, population, alcohol measurement methods and main results are provided in Appendix D.

2.7.1 Study characteristics

A summary of the general characteristics of the studies is provided in Tables 2.7.1 (cohort studies) and Table 2.7.2 (case control studies). Two papers were based on established prospective cohort studies described in Box 2.1, Chapter 2.2; the Copenhagen City Heart Study (Barstad et al 2005) and the Swedish Mammography Cohort (Larsson et al 2006). The paper by Allen et al (2009) has been previously described in Chapter 2.3.1.

The largest cohort study included in the present review of the association between alcohol consumption and gastric cancer identified approximately 3500 cases of gastric cancer (Sung et al 2000). A further two cohort studies, identified approximately 800-1000 cases (Tran et al 2005, Allen et al 2009). The remaining cohort studies identified less than 400 incident cases of gastric cancer.

Table 2.7.1 Alcohol and gastric cancer: general characteristics of cohort studies

Authors	Year	Country	Outcome/No outcome	Age range (M/Mdn)	Sample base	Sample selection
Allen	2009	UK (women)	821/1,274,272	>55	breast screening clinics	random selection
Barstad	2005	Denmark	122/28,341	21-93	population of Copenhagen	random sample
Freedman	2007	USA	375/474,231	>50 (Mdn=62.5)	members of American Association of Retired Persons	volunteers
Huang	2000	Japan (women)	636/877	40-79	city cancer hospital,	n/s
Kasum	2002	USA (women)	56/34,294	55-69	state drivers licence list	representative random sample
Larsson	2006	Sweden (women)	160/61,273	40-76	regional population	volunteers
Sasazuki	2002	Japan (men)	293/19,364	40-59	general population	n/s
Sjödahl	2006	Norway	251/69,751	>20	regional population	volunteers
Sung	2007	Korea	3,452/666,182	M=44	govt. employees, teachers insured by National Health Insurance Program	representative sample
Tran	2005	China	1,152/28,432	40-69 (M=52)	regional population	volunteers

Of the larger case control studies, Lindblad et al (2005) conducted a case-control study nested in the General Practitioner Research Database (GPRD) which contains more than 35 million patient-years of British primary care data and contains prospectively recorded information routinely recorded by GPs during their standard medical care; cases were all patients on the database with a diagnosis code indicating gastric cancer and controls, free of cancer, were randomly selected from the same database. Wu et al (2001) used a US state cancer registry to select cases and controls were randomly sampled from the local population by use of a systematic algorithm based on the address on the case patient and Kikuchi et al (2002) selected cases from one of nine hospitals in the Tokyo Metropolitan Area and controls were recruited from several health check programs in a hospital in the same area. The majority of case control studies identified less than 500 gastric cancer cases.

Table 2.7.2 Alcohol and gastric cancer: general characteristics of case control studies

Authors	Year	Country	Cases/ Controls	Age range (M/Mdn)	Sample base	Sample selection
Benedetti	2009	Canada	215/570	35–75	city hospitals /electoral lists	consecutive/ random selection
Chow	1999	Poland	464/480	21-79	22 hospitals/city population	random selection/random sample
Kikuchi	2002	Japan,	718/883	20-69	1 hospital in Tokyo	consecutive/ non-random selection
Lagergren	2000	Sweden	262/820	<80	All hospitals/general population	consecutive/ random selection
Lindblad	2005	United Kingdom	1,023/10,000	40-84	national GP research database	consecutive/ random sample
Munoz	2001	Venezuela	302/485	>35	city hospital/local population	consecutive/non-ransom selection
Rao	2002	India	170/2,184	30-75	city cancer hospital	n/s
Suw'gruang	2008	Thailand	101/202	M=53	hospitals in two regions	consecutive/ n/s
Wu	2001	USA	770/1,356	30-74	state cancer registry / local neighbourhood	consecutive/ random sample
Ye	1999	Sweden	292/485	40-79	general population	consecutive/ random sample
Zaridze	2000	Russia	448/610	20-74	two main cancer-treatment hospitals in Moscow	consecutive/non-random selection

2.7.2 Study quality

The quality scores assessed according to the NOS are presented in Table 2.7.3. Overall, cohort studies were of a moderate to high quality, scoring over seven stars. The quality of case control studies ranged from those of low quality (Suwanrungruang et al 2008) to those of high quality with eight out of nine stars (Lagergren et al 2000, Zaridze et al 2000).

On the basis of sample selection, cohort studies scored highly with either three or four stars out of four. Of the three studies that scored three stars, they either failed on not showing that the outcome of interest was absent at baseline (Barstad et al 2005) or their study population was a selected from a sub-group of the general population (Huang et al 2000, Sung et al 2007). For outcome assessment, most studies scored either two or three stars. Of those that only scored one or two stars, Sjödahl et al (2006) and Freedman et al (2007) provided no details of any loss to follow-up in their cohort. Tran et al (2005) relied on identification of gastric cancer cases through self-reporting from their study population.

Table 2.7.3 Gastric cancer: assessment of study quality

	Selection* (out of 4)	Comparability* (out of 2)	Outcome/Exposure[1]* (out of 3)	Total
Cohort				
Alllen 2009	4	2	3	9
Barstad 2005	3	2	3	8
Freedman 2008	4	2	1	7
Huang 2000	3	1	3	7
Kasum 2002	4	1	3	8
Larsson 2006	4	2	3	9
Sasazuki 2002	4	2	3	9
Sjödahl 2006	4	2	2	8
Sung 2007	3	2	3	8
Tran et al 2005	4	1	2	7
Case Control				
Benedetti 2009	3	2	1	6
Chow 1999	2	2	2	6
Kikuchi 2002	2	2	2	6
Lagergren 2000	3	2	3	8
Lindblad 2005	3	2	2	7
Munoz 2001	3	2	1	6
Rao 2002	3	1	2	6
Suwanrungruang 2008	2	1	1	4
Wu 2001	3	2	2	7
Ye 1999	3	2	2	7
Zaridze 2000	3	2	3	8

** High quality characteristics within each of these items were awarded a star, up to a maximum of four stars for selection, two stars for comparability and three stars for assessment: [1] Outcome for cohort, exposure for case-control studies*

Case control studies scored between two and three stars for sample selection. Of those that scored two, most failed because they used controls from a hospital setting and failed to demonstrate that gastric cancer was absent from their control group at recruitment. Of those studies who excluded those with a previous history of cancer cases from their control group, only Rao et al (2002) excluded patient controls admitted to hospital for alcohol or tobacco related diseases. For exposure assessment, the majority of case control studies scored either two or three stars. Of those that only scored two, most were not awarded the third because they did specify how they addressed possible interviewer bias or failed to provide details of response rates among cases and controls. In addition, the paper by Lindblad et al (2005) also failed because alcohol consumption data was based on information from medical records for which information on drinking levels was incomplete for 60% of cases and 40% of controls.

There was considerable variety across studies when controlling for the main risk factors for gastric cancer i.e., helicobacter pylori (*H* pylori) infection, diet and smoking. Four studies did not collect any information on the afore-mentioned risk factors and results were adjusted for age only (Huang et al 2000, Rao et al 2002, Tran et al 2005, Suwanrungruang et al 2008). Smoking terms, including cigarettes smoked per day, pack years of smoking and smoking status (current vs. never), were included in the models of the remaining studies and each study was awarded a star on the grounds that smoking is considered a moderate risk factor for gastric cancer. Measures of diet were controlled for in five studies; whole and refined grains intake and orange and yellow vegetables (Kasum et al 2002),

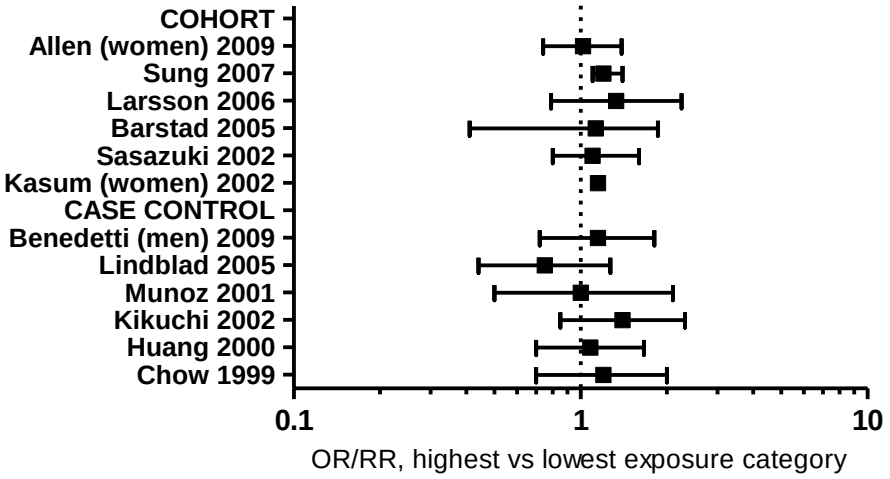
fruit, green or yellow vegetables, salted cod roe or fish (Sasazuki et al 2002) and for intake of fresh fruit and vegetables only (Lagergren et al 2000, Larsson et al 2006, Freedman et al 2008). Only two studies controlled for *H* pylori infection status (Ye et al 1999, Kikuchi et al 2002). Eight studies also controlled for varying measures of socio-economic status (SES). In two studies, SES was not defined (Munoz et al 2001, Kikuchi et al 2002). Ye et al (1999) used lifetime occupational experience as their measure of SES. The remaining studies controlled for education; levels/type of education (Freedman et al 2008), years of education (Larsson 2006 et al, Sjödahl et al 2007) or an undefined term of 'education' (Chow et al 1999, Lagergren et al 2000).

2.7.3 Results: total alcohol intake and risk of gastric cancer[12]

Fourteen studies reported on the association between total alcohol consumption and gastric cancer. OF these, five studies reported on the association between gastric cancer and 'recent' alcohol consumption; defined as intake in the previous year (Munoz et al 2001, Barstad et al 2005, Larsson et al 2007, Sung et al 2007), or alcohol intake in the previous two years (Chow et al 1999). Two studies reported on the association between gastric cancer with lifetime alcohol intake; Benedetti et al 2009 defined lifetime intake as any period when alcohol was drunk at least once a week or nearly every day and Kikuchi et al (2002) and (Suwanrungruang et al 2008) did not specify a measure for their 'lifetime' drinkers. The remaining six studies did not specify a reference period (Huang et al 2000, Kasum et al 2002, Sasazuki et al 2002, Lindblad et al 2005 Rao et al 2002, Allen et al 2009). A summary of gastric cancer risk estimates, comparing the highest versus the lowest alcohol exposure category, is presented in Figure 2.7.1. Two studies reported only on the association between drinking status and gastric cancer and are not included in Figure 2.7.1; Rao et al (2002) found no association (OR 0.8, 95% CI 0.4-1.3, *p* value =0.2) between 'alcohol' drinkers and gastric cancer compared to non-drinkers and Suwanrungruang et al (2008) reported a statistically non-significant increase risk among 'ever' drinkers compared to non-drinkers (OR 1.4, 95% CI 0.62-2.66).

[12] Multivariate relative risks/odds ratios are presented unless otherwise stated

Figure 2.7.1 Alcohol consumption and gastric cancer, highest versus lowest exposure (odds ratio/relative risk and 95% confidence intervals)



The majority of cohort studies were consistent in reporting a non-significant 20-40% increased risk of gastric cancer, at the highest alcohol exposure level (range 25-40 grams per day [g/d], Figure 2.9.1). Of the two largest cohort studies, Sung et al (2007) reported a small (20%) statistically significant increase of gastric cancer for Korean men drinking (≥25 g/d), compared to non-drinkers with strong evidence of a dose response relationship (*p*trend 0.0001). Allen et al (2009), however, did not find any association between alcohol consumption and gastric cancer in women, at any level of drinking, compared to women drinking <2 drinks per week [d/w]. In contrast, non-drinkers in this study did have a statistically significant increased risk (RR 1.27, 95% CI 1.12-1.44) of gastric cancer. Evidence of a dose response relationship in this study was very weak (*p value for trend* =0.2). Although women in a Swedish cohort drinking >40 grams per week (g/w), compared to non-drinkers, had a small and non-significant increased risk of gastric cancer, there was little evidence (*p value for trend* =0.14) of a dose response relationship (Larsson et al 2006). Similar findings were reported by Sasazuki et al (2002) in a cohort of Japanese men drinking >325 g/w (*p value for trend* =0.66). Kasum et al (2002) also reported an increased risk of gastric cancer for women drinking >2 drinks per day [d/d], compared to non-drinkers. Although confidence intervals were not provided in the paper, there were only eight women in the highest alcohol exposure category

In line with the findings of the cohort studies, four of the seven case control studies also reported a 20-40%, non-significant, increased risk of gastric cancer at the highest alcohol exposure category; two studies for consumption in the previous year (Chow et al 1999, Suwanrungruang et al 2008) and two for measures of 'lifetime' drinking (Kikuchi et al 2001, Benedetti et al 2009), compared to a range of reference groups. No formal tests for the significance of the dose response trend were undertaken in these studies. Drinking ≥34 units per week [u/w] in the previous two years, compared to up to 2 units per day, was associated with a non-significant decreased risk of gastric cancer in a UK nested case

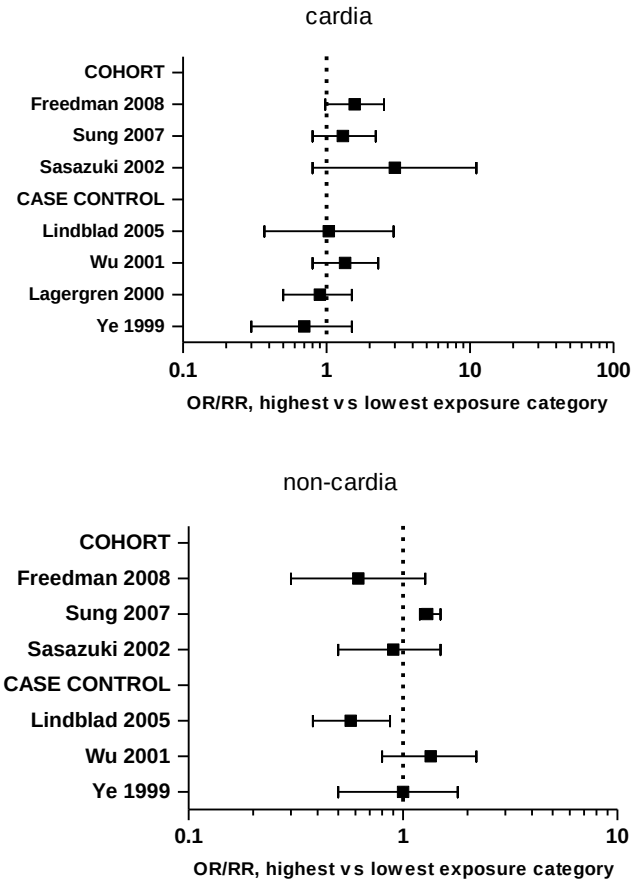
control study (Lindblad et al 2005). The study by Lindblad et al was also characterised by a large number of drinkers (50%) in their study population whose consumption details were unknown. Analysis of gastric cancer risk in this group of drinkers found no evidence of an association with gastric cancer (>34 u/w; OR 0.99, 95% CI 0.80-1.24).

2.7 3.1 Results: total alcohol intake and risk of gastric cancer by tumour site

Nine studies specified the risk of gastric cancer from alcohol consumption by tumour site (gastric cardia and gastric non-cardia). Two studies reported on the association between drinking status and gastric cancer by tumour site. In a Chinese prospective cohort study a small decreased risk of both cardia (RR 0.84, 95% CI 0.72-0.97) and non cardia (RR 0.79, 95% CI 0.61-1.02) gastric cancer was reported for those reporting any drinking in the last 12 months, compared to those not drinking in last 12 months (Tran et al 2005). Zaridze et al (2000), in a hospital based case control study, reported a non-significant two-three fold increased risk of gastric cardia and non-cardia cancer for men who had drank alcohol in their lifetime compared to abstainers. There was no association in this study for either tumour site in female drinkers. The remaining studies investigated the dose response association between alcohol consumption and gastric cancer tumour site. A summary of risk estimates, comparing the highest versus the lowest alcohol exposure category, is presented in Figure 2.7.2.

In a large prospective cohort study, Sung et al (2007) reported a 30% increased risk in both tumour sites for men drinking >25 g/d, compared to non-drinkers, though this was only statistically significant for non cardia gastric tumours. There was no association at lower levels of drinking. There was strong evidence of a statistically significant dose response trend (*p value for trend* =0.0002) between alcohol consumption and non-cardia tumours, but not for cardia tumours (*p value for trend* =0.5914). In a further two prospective cohort studies, Sasazuki et al (2002) and Freedman et al (2008) observed a statistically non-significant three fold (*p value for trend* =0.66) and thirty per cent (*p value for trend* =0.12) increased risk of gastric cardia tumours respectively, in those drinking approximately >3 d/d, compared to non-drinkers (Freedman et al) and those drinking 0-3 times per month (Sasazuki et al). Freedman et al (2008) also observed a 40% decreased risk of non-cardia tumours in those drinking >3 d/d. Although drinking at lower levels was associated with a positive association with this tumour type, there was no evidence of a dose response relationship (*p value for trend* =0.15). No association between non-cardia tumours and alcohol consumption was reported by Sasazuki et al (2002).

Figure 2.7.2 Alcohol consumption and gastric cancer, highest versus lowest exposure category; by tumour site: (odds ratio/relative risk and 95% confidence intervals)



Of the case control studies, Wu et al (2001) observed a non-significant 35% increased risk in both tumour sites for those drinking >36 d/w, but not at lower levels of consumption and no evidence of a dose response association (cardia; *p value for trend* =0.42; non-cardia; *p value for trend* =0.29). In a nested case control study, alcohol consumption of up to >34 u/w was not associated with gastric cardia cancer, but did significantly reduce the risk of non-cardia gastric cancer (Lindblad et al 2005). In the remaining case control studies, Ye et al (1999) and Lagergren et al (2000) did not find any association between an increased risk of gastric cardia and non-cardia tumours, and lifetime alcohol consumption.

2.7.4 Results: drinking dimensions and risk of gastric cancer

One study reported on the association between drinking frequency and gastric cancer. Sjödahl et al (2007) observed positive associations between all measures of drinking frequency in those drinking in the 14 days prior to baseline (drinking occasionally: HR 1.24, 95% CI 0.80-1.91; 1-4 times a week: HR 1.30 95% CI 0.78-2.16; or ≥ 5 times a week: HR 1.49, 95% CI 0.78-2.83) and gastric cancer, compared to never drinkers.

2.7.5 Results: drink type and risk of gastric cancer

Three prospective cohort and four case control studies, investigated the association between alcohol drink type and gastric cancer. A summary of risk estimates, comparing the highest versus the lowest alcohol exposure category, is presented in Figure 2.7.3. Overall, wine intake was associated with a decreased risk of gastric cancer in the majority of studies. The evidence of a positive association between gastric cancer and beer and spirit drinking was more mixed.

Wine

In a Danish prospective cohort study, the risk, adjusted for age and smoking only, of gastric cancer, decreased with increasing wine intake (>13 glasses per week; RR 0.16, 95% CI 0.02-1.18, *p value for trend* =0.02) with trend analysis showing a statistically significant 40% decreased risk of gastric cancer for each glass of wine per day compared to non-wine drinkers (Barstad et al 2005). All three case control studies also reported an inverse association between wine drinking in the highest alcohol exposure category and gastric cancer. In studies by Ye et al (1999) and Wu et al (2001), wine drinking was inversely and dose-dependently associated with risk for cardia cancer (*p value for trend* =0.03 and 0.05, respectively), and to a lesser extent for non-cardia gastric cancer (*p value for trend* =0.08 and 0.04, respectively).

Beer

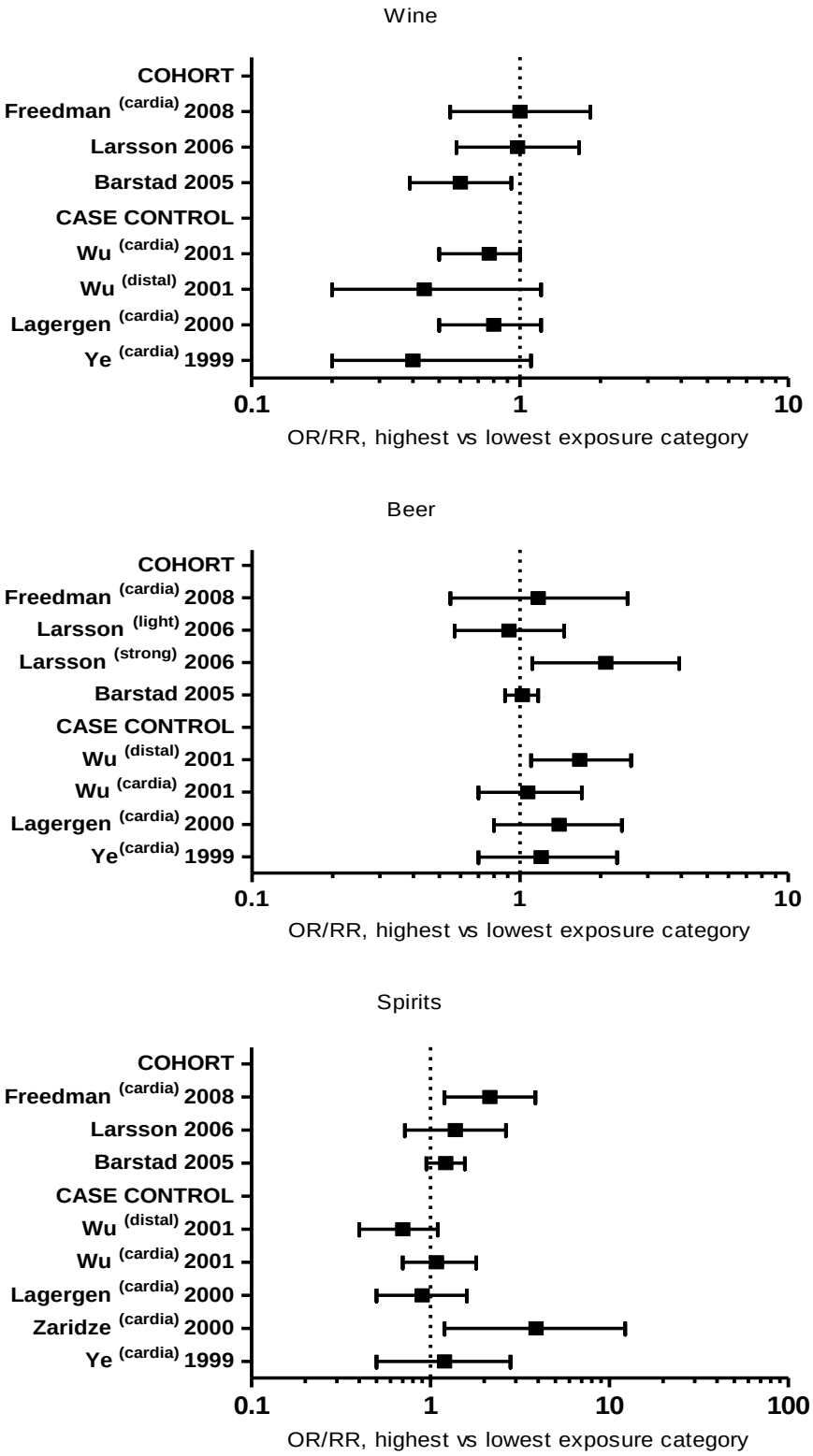
The majority of studies reported a positive association between beer intake and gastric cancer. Only two studies reported evidence of a possible dose response association. Medium and strong beer consumption, compared to non-drinkers was associated with a statistically significant two-fold increased risk (*p value for trend* =0.02) of gastric cardia cancer in Swedish women (Larsson et al 2006). In the same study, women drinking 'light' beer were not at increased risk of gastric cardia cancer. In an American population based case control study, drinking >15 d/w (OR 1.67, 95% CI 1.10-2.60, *p value for trend* =0.09) was associated with a statistically significant increased risk of gastric cardia cancer, but no association was found between beer drinking and non cardia gastric cancer.

Spirits

Four studies reported a positive association between spirit drinking and gastric cancer at the highest exposure category. Freedman et al (2008) reported that men drinking >3 'spirit' drinks p/d, compared to those drinking between >0-1 'spirit' drinks p/d had a statistically significantly two-fold increased risk of gastric cardia cancer with some weak evidence of a dose response trend (*p value for trend* =0.023). A similar increase in risk of cardia gastric cancer ,with amount drunk, was reported by Zaridze et al (2000) for men drinking >10.4 litres of vodka per year (OR 3.9, 95% CI 1.2-12.3, *p value for trend* =0.03), compared to non-drinkers. Wu et al (2001), on the other hand, found no

association between gastric cardia cancer and spirit drinking, but did observe a 30% decreased risk of non-cardia gastric cancer in the highest exposure category (>15 d/w, *p value for trend* =0.02).

Figure 2.7.3 Alcohol consumption and risk of gastric cancer, highest versus lowest exposure category; by drink type (odds ratio/relative risk and 95% confidence intervals)



2.7.7 Effect modification

The effect modification of other factors on the alcohol-gastric cancer association was reported in two cohort and one case control study. In a large Korean cohort study, Sung et al (2007) reported that smoking >20 cigarettes p/d combined with alcohol consumption of >25 g/d, was associated with a nearly five-fold increased risk of cardia gastric cancer (HR 4.5, 95% CI 1.7-11.9), and a two-fold increased risk of non cardia gastric cancer compared to nonusers. The interaction between smoking and alcohol drinking was not statistically significant for total gastric cancer ($P_{interaction=}$0.48), cardia ($P_{interaction=}$0.68) or non-cardia cancer ($P_{interaction=}$0.89). Sjödahl et al (2008) reported similar findings in a Norwegian cohort study; smoking of >20 cigarettes p/d combined with drinking >5 'times' within the past fourteen days was associated with a 4-fold increased risk of gastric cancer compared to nonusers. The interaction between tobacco smoking and alcohol drinking was not statistically significant regarding total gastric cancer ($P_{interaction=}$0.32), non-cardia gastric cancer ($P_{interaction=}$0.44) or cardia cancer ($P_{interaction=}$0.89). In a hospital based case control study, Zaridze et al (2000) reported no significant interaction ($P_{interaction=}$0.51) between helicobacter pylori status and vodka drinking.

2.7.8 Summary and conclusions

The present review identified 21 papers, published between 1999 and 2009, which examined the association between alcohol consumption and gastric cancer. Overall, the majority of cohort studies were consistent in reporting a non-significant 20-40% increased risk of gastric cancer, at the highest alcohol exposure level (range 25-40 g/d, approximately 2.5-3.5 'standard' drinks). Drinking below this level was rarely associated with an increased risk of gastric cancer. Only one study (Sung et al 2007) reported a statistically significant dose response relationship. A meta-analysis of two cohort and fourteen case control studies, published between 1996 and 2000 (Bagnardi et al 2001), reported pooled relative risks (PRR) for selected alcohol intake levels all of which showed a positive (and statistically significant) association with gastric cancer; (25 g/d: PRR 1.07, 95% CI 1.04-1.10; 50 g/d: PRR 1.15, 95% CI 1.09-1.22; 100g/d: PRR 1.32, 95% CI 1.18-1.49). Forman et al (2006), however, in a meta-analysis of five cohort and thirteen case control studies (published between 1980 and 2000) reported no significant linear increase in risk of gastric cancer with amount drunk; the PRR from the cohort studies was 0.99 (95% CI 0.97-1.02) per 10 g/day (*P* Het =0.7) and the PRR from the case-control studies was 1.02 (95% CI 1.00-1.04) per 10 g/day (*P* Het =0.04).

The lack of adjustment for *H* pylori status and diet in all the papers included in the present review (including the meta-analyses above) is a significant limitation. *H* pylori infection and diet are the main known causative agents of gastric cancer and are potential confounders of the association between alcohol and gastric cancer (WCRF/AICR 2007). Some studies have suggested that moderate and lifetime drinkers have a lower risk of *H* pylori infection than people who do not drink alcohol, though

the evidence remains inconclusive (Daroch et al 2001, Zhang et al 2010). A diet high in salt, carbohydrate and foods rich in nitrate or nitrite and their derivatives has been associated with an increase in risk. Conversely, a decrease in risk with higher intake of fresh fruits and vegetables has been consistently observed in epidemiological studies of gastric cancer (WCRF/AICR 2007). Studies examining diet quality of individuals who drink any kind of alcoholic beverage, have found that people who drink the largest quantities of alcohol, even infrequently, have the poorest quality diets. Conversely, people who drink the least amount of alcohol, regardless of drinking frequency, have the best quality diets (Cerhan et al 2004, Grosbeak et al 2004, Breslow et al 2006). It is, therefore, likely that confounding from *H* pylori status and diet will account for the positive associations between alcohol consumption and gastric cancer reported in the present review.

The evidence of an association between tumour sites (cardia and non-cardia) and alcohol consumption was inconsistent. Risk estimates for cardia and non-cardia gastric cancer tumours generally followed those reported for the association between total gastric cancer and alcohol consumption in each study reporting on this aspect. Small numbers in each stratum for most studies and the strong possibility of misclassification of these tumour sites (Sasazuki et al 2002) prevent any firm conclusions being drawn concerning these tumour sites and their association with alcohol consumption.

Evidence from the present review was consistent in reporting an inverse association between wine drinking and gastric cancer. Three of the six studies reporting on this aspect, observed a statistically significant dose response relationship. In two of these studies, both took into account the strong inverse social class gradient for gastric cancer by controlling for SES. In contrast, results were inconsistent for beer and spirit drinking and positive association observed for these drink types tended to reflect the association with gastric cancer observed for all alcohol consumption in each individual study. In addition, reverse causality is often a problem in observational studies; the level of alcohol exposure may diminish as an individual ages or becomes ill, which can lead to an underestimation of the disease risk (Lewis and Smith 2005). Only the case control studies in the present review reported an inverse association between wine and gastric cancer and alcohol consumption was assessed relatively close to the cancer diagnosis and cases may have altered their alcohol intake or their report of it (Freedman et al 2011). The possible protective effect of wine observed in the present review, is also not consistent with the findings of earlier reviews (Barstad et al 2005, Forman et al 2006). These reviews concluded that the evidence from cohort studies (n=2) did not support an association between type of alcohol beverage and gastric cancer whilst the evidence from case control studies (n=7) was mixed and inconsistent. There are, also some plausible biological mechanisms whereby wine may hypothetically prevent gastric cancer; studies have shown anti-carcinogenic properties of resveratrol and several other factors present in wine, but not in beer and spirits (Jang et al 1997, Sgambato et al 2001, Soleas et al 2002); and growth of *H* pylori infection has been suggested by some to be inhibited by wine intake (Murray et al 2002, Gao et al 2010). The absence of any adjustment or measure of

effect modification for *H* pylori infection, in papers included in the present review is, therefore, a major limitation in assessing a possible inverse association between wine and gastric cancer.

In conclusion, the positive associations between total alcohol consumption and gastric cancer and the protective effect of wine observed in the present review are likely to be explained by confounding from *H* pylori and diet. Further large prospective cohort studies which control for the effects of diet and *H* pylori infection and allow further investigation of the effect modification of these risk factors are required.

2.8 Kidney cancer

Kidney cancer: summary of evidence from previous reviews
Overall, studies on cancers of the kidney show no association with alcohol consumption (IARC 1988b, WCRF/AICR). Bagnardi et al (2001) in a meta-analysis of two case control studies observed an inverse association between alcohol consumption and kidney cancer (25g/d; RR 0.88, 95% CI 0.77-1.02 and 100 g/d; RR 0.62, 95% CI 0.36-1.06).

This literature review identified ten papers, published between 1999 and 2009, which examined the association between alcohol consumption and risk of kidney (renal cell) cancer. There were five cohort and five case control studies available for appraisal. Tables for each paper, describing the study aims, population, alcohol measurement methods and main results are provided in Appendix D.

2.8.1 Study characteristics

A summary of the general characteristics of the studies is provided in Table 2.8.1 below. Two papers were based on established prospective cohort studies described in Box 2 Chapter 2.2; the Health Professionals Follow-up Study and Nurses Health Study (Lee et al 2006) and the Swedish Mammography Cohort (Rashidkhani et al 2005). The paper by Allen et al (2009) has been previously described in Chapter 2.3.1. In the paper by Mahabir et al (2005), the study population consisted of a sample of male smokers living in south-western Finland, who had been recruited to a randomised control trial

Of the five case control studies, three were population based and two hospital based. In an American population case control study, cases were selected from regional cancer registries and controls either randomly sampled from the states driver's license records (Parker et al 2002) regional (Hu et al 2008) or national populations (Gerving et al 2007). An Italian case control study drew both cases and controls from a network of general hospitals and university clinics in the areas under surveillance (Pelucchi et al 2002). In the remaining study (Hsu et al 2007) no details were provided of case recruitment and controls were recruited from hospitals across four countries (Russia, Romania, Poland and Czech Republic).

Table 2.8.1 Alcohol and kidney cancer: general characteristics of studies reviewed

Authors	Year	Country	Outcome/No outcome Case/Control	Age range (M/Mdn)	Sample base	Sample selection
Cohort studies						
Allen	2009	UK (women)	1,141/1,279,155	>55	breast screening clinics	random selection
Lee	2006	USA	248/136,752	30-55	male health professionals, female nurses	random selection
Mahabir	2005	Finland (men-)	195/27,016	50-69	regional population	volunteers
Nicodemus	2003	USA (women)	124/34,513	55-69	state driver license lists	random sample
Rashidkhani	2005	Sweden (women)	93/46,479	40-76	regional population	volunteers
Case control studies					**cases/controls**	
Greving	2007	Sweden	855/1,204	20-74 (M=63/64)	regional population	consecutive/ random selection
Hsu	2007	Central Europe	1,065/1,069	20-79	hospital	unspecified/non-random selection
Hu	2008	Canada	1,138/5,039	20-76	regional population	consecutive/ random selection
Parker	2002	USA	406/2,249	40-85	cancer registry /state driver license lists	consecutive/ random sample
Pelucchi	2008	Italy	1,115/2,582	23-79 (M=60)	hospital	consecutive/non-random selection

Abb: n/s not specified; M=mean; Mdn= median

2.8.2 Study quality

The quality scores, assessed according to the NOS, are presented in Table 2.8.2. Overall studies were of a moderate to high quality, scoring between 6-7 stars.

Table 2.8.2 Kidney cancer: assessment of study quality

	Selection* (out of 4)	Comparability* (out of 2)	Outcome/Exposure[1]* (out of 3)	Total
Cohort				
Allen 2009	4	2	3	9
Lee 2006	3	2	3	8
Mahabir 2005	3	2	2	7
Nicodemus 2004	4	1	3	8
Rashidkhani 2005	4	2	3	9
Case Control				
Greving 2007	4	2	2	8
Hsu 2007	2	2	2	6
Hu 2008	3	2	1	6
Parker 2002	4	2	3	9
Pelucchi 2008	3	2	1	6

* High quality characteristics within each of these items were awarded a star, up to a maximum of four stars for selection, two stars for comparability and three stars for assessment; [1] Outcome for cohort, exposure for case-control studies

On the basis of sample selection, cohort and cases control studies scored highly with either three or four stars out of four. A number of studies failed in this item because of the potential selection bias introduced by their choice of study populations i.e. groups of nurses and health professionals (Lee et

al 2006), hospital controls (Hsu et al 2007, Pelucchi et al 2008) and 'current' smokers (Mahabir et al 2005). Greving et al (2008) failed to specify if controls had been excluded for a prior history of kidney cancer. In addition, two case control studies attempted to minimize further selection bias amongst controls by excluding patients with chronic conditions (particularly those associated with smoking and alcohol drinking), digestive tract diseases and alcohol-related traumas (Pelucchi et al 2008, Hsu et al 2008).

All the cohort studies scored maximum stars for outcome assessment. Exposure assessment in the case control studies, however, varied in quality. Interviewer bias could not be ruled out in three studies since the blinding status of the interviewers was not specified (Hsu et al 2007, Hu et al 2008, Pelucchi et al 2008). Non-response bias may affect results in the studies by Greving et al (2008) and Hu et al (2008) due to differential response rates among cases and controls: approximately 65% response rate for cases and controls. Response rates were not provided in one study (Pelucchi et al 2008).

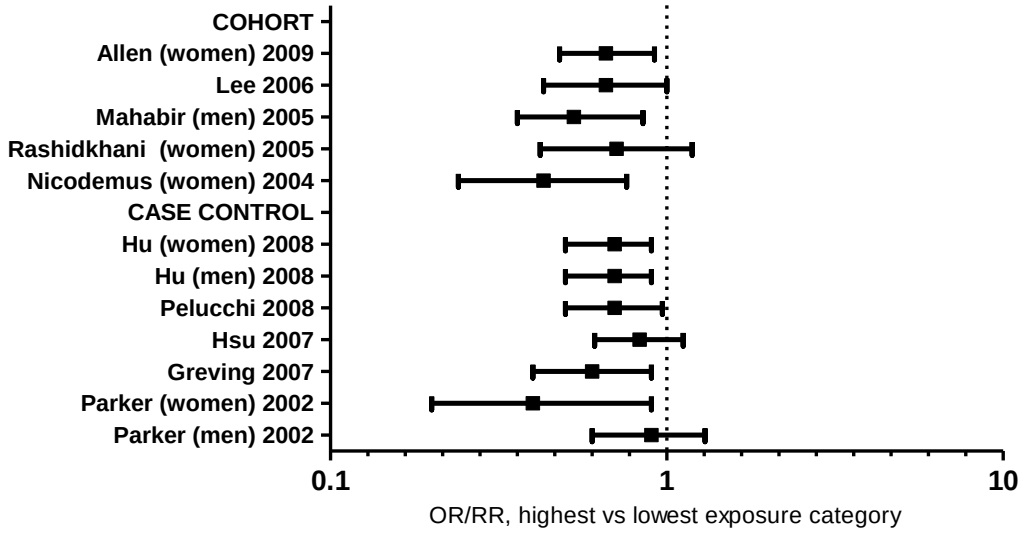
Established risk factors for kidney cancer and possible confounders of the alcohol and kidney cancer association e.g. age and smoking, were generally well controlled for across all studies. Smoking terms, including cigarettes smoked per day, pack years of smoking and smoking status, were included in the models of eight of the nine studies. Rashidkhani et al (2005), however, only controlled for smoking in a sub-cohort analyses involving 41 cases, the results of which were not reported in their paper. Obesity, measured by body mass index (BMI $\geq$30 kg/m^2, was not controlled for in one study (Nicodemus et al 2003). A further four studies also controlled for a history of hypertension (Mahabir et al 2005, Rashidkhani et al 2005, Lee et al 2006, Hsu et al 2007).

2.8.3 Results: total alcohol intake and kidney cancer[13]

Seven studies reported on the association between kidney cancer and 'recent' alcohol intake defined as alcohol consumption in the preceding year in four studies (Nicodemus et al 2003 Mahabir et al 2005, Lee et al 2006, Pelucchi et al 2008), consumption in the previous two years (Hu et al2008), or five years (Greving et al 2007) and during the last 6 months (Rashidkhani et al 2005). Two studies reported on the association between kidney cancer with lifetime alcohol intake defined as drinking over all adult years (Parker et al 2002) and usual weekly consumption during different periods of adult life (i.e., ages $\leq$25, 26–40, 41–50, 51-60, and >60 years) (Hsu et al 2007). Allen et al (2009) did not specify a reference period. A summary of kidney cancer risk estimates, comparing the highest alcohol versus the lowest alcohol exposure category, is presented in Figure 2.8.1. Cohort and case control studies were consistent in reporting an inverse association between kidney cancer at the highest alcohol exposure category (range >3 grams to >20 grams per day [g/d]).

[13] Multivariate relative risks/odds ratios are presented unless otherwise stated

Figure 2.8.1 Alcohol consumption and kidney cancer, highest versus lowest exposure category, by study type (odds ratio/relative risk and 95% confidence intervals)



In the largest cohort study, Allen et al (2009) reported a statistically significant 30% decreased risk of kidney cancer in women drinking >15 drinks per week [d/w] compared to women drinking <2 d/w. All other intake categories were inversely associated with kidney cancer and there was some evidence of a dose response relationship (*p value for trend*=0.03). In the same study, non-drinkers had a small increased risk, of borderline statistical significance, in gastric cancer (RR 1.12, 95% CI 1.00-1.26). Lee et al (2006) observed a weak, statistically significant, protective effect against kidney cancer, in a cohort of American health professionals, for those drinking >15 g/d, compared to non-drinkers with weak evidence of a dose response relationship (*p value for trend*=0.07). In a Finnish study, male smokers drinking a median of 39 g/d, compared to men drinking <2.5 g/d (including never and ex-drinkers) had a statistically significant reduced risk of kidney cancer (RR 0.53, 95% CI 0.34-0.83). Lower levels of drinking were also inversely associated with kidney cancer and there was statistically significant dose response relationship (Mahabir et al 2005). In the two remaining cohort studies, very low levels of drinking in women (3 to 4 g/d) were also inversely associated with kidney cancer, compared to those drinking <2.5 g/d (Rashidkhani et al 2005) and non-weekly drinkers (Nicodemus et al 2004).

In an American population based case control study (Parker et al 2002), women drinking at any level had a reduced risk of kidney cancer (>35 grams per week [g/w], OR 0.4, 95% CI 0.2-0.9, *p value for trend*=0.04), compared with never drinkers. The study did not support an inverse association between men drinking at similar levels and risk of kidney cancer. In a Canadian population based case control study (Hu et al 2008), men and women drinking at any level, had a reduced risk (*p value for trend*= 0.04 and 0.008, respectively) of kidney cancer, compared to non-drinkers. Pelucchi et al (2008), in their Italian hospital based case control study, reported a significant dose response relationship (*p value for trend* =0.01) with consumption of >4 drinks per day [d/d] associated with a statistically

significant protective effect. Greving et al (2007) also observed a dose response relationship (*p value for trend* =0.03), but this protective effect was only statistically significant at the highest alcohol intake level (>620 grams per month) compared to non-users of alcohol.

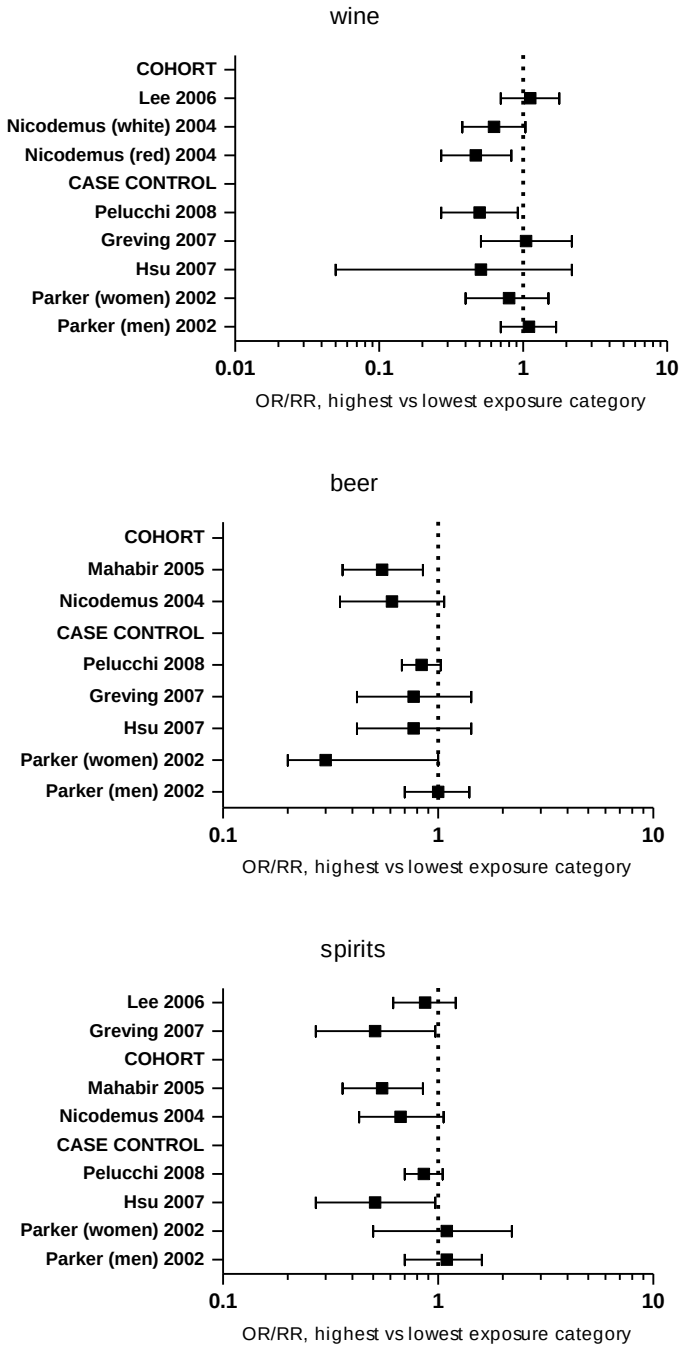
2.8.4 Results: drinking dimensions and risk of kidney cancer

One paper, Pelucchi et al (2008), considered other aspects of drinking behaviour and risk of kidney cancer. There was no trend in risk of kidney cancer with duration of drinking (>45 yrs; OR 0.97, 95% CI 0.76-1.24, *p value for trend*=0.94) compared to non-drinkers and age at which participants started drinking alcohol (≥23 years of age, OR 1.02, 95% CI 0.75-1.39, *p value for trend*=0.81) compared to those aged ≤16 years.

2.8.5 Results: drink type and risk of kidney cancer

Three cohort studies and four case control studies reported on the association between drink type and kidney cancer. A summary of risk estimates, comparing the highest exposure versus the lowest alcohol exposure category, are presented in Figure 2.8.2. Overall results by drink individual type in each paper reflect those reported for the association between total alcohol consumption and kidney cancer.

Figure 2.8.2 Alcohol consumption and risk of renal cell cancer, highest versus lowest exposure category; by drink type (relative risk/odds ratio and 95% confidence intervals)



2.8.6 Results: effect modification

The effect modification of other factors on the alcohol-kidney cancer association was reported in two cohort studies and two case control studies. Lee et al (2006) reported that the association between total alcohol consumption and kidney cancer were not modified by body mass index [BMI] ($P_{interaction=}$0.71), a history of hypertension ($P_{interaction=}$0.42) or smoking status (current vs. never, $P_{interaction=}$0.63). In the study by Mahabir et al (2005), no evidence was found for any significant interactions between total alcohol intake, in male smokers, within strata defined by age

($P_{interaction=}$0.73), BMI ($P_{interaction=}$0.30) or cigarettes smoked per day ($P_{interaction=}$0.14) and kidney cancer.

In the two case control studies, Pelucchi et al (2008) found no significant heterogeneity for total alcohol consumption across strata of age ($P_{interaction=}$ 0.92), BMI ($P_{interaction=}$0.40) and smoking ($P_{interaction=}$0.51). Hu et al (2008) reported a significant inverse association between total alcohol intake and kidney cancer in men and women among never smokers (OR 0.6, 95% CI 0.4-0.9) for the group with the highest alcohol intake (>22.9 g/d), compared to non-drinkers. The inverse association also appeared in never smokers, but the difference was not statistically different (OR 0.6, 95% CI 0.3-1.2). Hu et al. also reported inverse associations with kidney cancer related to total alcohol consumption in men and women with who had a BMI >25 or <25 kg/m^2.

2.8.7 Summary and conclusions

This review identified five prospective cohort and five case control studies, published between 1999 and 2009, which examined the association between alcohol consumption and risk of kidney cancer. Study quality was generally of a moderate to high level and smoking and obesity, possible confounders of the association between alcohol and kidney cancer were controlled for in all studies. Overall, the evidence presented suggests a weak protective effect of moderate alcohol consumption (approximately 12-24 g/d), irrespective of drink type, for both men and women, against the development of kidney cancer. Evidence of an inverse association between alcohol consumption and kidney cancer is consistent with the findings of previous, meta and pooled-analyses and international reviews. Bagnardi et al (2001) in a meta-analysis of two case control studies (n=921 cases) observed an inverse association between alcohol consumption and kidney cancer (25g/d; pooled RR (PRR) 0.88, 95% CI 0.77-1.02 and 100 g/d; PRR 0.62, 95% CI 0.36-1.06). In a recent pooled analysis of twelve prospective studies (including four cohort studies identified in this review and data from four previously unpublished studies) on alcohol intake and kidney cancer, drinking ≥15 g/d reduced the risk of kidney cancer by approximately thirty per cent (PRR 0.72, 95% CI 0.60-0.86, *p value for trend* <0.01, *P* heterogeneity among studies =0.99) (Lee et al 2007b). The WCRF/AICR (2007) systematic review also observed that many of the study's estimates in their review were in the direction of a protective effect, but concluded that a substantial effect of alcohol on kidney cancer was still unproven since the biological mechanisms whereby alcohol would mediate a protective effect against kidney cancer were unknown (WCRF/AICR 2007).

Residual confounding from smoking and obesity could explain the inverse associations observed between alcohol consumption and kidney cancer. Lee et al (2007b) in their pooled analysis of twelve cohort studies, however, did not find any evidence that weight and smoking status modified the association between alcohol consumption and kidney cancer. Smoking was the strongest confounder

for the association between alcohol intake and kidney cancer among the potential risk factors (weight, history of hypertension, folate intake, oral contraceptive use) controlled for in the pooled analysis and adjustment for smoking strengthened the inverse association reported in the paper. With more thorough control for smoking, the true inverse relationship may, therefore, have been stronger. There was no evidence of a statistically significant interaction, in the present review, between alcohol consumption and obesity, and alcohol consumption and smoking. However, small numbers in each stratum in all the studies reporting on the interaction between alcohol and smoking, and obesity mean that a modifying effect of either smoking or obesity on the alcohol-kidney cancer association still cannot be completely ruled out.

Bias as a result of measurement error, from under-reporting of alcohol consumption especially among heavy drinkers, may account for the inverse associations observed in the present review. All studies used food frequency questionnaires to collect information on alcohol consumption and this method, compared to other approaches, has been shown to underestimate true levels of alcohol consumption (Feunekes et al 1999, McCann et al 1999). Whether levels of under-reporting of alcohol consumption are of a sufficient amount to account for the inverse associations between alcohol and kidney cancer has yet to be demonstrated.

In summary the findings of this review are suggestive of a possible inverse association between alcohol consumption and kidney cancer for both men and women. There is little evidence, however, of biological mechanisms that would mediate a protective effect of alcohol against RCC. Alcohol consumption has been associated with decreased risk of type 2 diabetes mellitus possibly through a mechanism involving decreased insulin resistance and diabetes mellitus is positively related to RCC (Rashidkhani et al 2005). It is also possible that alcohol consumption, which can contribute to lower blood pressure levels when drunk moderately, might prevent or limit renal fibrosis and chronic renal failure via improved vascular function (Mahabir et al 2005). Furthermore, based on alcohol metabolism and the production of reactive oxygen species, alcohol would be expected to increase the risk of RCC. Alcohol may also interfere with folate absorption, transport, and metabolism, potentially limiting folate stores in tissues. This could contribute to RCC via abnormal DNA methylation (Mahabir et al 2005).However, the small number of studies, heterogeneous study populations, the small number of kidney cancer cases identified in each study and possible under-reporting of alcohol consumption prevent any definitive conclusions being drawn about the relationship between alcohol consumption and kidney cancer. There is, therefore, a need for additional studies to solidify alcohol's role as a consistent and believable protective factor in the development of kidney cancer and which include a sufficient range of drinkers to investigate an association between heavy alcohol consumption and risk of kidney cancer.

2.9 Laryngeal Cancer

Laryngeal cancer: summary of evidence from previous reviews
Epidemiological studies clearly indicate that alcohol consumption is causally related to laryngeal cancer. There is no indication that the effect is dependent on type of beverage (Lowenfels 1975, IARC1988B, WCRF/AICR).

The literature search identified 13 papers from 10 studies, published between 1 January 1999 and 30 September 2009, which examined the association between alcohol consumption and laryngeal cancer. Four papers were based on one hospital case control study carried out in Italy and Switzerland. All four have been included in this review since they looked at different aspects of the association between alcohol intake and risk of laryngeal cancer; from total alcohol intake (Garavello et al 2006); in women (Gallus et al 2003); in a population of non-smokers (Bosetti et al 2002); and on the joint effect of alcohol and smoking on risk of laryngeal cancer Talamini et al (2002). Tables for each paper, describing the study aims, population, alcohol measurement methods and main results are provided in Appendix D.

2.9.1 Study characteristics.

A summary of the general characteristics of the papers are provided in Table 2.9.1 below.

In the only cohort study identified in the present review, Allen et al (2009) recruited their study population from women attending breast screening clinics in the United Kingdom (see section 2.3.1 for further details of this study) identifying 138 cases of laryngeal cancer over a mean follow up period of 7.2 years. Of the nine case-control studies that examined the association between laryngeal cancer and alcohol consumption, eight studies were hospital based. In these studies, cases were selected from hospitals study area and non-random samples of controls were recruited from the same network of hospitals as the cases. In the remaining study, Ramroth et al (2004) recruited cases from treatment clinics and controls from a random sample of the local population from population registries registry Study size varied considerably from 51 cases (Pacella-Norman et al 2002, Gallus et al 2003) to approximately 700 cases (Garavello et al 2006).

Table 2.9.1 Alcohol and laryngeal cancer: general characteristics of studies reviewed

Authors	Year	Country	Outcome/No outcome Case/Control	Age range (M/Mdn)	Sample base (cases/controls)	Sample selection (cases/controls)
Cohort studies						
Allen	2009	UK (women)	138/1,280,158	>55	breast screening clinics	random selection
Case control studies						
Bosetti	2002	Italy/Switz.	162/160	30-70 (Mdn=60)	Regional hospitals	consecutive/ non-random selection
De Stefani	2004	Uruguay (men)	320/640	30-89	hospital	consecutive// non-random selection
Gallus	2003	Italy/Switz. (women)	68/340	<79 (Mdn=60)	*See Bosetti 2002*	
Garavello	2006	Italy/Switz.	672/3,454	30-80 (M=61/58)	*See Bosetti 2002*	
Hashibe	2007a	Various*	384/918	n/s	hospital	
Menvielle	2004	France (men)	504/242	n/s	hospital	consecutive/ non-random selection
Pacella	2002	South Africa (men)	51/2,900	18-74	two city hospitals	consecutive/ n/s
Ramroth	2004	Germany	257/769	M=62	hospital /general population	consecutive/random sample
Sapkota	2007	India	511/718	>18	hospital	consecutive// non-random selection
Schlecht	2001	Brazil	194/1,578	n/s	hospital	Selected cases/ non-random selection
Talamini	2002	Italy/Switz.	527/1,297	30-79 (Mdn=61)	*See Bosetti 2002*	
Zvrko	2008	Montenegro	108/108	38-85 (60)	hospital	all/ non-random selection

*Romania, Hungary, Poland, Russia, Slovakia. Abb: n/s not specified; M=mean; Mdn= median

2.9.2 Study quality

The quality scores assessed according to the NOS are presented in Table 2.9.2. Overall, studies on laryngeal cancer were of moderate to high quality scoring 7-8 stars out of a possible nine stars.

Table 2.9.2 Laryngeal cancer: assessment of study quality

	Selection* (out of 4)	Comparability* (out of 2)	Outcome/Exposure[1]* (out of 3)	Total
Allen 2009	4	2	3	9
Bosetti 2002, Talamini 2002, Gallus 2003, Garavello 2006[2]	3	2	2	7
De Stefani 2004	3	2	3	8
Hashibe 2007	2	2	1	5
Menvielle 2004	2	2	3	7
Pacella 2002	3	2	2	7
Ramroth 2004	3	2	1	6
Sapkota 2007	3	2	1	6
Schlecht 2001	3	2	3	8
Zvrko 2008	3	2	2	7

***** High quality characteristics within each of these items were awarded a star, up to a maximum of four stars for selection, two stars for comparability and three stars for assessment [1] Outcome for cohort, exposure for case-control studies [2] all four papers derived from one case control study

All case control studies tried to minimize selection bias by frequency matching cases and controls on age, residence and gender. In addition to excluding people admitted to hospital with neoplastic conditions from their control group, two studies further sought to minimize selection bias by selecting controls admitted to hospital for diseases not related to smoking and alcohol use (Bosetti et al 2002 etc, De Stefani et al 2004). Schlecht et al (2001) excluded people with mental disorders (including alcoholism) though included people who were admitted for digestive system diseases without specifying if those with alcoholic liver disease were excluded. Menvielle et al (2004) and Pacella-Norman et al (2002) chose cancer patients as their control group though patients with alcohol related cancers (defined as bladder, liver or pancreas cancer) were excluded since these neoplasms were considered to be associated with alcohol consumption. Ramroth et al (2004) did not specify any exclusion criteria for their control group. The majority of case control studies reported response rates for cases and controls exceeding 90%. In a population based case control study, there was a low-response rate (38%) among controls (Ramroth et al 2004) and Menvielle et al (2004) reported response rate of 80% and 86% among cases and controls respectively. Studies performed poorly on exposure assessment with only one study stating that interviewers were blinded to case status (Schlecht et al 2001) Outcome measurement was clearly defined in all studies with the exception of Menvielle et al (2004) paper which did not specify how the outcome was defined and measured.

All studies received maximum stars for comparability. Age and smoking were controlled for in all studies. Adjustment for smoking was detailed across all studies and included measures of amount smoked per day, duration and status of smoking. Adjustment for other known, and possible, confounders of the alcohol-laryngeal cancer association varied across studies. A number of measures were used as proxies for socio-economic status (SES). Allen et al (2009) used the Townsend index; a UK area based measure (including unemployment, overcrowding, owner-occupier status, and car ownership) of deprivation. Four studies used education as a measure of SES (Bosetti et al 2000 etc, Pacella-Norman et al 2002, Ramroth et al 2004, Hashibe et al 2007). Pacella-Norman et al (2002) further controlled for occupation status. Saptoka et al (2007) did not define their measure of SES. Only one study controlled for fruit and vegetable intake (Hashibe et al 2007).

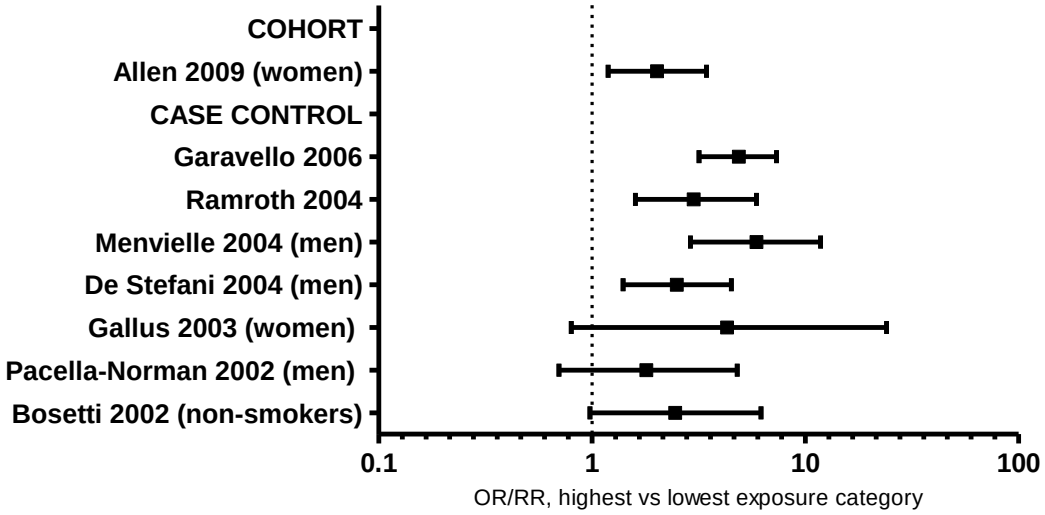
2.9.3 Results: total alcohol intake and risk of laryngeal cancer[14]

Eight studies, providing ten papers, reported on the association between total alcohol consumption and laryngeal cancer. Of these, two studies providing four papers reported on the association between laryngeal cancer and ‘recent’ alcohol consumption; defined as intake in the previous year (Bosetti et al 2002, Gallus et al 2003, Garavello et al 2006, Hashibe et al 2007). Two studies reported on the association between larnygeal cancer with lifetime alcohol intake; Ramroth et al (2004) defined as

[14] Multivariate relative risks/odds ratios are presented unless otherwise stated

alcohol consumption 10 years before survey interview and De Stefani et al (2004) did not specify a measure for their 'lifetime' drinkers. The remaining four studies did not specify a reference period (Pacella-Norman et al 2002, Menvielle et al 2004, Zvrko et al 2008, Allen et al 2009). A summary of laryngeal cancer risk estimates, comparing the highest versus the lowest alcohol exposure category, is presented in Figure 2.9.1. In a case control study, not included in Figure 2.9.1, Zvrko et al (2008) reported that, based on multiple logistic regression analyses, drinking >2 drinks per day [d/d] was independently related to laryngeal cancer (OR 4.96, 95% CI 2.04-12.04, p-value =0.000), but drinking >4 d/d or drinking for >40 years was not.

Figure 2.9.1 Alcohol consumption and laryngeal cancer, highest versus lowest exposure category, by study type (odds ratio/relative risk, 95% confidence intervals)



In a large UK prospective cohort study (Allen et al 2009), women drinking >15 drinks per week [d/w], compared to those drinking <2 d/w had a two-fold statistically significant increased risk of laryngeal cancer. Positive, but not statistically significant, associations were observed at all other alcohol intake levels and among non-drinkers, with no strong evidence of a statistically significant dose response relationship (*p value for trend* =0.08). Non-significant positive associations were also reported by Gallus et al (2003) for women drinking >5 d/d (*p value for trend* =0.062) compared to those drinking <3d/d. From the same study however, Garavello et al (2006), in mixed population of men and women, observed a statistically significant association at all alcohol intake levels with the highest intake category showing an approximate 500% increase in risk for >12 d/d, compared to those drinking <2 d/d, with a strong statistically significant dose response relationship (*p value for trend* <0.0001).

Two further case control studies observed positive and statistically significant associations between alcohol consumption and laryngeal cancer across all alcohol intake levels, compared to those drinking

≤2 d/d (Ramroth et al 2004) and 'occasional' drinkers (Menvielle et al 2006). Both studies reported increases of between 300% and 500% at the highest alcohol exposure category (>150 grams per day [g/d] and >12 d/d, respectively). In the remaining study, Hashibe et al (2007a) reported moderately raised risks at all intake levels (maximum of >420 grams per week) in a multi-centre hospital based case control study, with weak evidence of a dose-response relationship (*p value for trend* =0.08).

2.9.3.1 Results: total alcohol intake and risk of laryngeal cancer by tumour site

Five case controls studies reported on the association between alcohol consumption and risk of laryngeal cancer by tumour site; the glottis (the central part of the larynx), the supra glottis (the area above the glottis), or more rarely in the sub glottis. Three of the five studies also reported on the association between alcohol consumption and, the very rare, hypopharyngeal cancer (the hypopharynx is the part of the throat that lies beside and behind the larynx).

De Stefani et al (2004) observed a stronger effect of alcohol consumption on the odds of developing hypopharyngeal cancer compared to laryngeal cancer; compared to never drinkers, the odds ratio (OR) for hypopharyngeal cancer in those drinking 1-48 g/d was 2.3 (95% CI 0.7-8.1) and >192 g/d; 12.8, (95% CI 4.0-41.2, *p value for trend* <0.0001). On the other hand, cancers of the larynx displayed less impressive effects; 1-48 g/d; OR 0.8 95% CI 0.4-1.5 and >192 g/d; OR 2.5, 95% CI 1.4-4.5, *p value for trend* <0.0001. Differences between sites were of statistical significance (*p*-value for heterogeneity=0.03). Di Stefani et al (2004) also noted that whereas the effect of alcohol drinking was much higher in patients with hypopharyngeal lesions, tobacco smoking displayed higher effect in laryngeal cancer. These differences by site were statistically significant (*p*-value for heterogeneity=0.04 for tobacco and 0.02 for alcohol drinking).

In a French case control study, Menvielle et al (2004) observed statistically significant increased odds ratios at all alcohol intake levels (highest exposure level, >13 g/d) for cancers of the hypopharynx, glottis and the supraglottis. Odds ratios were of a greater magnitude for cancers of the hypopharynx (<13 g/d; OR 11.7, 95% CI 5.1-27.2) than those reported for the glottis (OR 2.9, 95% CI 1.1-7.1) and supraglottis (OR 4.1, 95% CI 1.4-11.5) though no test for heterogeneity between cancer sites was reported. In an Indian population based case control study, Sapkota et al (2007) reported no difference in the odds ratios for alcohol consumption and cancers of the supraglottis (OR 3.76, 95% CI 1.25-11.30) and hypopharynx (OR 2.22, 95% CI 1.11-4.45).

In a German study, increased risks were observed in the highest category (>150 g/d) of alcohol consumption, more than twice as high for supraglottic than for glottic and subglottic tumours (Ramroth et al 2004). This effect was not found in a study in central and eastern Europe where risk

estimates for frequency, duration, and cumulative alcohol consumption categories were moderate for both glottic and supraglottic cancers (Hashibe et al 2007).

2.9.4 Results: drinking dimensions and risk of laryngeal cancer

De Stefani et al (2004) and Hashibe et al (2007a) observed a possible dose response relationship for duration of drinking (*p value for trend* = 0.06), however, most point estimates were not of statistical significance and in only men drinking between 40-49 years in De Stefani's study was it of statistical significance. Talamini et al (2002) reported a two-fold increased risk for those drinking less than 35years, but for those drinking >35 years, compared to non-drinkers.

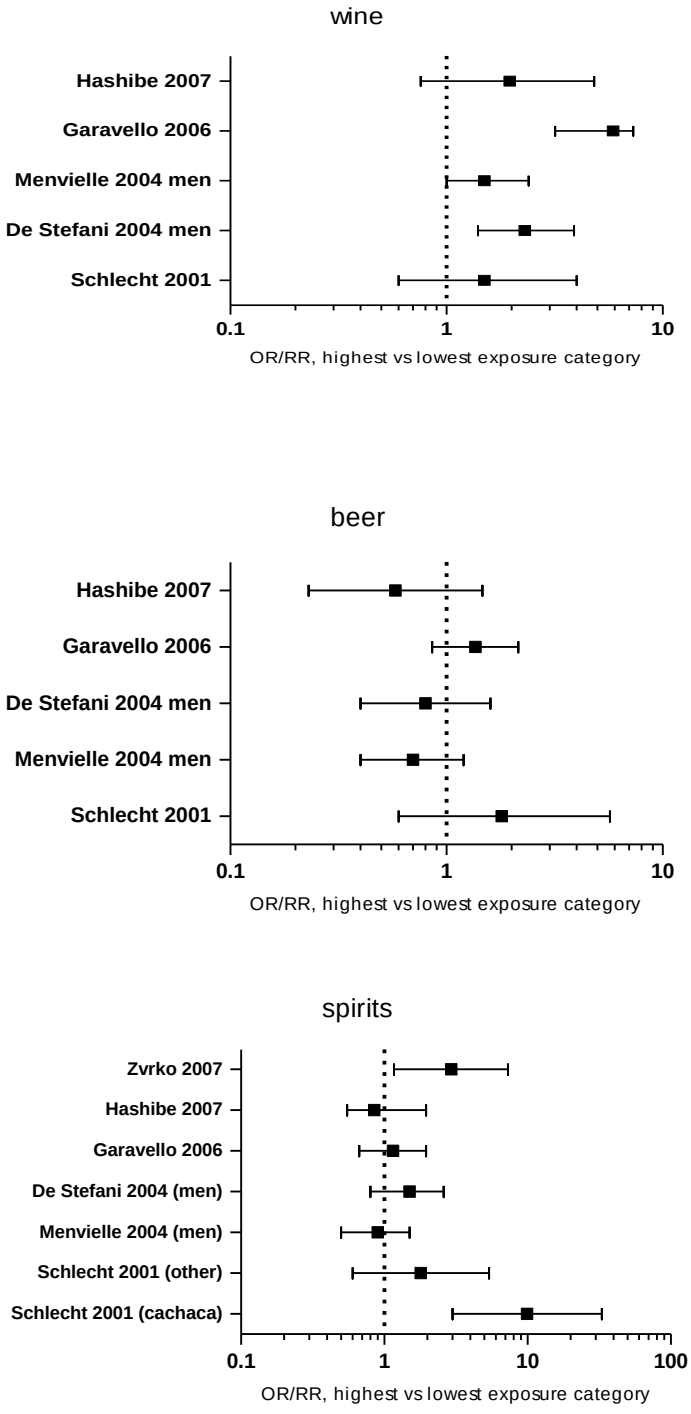
2.9.5 Results: drink type and risk of laryngeal cancer

The association between alcohol beverage type and risk of laryngeal cancer was investigated in six studies. A summary of laryngeal cancer risk estimates, comparing the highest versus the lowest alcohol exposure category, by drink type is presented in Figure 2.9.2.

Garavello et al (2006) reported that in an Italian population characterized by frequent wine consumption, wine was the beverage most strongly related to the risk of laryngeal cancer. Significant trends in risk were found wine drinkers, with odds ratios (ORs) of 1.12 95% CI 0.83-1.50 for drinkers of 3-4 d/d, and 5.91 95% CI 3.18-7.33 (*p value for trend* <0.0001) for >12 d/d, compared to abstainers or light drinkers. After allowance was made for wine intake, the ORs for beer drinkers were 1.65 (95% CI 1.31-2.10) for 1-2 d/d, and 1.36 (95% CI 0.86-2.15) for >3 d/d, as compared to non-beer drinkers; corresponding values for spirits drinkers were 0.88 (95% CI 0.70-1.11) and 1.15 (95% CI 0.67-1.96). Di Stefani et al (2004) reported similar results from a Uruguayan case control study with lifetime drinking of wine, the preferred alcoholic beverage in Uruguay having the strongest association with laryngeal cancer compared to either beer or spirits. In a French study, Menvielle et al (2004) also noted a statistically significant association among 'current' wine drinkers only, but not amongst 'current' drinkers of beer or spirits, when compared to non-drinkers.

In a study from Brazil, Schlecht et al (2001) observed an increased risk of laryngeal cancer from wine, beer and spirits, but none of the point estimates were statistically significant (Schlecht et al 2001). In this study, only cachaca, the predominant choice of alcoholic beverage in southern Brazil, displayed a strong dose response relationship in risk increase of laryngeal cancer with cumulative consumption. Zvrko et al (2007) reported statistically significant increased risks among spirit drinkers though no other drink type was reported.

Figure 2.9.2 Alcohol consumption and laryngeal cancer, by drink type (odds ratio/relative risk and 95% confidence intervals)



2.9.6 Results: effect modification

The joint effect of cigarette smoking and alcohol drinking on the risk of laryngeal cancer was examined by four studies. Talamini et al (2002) reported that, compared to never smokers and abstainers or light drinkers, the risk of laryngeal cancer increased with increasing alcohol consumption in each stratum of smoking habit. The same held true for smoking within strata of alcohol intake. The OR for highest levels of alcohol drinking and current smoking was 177.2 (95% CI 65.0-438.3), compared to non-smokers drinking less then <14 d/w. De Stefani et al (2004) also observed that both smoking and alcohol have an independent effect on laryngeal cancer risk with results following a multiplicative model, with an OR for >25 cigarettes a day and >121ml p/d, of 42.2 (95% CI 18.9-94.6), compared to those smoking <14 cigarettes per day and drinking < 60ml p/d.

Ramroth et al (2004) observed that compared to never smokers and light drinkers, the risk of laryngeal cancer increased with increasing alcohol consumption in each stratum of smoking habit. The same held true for smoking within strata of alcohol intake. The OR for highest level of tobacco and alcohol consumption was 52.6 (95% CI: 17.9, 154.6, $P_{interaction=}$0.75). In a small Italian case control study (Gallus et al 2003), the OR for women who smoked ≥15 cigarettes p/d and drank ≥3 d/d was 318 (95% CI: 71–1434), compared to never and ex-smokers drinking <3 d/d. Never and ex-smokers drinking ≥3 d/d had an OR of 1.3 (0.2–10.9). Gallus et al (2003) reported that smoking and alcohol consumption appear to have a multiplicative effect on laryngeal cancer risk ($P_{interaction=}$0.45 on the additive scale).

2.9.7 Summary and conclusions

The literature search identified 13 papers from 10 studies, which examined the association between alcohol consumption and risk of laryngeal cancer. The studies were generally of good quality and all controlled for smoking, one of the major risk factors for laryngeal cancer. Although alcohol is also considered to be an important risk factor for laryngeal cancer (IARC 1988, WCRF/AICR 2007), the evidence presented in this review is inconsistent when considering the exact nature of the dose response relationship between alcohol and laryngeal cancer. Although dose response relationships were evident in a number of studies, point estimates were only statistically significant at >5 d/d. This does not rule out an effect of low to moderate levels of drinking since many of studies included current light drinkers in their reference group. This prevented investigation of low levels of drinking on increased laryngeal cancer risk and more than likely contributed to underestimating risk at moderate and heavy levels of alcohol consumption. In a meta-analysis of twenty case control studies, Bagnardi et al (2001) reported a statistically significant increase in risk of laryngeal cancer associated with drinking 25 g/d (pooled RRR 1.38, 95% CI 1.32-1.45, *P* test for heterogeneity <0.05) and an approximate 400% increase in risk of laryngeal cancer associated with drinking on average 100 g/d.

The majority of studies investigating the association between laryngeal cancer and drink type reported a dose response effect for wine, but not beer or spirits, suggesting a possible carcinogenic effect of wine intake. However, in each of these studies, wine happened to be the most common alcoholic beverage in each of the populations studied. Previous studies have also shown increased risks of laryngeal cancer risk for beer drinkers. This different pattern of risk from studies in different populations according to type of alcoholic beverages could be due to the different level of consumption of each alcoholic beverage in these populations. The apparent discrepancy between studies can also be explained in terms of different characteristics of heavy drinkers in various populations. Thus, where wine is the most common alcoholic beverage, wine drinkers are at highest risk. Schlecht et al (2001) in their study set in southern Brazil found that the strongest statistical association was with cachaca, the most popular consumed beverage in that area. It is, therefore, likely to be ethanol per se that has an effect on laryngeal cancer rather than components of alcoholic beverages.

In a recent pooled analysis, results demonstrated that the larynx was the organ within the head and neck that was most susceptible to the effects of cigarette smoking (Hashibe et al 2007). The higher risk estimates for hypopharyngeal cancer, compared to laryngeal cancer, reported in three studies identified in the present review, may therefore suggest that the two tumour sites are distinct epidemiological entities. Since hypopharyngeal mucosa is in direct contact with alcohol, whilst on the other hand, laryngeal mucosa is most strongly exposed to inhaled tobacco, this mechanism could fit with the hypothesis that alcohol drinking may influence laryngeal cancer risk, by enhancing the effects of tobacco or other environmental carcinogens (Altieri et al 2005). However, some caution needs to be taken when interpreting the results of these studies. Notwithstanding the selection bias present in these hospital case control studies which could attenuate the risk estimates, other design weaknesses present in the studies could alter the risk estimates i.e. odds ratio based on small number of cases with hypopharyngeal cancers (De Stefani et al 2004) or high non response rates among both cases and controls (Menvielle et al 2004). This said, the effect would be the same for estimates for laryngeal cancer, therefore, hypopharyngeal cancer would still continue to show a significantly stronger association with alcohol consumption compared to laryngeal cancer. Cancers of the hypopharynx and larynx have often been analysed as a single entity in several studies in the past and this was also the case for a number of studies reviewed here, where either the risk estimates for laryngeal cancer also included hypopharyngeal cases or the outcome itself was not clearly defined by explicitly excluding hypopharyngeal cancers. The findings here would suggest that the two sites, laryngeal and hypopharyngeal, should not be analysed as a single cancer in the future.

Overall, despite weakness in study design, the small size of many of the studies and the potential for residual confounding from socio-economic status and diet, studies consistently observed a strong association between alcohol consumption and risk of laryngeal cancer. Effects of drink type were

inconclusive though the weight of evidence would suggest that alcohol itself and not the type of drink is the most important factor in determining risk of laryngeal cancer. Further studies are required to explore the effects of alcohol (and tobacco) on laryngeal and hypopharyngeal cancer.

2.10 Liver cancer

Liver cancer: summary of evidence from previous reviews
IARC 1988b concluded in their international literature review that although potential confounding due to hepatitis B virus, tobacco smoking and aflatoxin was not explored in all the studies; whenever it was, it did not alter the findings qualitatively. The available results, taken together, therefore indicated that alcohol consumption is causally related to liver cancer. (IARC 1988b). A meta-analysis of studies (3 cohort and 17 case control studies published between 1966 and 1999) on liver cancer and alcohol consumption only observed a small, and weak, statistically significant risk of liver cancer at low (25 g/d; RR 1.17, 95% CI 1.11-1.23) to moderate (50 g/d; RR 1.36, 95% CI 1.23-1.51) levels of consumption, compared to non-drinkers and even heavy levels of alcohol intake (100 g/d) only had a RR of 1.86 (95% 1.53-2.27) (Bagnardi et al 2001).

This literature review identified 11 papers from 10 studies, published between 1999 and 2009, that examined the association between alcohol consumption and the risk of liver cancer (hepatocellular carcinoma). There were two cohort studies and eight case control studies. Tables for each paper, describing the study aims, population, alcohol measurement methods and main results are provided in Appendix D.

2.10.1 Study characteristics

A summary of the general characteristics of the studies is provided in Table 2.10.1 below.

Table 2.10.1 Alcohol and liver cancer: general characteristics of studies reviewed

Authors	Year	Country	Outcome/No outcome Case/Control	Age range (M/Mdn)	Sample selection	Sample selection
Cohort studies						
Allen	2009	UK (women)	337/1,279,959	>55	breast screening clinics	random selection
Mori	2000	Japan	55/3,004	>30 (M=58)	national health screening programme	not specified
Case control studies			**cases controls**			
Donato	2002	Italy	464/824	40-75 (M=64)	2 regional hospitals	consecutive/non-random selection
Hassan	2008	USA	319/1,061	(M=60/62)	state hospital	consecutive/non-random selection
Kuper	2000	Greece	333/360	>18	city hospital	not specified
Marerro	2005	USA	210/420	(M=56/55)	city hospital	consecutive/non-random selection
Munaka	2003	Japan	78/138	34-92 (M=66/67)	city hospital	non-random selection
Ohishi	2008	Japan	224/644	(M=67)	general population	random sample
Sakamoto	2006	Japan	209/381	40-79 (Mdn=69/61)	2 regional hospitals	consecutive/non-random selection
Takeshita	2000	Japan	102/125	(M=62/60)	20 regional hospitals	consecutive/non-random selection

Abb: n/s not specified; M=mean; Mdn= median

For the majority of studies in the review, the number of liver cancer cases identified did not exceed 500; the largest case control studies in this review recruited approximately 500 cases and 800 controls (Donato et al 2002, Hassan et al 2008) and the smallest case control study recruited only 78 cases and

138 controls (Munaka et al 2003). Of the case control studies, Ohishi et al (2008) nested their study within a cohort of atomic bomb survivors in Japan, identified through Japanese cancer registries. Controls were randomly selected from the same cohort, from those who matched cases on age, gender, radiation exposure. Two studies recruited two control groups; hospital patients and patients with chronic liver disease, but without liver cancer (Sakamoto et al 2006) and patients with cirrhosis and patients with no liver disease (Marerro et al 2005).

2.10.2 Study quality

The quality scores assessed according to the NOS are presented in Table 2.10.2. Overall, studies were of a moderate to high quality, scoring between 6-7 stars.

Table 2.10.2 Liver cancer: assessment of study quality

	Selection* (out of 4)	**Comparability* (out of 2)**	**Outcome/Exposure[1]* (out of 3)**	**Total**
Cohort				
Allen 2009	4	2	3	9
Mori 2000	4	2	2	8
Case Control				
Donato 2002	3	2	3	8
Hassan 2008	3	2	2	7
Kuper 2000	3	2	2	7
Munaka 2003	2	1	1	4
Marerro 2005	2	1	3	6
Ohishi 2008	3	2	2	7
Sakamoto 2006	2	2	2	6
Takeshita 2000	3	1	3	7

* High quality characteristics within each of these items were awarded a star, up to a maximum of four stars for selection, two stars for comparability and three stars for assessment; [1] Outcome for cohort, exposure for case-control studies

Although the cohort study Mori et al (2000) scored highly on the NOS, the study lacked statistical power because of the small number of cases (n=50) identified over a follow up period of four years.

Attempts to address selection bias varied across the case control studies. Kuper et al (2000) excluded patients with conditions related to smoking and alcohol consumption, only including among their controls, patients hospitalised for injuries or for eye, ear, nose or throat (excluding laryngeal cancer) conditions. Donato et al (2002), however, excluded patients admitted to hospital with injuries because of the relation between such conditions and alcohol abuse and patients with malignant neoplasms and those admitted with liver disease. A further two studies also excluded patients with prior history of liver disease from their control group (Sakamoto et al 2006, Takeshita et al 2000). In three studies, no exclusion criteria were specified (Munaka et al 2003, Marerro et al 2005, Ohishi et al 2008).

Response rates among both cases and controls in the majority of studies exceeded 85% with the exception of Sakamoto et al (2006) which had a 73% response rate among controls and 98% among cases). In three remaining case control studies, no information was provided on response rates among

cases and controls (Marerro et al 2005, Munaka et al 2003, Takeshita et al 2000). Interviewer bias was also a potential issue for all the case control studies, since blinding status was not specified in any of the studies.

Measurement error for alcohol intake was also a potential source of bias across studies. In the cohort studies information on alcohol consumption was only collected at baseline although given the short period of follow up in both studies (<7 years), it is possible that such error would have a minimal effect. Seven of the eight cases control studies sought to measure either lifetime intake or intake at specified periods throughout a participant's drinking history. In each of these studies, questions on these aspects of an individual's drinking history were not based on validated drinking history measurement tools, but on questions designed specifically for the study. Only the case control study by Kuper et al (2000) looked at risk of liver cancer based on a consumption levels within a year of being interviewed for the study. Although this approach is less prone to measurement error noted in the other case control studies, it does not take into account the latency period for liver cancer which will be considerably longer than an individual's level of alcohol consumption over a one year period.

The three most common risk factors controlled for in studies investigating association between alcohol consumption and liver cancer were age (in all studies), the hepatitis C (and hepatitis B) virus (Mori et al 2000, Kuper et al 2001 Donato et al 2002, Sakamoto et al 2006, Ohishi et al 2008, Hassan et al 2008) and smoking (Marerro et al 2005, Sakamoto et al 2006, Takeshita et al 2000). Marerro et al (2005) further adjusted for obesity (defined as BMI> 30kg/m^2) and in one study, only age and gender were controlled for (Munaka et al 2003).

2.10.3 Results; total alcohol intake and risk of liver cancer[15]

All 10 studies reported on the dose response association between total alcohol consumption and liver cancer. Nine studies reported on the association between 'lifetime' drinking and liver cancer and one study on the association between 'recent' drinking and liver cancer (Allen et al 2009). A summary of liver cancer risk estimates, comparing the highest versus the lowest alcohol exposure category, is presented in Figure 2.10.1.

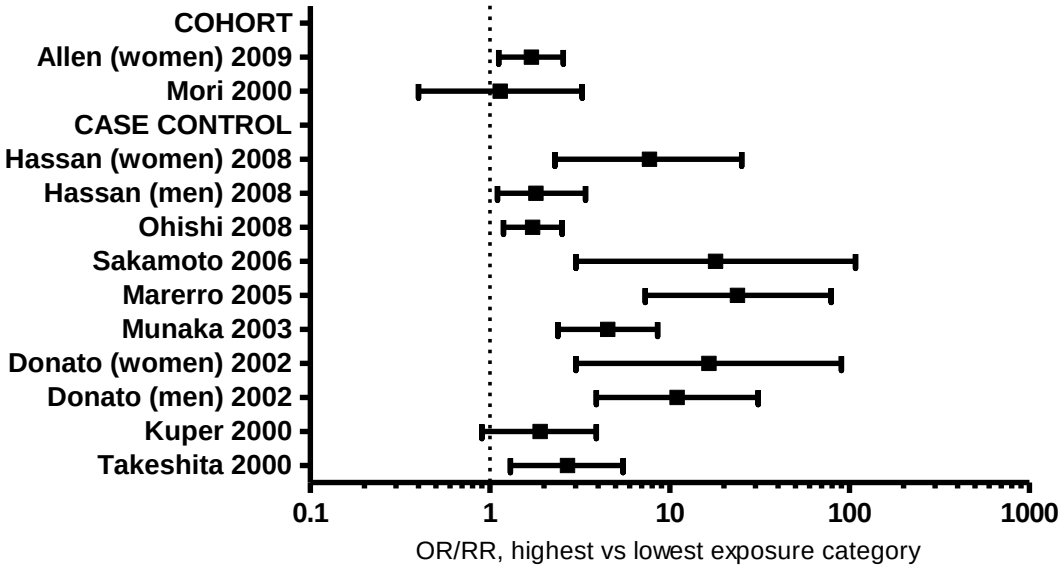
'Recent' drinking

Allen et al (2009) observed a statistically significant increased risk of liver cancer at the highest alcohol exposure category (>15 drinks per week [d/w]; RR 1.70, 95% CI 1.12- 2.56, *p value for trend* =0.03), compared to those drinking <2 d/w. In the same study, however, drinking below <3-<6 d/w was not associated with an increased risk of liver cancer (RR 0.94, 95% CI 0.72-1.21) whilst 'never-

[15] Multivariate relative risks/odds ratios are presented unless otherwise stated

drinkers had a 40% (RR 1.41 95% CI 1.16-1.72) increased risk of liver cancer compared to the reference group (Allen et al 2009).

Figure 2.10.1 Recent and lifetime alcohol consumption and liver cancer: highest versus lowest exposure category, by study type (odds ratio/relative risk, 95% confidence intervals)



Lifetime drinking

In a Japanese prospective cohort study, a history of 'habitual' alcohol consumption (those drinking at >1 d/w for ≥20 years) was associated with a non-significant 14% increased risk of liver cancer (Mori et al 2000). In the largest case control study of the alcohol-liver cancer association in the present review, Donato et al (2002) reported a statistically significant increased risk for Italian men and women drinking more than >80 grams per day [g/d] during 'peak' (i.e. intake during their decade of which consumption was the highest) exposures in their lifetime. Although there was evidence of a dose response relationship (though no *p* value for trend was reported), intake of less than ≤80 g/d was not associated with a statistically significant increased risk of liver cancer in either men or women. Donato et al. also found no strong evidence for substantial differences between men and women in the liver cancer risk curves by alcohol intake though no test for heterogeneity was undertaken. In a similar sized study in the USA, Hassan et al (2008) observed a statistically significant increase of liver cancer for lifetime heavy drinking (>60 millilitres per day [ml/d] (approximately >48 g/d[16]), compared to never drinkers. Marrero et al (2005) also reported an increased risk for liver cancer at the highest exposure level only (≥1500 gram-years[17]) compared to patient controls with no history of liver disease and also for controls with cirrhotic disease, The odds ratios among the former were four times higher than those for the latter. In a nested case controls study, Ohishi et al (2008) observed a modest

[16] one gram = approximately 1.25 milliliters
[17] gram years = average daily consumption (grams) multiplied by the total duration of alcohol exposure years

statistically significant increased risk of liver cancer for those drinking only >40 g/d during their lifetime with strong evidence of a statistically significant dose response relationship (*p value for trend* =0.008).

In three Japanese hospital case control studies, statistically significant positive associations were only evident at the highest alcohol exposure levels in each study, compared to the lowest intake group. Sakamoto et al (2006) observed a statistically significant increase in patients drinking >72 g/d in the previous two years, compared to non-drinkers. Sakamoto et al. also compared liver cancer cases to a second control group with chronic liver disease (CLD) and observed the same statistical significance at higher exposure levels as reported for hospital controls. The odds ratio for the control group of CLD patients (OR 5.0, 95% CI 1.3–19.2) was considerably lower than for the hospital controls (OR 10.2, 95% CI 1.7–60.5), but confidence intervals were wide and overlapping. Similar patterns and point estimates were also observed when the authors described history of alcohol consumption 10 years before interview and risk of liver cancer (Sakamoto et al 2006). Takeshita et al (2000) reported that higher cumulative amounts of alcohol consumption (>40 'drink-years' (drinks per day times years of drinking) over the last 30 years) showed a statistically significant association with liver cancer, compared to 0-20 'drink-years' over the last 30 years. Compared to non-drinkers, Munaka et al (2003) reported an increased risk of liver cancer for those drinking >600,000 ml (cumulative amount) during their lifetime, but no association was found at lower intake levels.

2.10.4 Results: drinking dimensions and risk of liver cancer

There were no studies investigating the associations between drinking dimensions (e.g. duration, frequency, pattern) and risk of liver cancer identified in this review.

2.10.5 Results: drink type and risk of liver cancer

There were no studies investigating the associations between drink type and risk of liver cancer identified in this review.

2.10.6 Results: effect modification

Two studies looked at interaction between hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (HCVAb). In a prospective cohort analysis based on 52 incident liver cancer cases, Mori et al (2000) reported that there was no significant interaction on both the additive or multiplicative scale, between HBsAg and HCVAb status and a history of habitual alcohol consumption. Donato et al (2002), reported higher odds-ratio values for cases with hepatitis C virus infection, followed by those with hepatitis B virus infection and finally by those without hepatitis virus infection; the OR for drinking >60 g/d was 7.0 (95% CI 4.5-11.1) for cases negative for both infections, whereas the ORs for drinking >60 g/d were, 109.0 (95% CI 50.9-233.0) for cases positive for HCVAb and 48.6 (95% CI 24.1-98.0) for cases positive for HbsAg, compared to drinkers of 0-60 g/d who were negative for

both infections. There was no significant interaction on the additive scale ($P_{interaction}$ >0.1), suggesting a multiplicative effect of hepatitis virus infection.

Kuper et al (2000) reported that heavy smoking (≥2 packs p/d) and heavy drinking (≥400 grams per week [g/w]) increased the odds (OR 9.6, 95% CI 3.4-27.5) of liver cancer occurring, compared to never smokers drinking <400 g/w. Heavy smokers drinking <400 g/w had an OR of 1.5 (95% CI 0.6-3.9). There was strong evidence of a statistically significant ($P_{interaction}$=0.0001) interaction on the multiplicative scale. Marerro et al (2005) evaluated the interactions of alcohol consumption, tobacco smoking, and obesity on the risk of liver, by comparing liver cancer patients with cirrhotic controls. They found that when compared to patients with lifetime exposure to tobacco (OR 2.5, 95% CI 1.7-15) or alcohol (OR 1.4, 95% CI 1.1-4.0) only, the risk of liver cancer was higher when both risk factors were present (OR 7.2, 95% CI 2.2-14.1). An increase in risk of liver cancer was also observed when exposure to alcohol was present with obesity (>100 drinks in lifetime and BMI > 30kg/m^2, OR 5.5, 95% CI 1.8-20). To assess whether the interactions between the alcohol, tobacco and obesity were additive or synergistic, Marrero et al calculated a Synergism index, and its 95% CI, based on the estimated odds ratio of the risk factors. A value greater than the reference unit (1.0) suggests that the effect of the joint exposures of two risk factors, is greater than the sum of the separate effects. Marrero et al (2005) reported that the synergistic indices for the interaction between alcohol and tobacco, tobacco and obesity, and alcohol and obesity were 3.3 (95% CI 1.8-5.7), 2.9 (95% CI 1.8-3.5) and 2.5 (95% CI 1.6-4.9), respectively. When all three variables were analysed together, the synergistic index was 1.6 (95% CI 1.1-4.3), indicating a possible synergism between the effects of alcohol, tobacco and obesity on the risk of liver cancer in their study population.

2.10.7 Summary and conclusions

This literature review identified two prospective cohort and eight case control studies, published between 1999 and 2009, examining the association between alcohol consumption and liver cancer.

The majority of studies reported on the association between 'lifetime drinking' and liver cancer. Despite considerable variation in measures of lifetime drinking, the majority of studies were consistent in observing a statistically significant increased risk of liver cancer at the highest levels of alcohol exposure (approximately >40 g/d), consistent with the findings of earlier studies (La Vecchia et al 1988, Tanaka et al 1992; 1995, Adami et al 1992). The evidence of an association between drinking <40 g/d and an increased risk of liver cancer was less convincing, with only a few studies reporting small, non-significant, positive associations with liver cancer. This could imply a threshold effect of alcohol drinking on the risk of liver cancer, however, a stronger effect of low to moderate levels of alcohol intake on the risk of liver cancer cannot by fully ruled out due to the range of reference groups used across the studies, recall bias in measuring lifetime drinking and small study

sizes. A previous meta-analysis of studies (3 cohort and 17 case control studies published between 1966 and 1999) on liver cancer and alcohol consumption only observed a small, and weak, statistically significant risk of liver cancer at low (25 g/d; RR 1.17, 95% CI 1.11-1.23) to moderate (50 g/d; RR 1.36, 95% CI 1.23-1.51) levels of consumption, compared to non-drinkers and even heavy levels of alcohol intake (100 g/d) only had a RR of 1.86 (95% 1.53-2.27) (Bagnardi et al 2001). A recent meta-analysis, of six cohort studies, reported a summary effect estimate of 1.10 (95% CI 1.02-1.17) per 10 g/d with no heterogeneity, though no *p* values were provided (WCRF/AICR 2007).

It has been hypothesised that the relationship between alcohol and liver cancer could differ for men and women; for women, a higher susceptibility to liver damage due to alcohol has been suspected on the basis of metabolic differences (Frezza et al 1990). A meta-analysis of the association between alcohol consumption and the risk of liver cancer based on ten studies for men and three for women, reported the effects of gender in modifying the effect of alcohol intake reaching statistical significance, with higher risks in women (Bagnardi et al 2001). Two studies in this review reported analyses of the association between alcohol consumption and liver cancer by gender with mixed results. Donato et al (2002) found no strong evidence, despite higher risk estimates among men, for substantial differences between men and women in the liver cancer risk curves by alcohol intake. However, because of the small number of women who drank a medium-high amount of alcohol in this study, these results should be considered cautiously. In contrast, Hassan et al (2008) reported higher odds ratios from women compared to men, but again estimates for women were based on less than twenty drinkers among cases and controls and accordingly confidence intervals were wider and overlapped those for men. No definite conclusion, therefore, on gender differences in the strength of the association between alcohol consumption and risk of liver cancer can be drawn at present and larger studies or further meta-analyses are necessary to explore this further.

It has also been hypothesized that heavy alcohol consumption may lead to liver cancer only through the production of liver cirrhosis as an intermediate step (Adami et al 1992). Alcohol may further promote the development of liver cancer by increasing tumour growth in people with cirrhosis or other chronic liver diseases (Mukaiya et al 1998). This hypothesis was not supported by the two studies in this review which looked at the effects of alcohol consumption on risk of liver cancer in two control groups of chronic liver disease and non-chronic liver disease patients, both of which found higher risks among their control groups of non chronic liver disease patients. This review does support, however, previous observations (Donato et al 1997, Tagger et al 1999), that alcohol drinking has a “pure” effect in increasing the risk of liver cancer and that its effect can be modified by hepatitis B or hepatitis C virus infection. An interactive effect of heavy smoking and heavy drinking in the development of liver cancer was found in two studies. This interaction is biologically plausible because tobacco smoke contains several mutagenic initiating agents as well as potential promoting agents, and heavy alcohol drinking is likely to have a promoting or growth-enhancing effect via the

process of cirrhosis. Thus, smoking and alcohol could act together along the same pathway resulting in liver cancer. In one study, no interaction between smoking, alcohol consumption and obesity was reported. Obesity, particularly central obesity, is however, associated with non-alcoholic fatty liver disease which increases the risk of cirrhosis and liver cancer. An interaction between obesity and alcohol intake has been identified in studies with chronic liver disease as the outcome (Liu et al 2010, Hart et al 2010) and it is likely that tobacco exposure further increases the risk. Indeed a similar synergistic effect between alcohol, tobacco and obesity has been observed in patients with oesophageal and stomach cancer (Marerro et al 2005). A limitation to these observations concerns the small samples inherent in subgroup analysis which restricts the precision of the risk estimates. Nevertheless these findings are consistent in suggesting an interactive effect of various lifestyle factors and an increased risk of liver cancer and underline the difficulty in unravelling the precise dose response relationship between alcohol consumption and increased risk of liver cancer.

Although the major risk for liver cancer development has been attributed to the hepatitis B and hepatitis C virus evidence other risk factors including history of cigarette smoking, heavy alcohol consumption and obesity may also contribute to the development of liver cancer. Research investigating the interactions of hepatitis B or C virus with lifestyle factors may provide further insight into the multi-factorial aetiology of liver cancer. In sum, the evidence in this review confirms established evidence of an increased risk of liver cancer from heavy/excessive alcohol consumption. Given that the development of liver cancer is a multistage, multi-factorial process the relative role of alcohol is likely to vary between countries depending on the prevalence of the other risk factors, particularly viral infection and obesity.

2.11 Lung cancer

Lung cancer: summary of evidence from previous reviews
Earlier systematic reviews concluded that In view of the lack of excess risk in case-control studies and the inconsistent results of cohort studies, there is no indication that alcohol consumption has a causal role in lung cancer (IARC1988b, WCRF/AICR 1997, Bandera et al 2001). In a meta-analysis of twelve cohort and thirteen case control studies published before 1999 reported that the evidence for a smoking-adjusted association between alcohol and lung cancer risk was limited to very high consumption groups (>60 g/d) in cohort and hospital-based case-control studies (Korte et al 2002).

The literature search identified 15 papers from 13 studies, published between 1 January 1999 and 30 September 2009, which examined the relationship between alcohol consumption and lung cancer. Of the 15 papers, eight were prospective cohort studies and five were case control studies with one case control study contributing two papers to the present review. Both papers were retained as they reported on different aspects of the alcohol and lung cancer association: 'recent' (Benedetti et al 2006) and lifetime alcohol consumption (Benedetti et al 2009). The literature search also identified one pooled analysis which was retained in the review; in the pooled analysis by Freudenheim et al (2005), six of the seven prospective cohort studies included had not previously published findings on the alcohol and lung cancer association during the search period covered by the present review.

2.11.1 Study Characteristics

A summary of the general characteristics of the studies is provided in Table 2.11.1 below. Tables for each study describing the study aims, population, alcohol measurement methods and main results are provided in Appendix D. Two papers were based on the established prospective cohort studies described in Box 2.1 Chapter 2.2; the Copenhagen City Heart study (Prescott et al 1999); and the European Prospective Investigation into Cancer and Nutrition (Rohrmann et al 2006).

A pooled analysis by Freudenheim et al (2005) was based on the 'Methods for the Pooling Project of Prospective Studies of Diet and Cancer' and included approximately 3,300 lung cancer cases. Inclusion criteria for cohort studies in the pooled analyses were >50 incident cases of lung cancer, an assessment of usual diet, a validation study of the diet instrument or of a closely related instrument, and assessment of smoking status at baseline. Seven cohort studies were included: the Canadian National Breast Screening Study, the Iowa Women's Health Study, the Netherlands Cohort Study, the New York State Cohort, the Tocopherol Carotene Cancer Prevention Study (see Woodson et al 1999), the Nurses' Health Study (see Section 2.4) and Health Professionals Follow-up Study (see Section 2.4).

The largest cohort study identified in the present review included approximately 5,000 incident cases of breast cancer (Allen et al 2009) and has been previously described in section 2.3.1. Two cohort

studies (Woodson et al 1999, Rohrmann et al 2006) and one case control study (Benedetti et al 2006) were of reasonable size, identifying over 1000 lung cancer cases

Table 2.11.1 Alcohol and lung cancer: general characteristics of studies reviewed

Authors	Year	Country	Outcome/No outcome Case/control	Age range (M/Mdn)	Sample base	Sample selection
Cohort studies						
Allen	2009	UK (women)	5,203/1,275,093	>55	breast screening clinics	random selection
Chao	2008	USA	210/83,960	45-69	state medical care programme	random selection
Djoussé	2002	USA	269/9,016	28-62	town	random selection
Freudenheim	2005	Various	3,317/396,630	>15	various	various
Prescott	1999	Denmark	674/27,486	>20	local population	random selection
Rohrmann	2006	Various	1,119/477,471	n/s	various	random selection
Shimazu	2008	Japan (men)	651/45,696	40-69	4 health authority areas	random selection
Toriola	2009	Finland (men)	65/2,202	42, 48, 54 and 60	regional population	representative sample
Woodson	1999	Finland (male smokers)	1059/26,052	50-69	regional population	random selection
Case control studies						
Benedetti	2006	Canada	1,795/2,000 and 700/570	35–75	city hospitals /state electoral lists	consecutive/random selection
De Stefani	2002	Uruguay	160/520	30-89	city hospitals	consecutive/random selection
Freudenheim	2003	USA	206/3,624	35-79	hospital/state driver license lists	consecutive/random selection
Kubık	2004	Czech Republic (women)	435/1,710	25–89	city hospital	consecutive/random selection
Ruano-Ravina	2004	Spain	132/187	M=64/62	city hospital	consecutive/random selection

Abb.: n/s= not specified; M=mean; Mdn= median

2.11.2 Study Quality

The quality scores assessed according to the NOS are presented Table 2.11.2. Cohort studies were of a high quality scoring 7-9 stars whilst case-control studies varied in quality with star ratings ranging from 4-7.

Selection bias, as measured by the NOS, was generally avoided in the cohort studies, with only two studies failing to achieve maximum stars because either their study population was a specific population subgroup i.e. teachers (Chao et al 2008) or they did not specify the exclusion of previous cases of lung cancer from their study population (Prescott et al 1999). For outcome assessment, Chao et al (2008) only had a follow-up period of four years (300,516 person-years) thereby reducing the study's power to detect a true association between lung cancer and alcohol consumption. Four cohort

studies failed to specify whether there was any loss to follow-up in their studies and in one European wide study different methods of outcome measurement were used depending on the country, with lung cancer diagnoses being based on population registries or by active follow-up through information obtained from study subjects, next of kin, health insurance records, and cancer and pathology registries (Rohrmann et al 2006).

Table 2.11.2 Lung cancer: assessment of study quality

	Selection* (out of 4)	Comparability* (out of 2)	Outcome/Exposure[1]* (out of 3)	Total
Cohort				
Allen 2009	4	2	3	9
Chao 2008	3	2	3	8
Djoussé 2002	4	2	2	8
Prescott 1999	3	2	3	8
Rohrmann 2006	4	2	1	7
Shimizu 2008	4	2	2	8
Toriola 2009	4	2	2	8
Woodson 1999	4	2	3	9
Case-control				
Benedetti 2006	3	2	2	7
De Stefani 2002	1	2	1	4
Freudenheim 2003	3	2	1	6
Kubik 2004	2	2	2	6
Ruano-Ravina 2004	3	2	2	7

* High quality characteristics within each of these items were awarded a star, up to a maximum of four stars for selection, two stars for comparability and three stars for assessment. [1] Outcome for cohort, exposure for case-control studies

Smoking and age were controlled for in all studies. The majority of studies controlled for 'current' smoking status (current, never, and former, which included the number of years since quitting), current smoking (cigarettes smoked per day) and duration of smoking (which was either measured by length of time smoked in years or in 'pack-years' calculated by multiplying amount smoked by smoking duration). Two studies controlled for 'current' smoking status and for cigarettes smoked per day (De Stefani et al 2002) or duration of smoking (Shimizu et al 2008). Two studies reported only controlling for length of time smoked (Kubik et al 2004, Ruano-Ravina et al 2004). In addition, two studies controlled for the effects of passive smoking; Freudenheim et al (2003) controlled for lifetime smoke exposure at home, at work and 'in other settings' and Shimizu et al (2008) controlled for passive smoking in the workplace (exposure of between 1-3 days/month, 1-4 days/week, and almost every day).

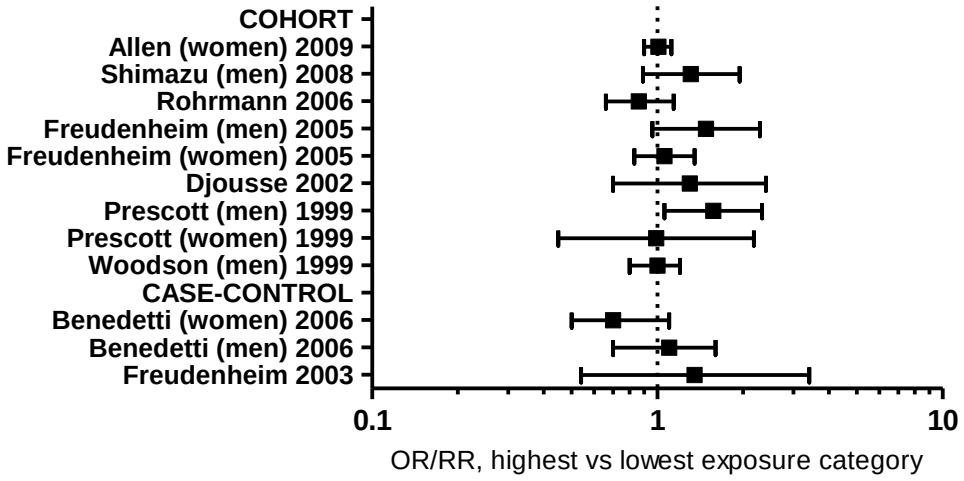
One study attempted to fully control for the effects of socio-economic status on the alcohol-lung cancer association; a summary index was developed that combined measures of income, education, occupation, occupational 'prestige', material standard of living and housing conditions (Toriola et al 2009). Two studies controlled for both years of schooling and household family income (Benedetti et al 2006, Chao et al 2008). Education was controlled for in eight studies though this varied from level of education (high school, university, no education) to years of schooling; and type of occupation in

one study (Ruano-Ravina et al 2004). Two studies did not control for any SES measures (Woodson et al 1999, Shimizu et al 2008).

2.11.3 Results: total alcohol intake and risk of lung cancer[18]

One pooled analysis, six cohort and two case-control studies, reported on the association between lung cancer and total 'recent' alcohol consumption. A summary of lung cancer risk estimates, comparing the highest alcohol exposure category versus the lowest alcohol exposure category, is presented in Figure 2.11.1. The highest alcohol exposure categories reported ranged from low (12 grams per day [g/d]; Benedetti et al 2006) and moderate levels of drinking (20-25 g/d; Djoussé et al 2002, Allen et al 2009) to >60 g/d (Rohrmann et al 2006, Shimizu et al 2008). In the remaining studies, the highest alcohol intake group reported was approximately 30-40 g/d. Two papers used a reference group comprising of non-drinkers, including former drinkers (Djoussé et al 2002, Freudenheim et al 2005) with the remaining papers using a reference group of occasional and low level drinkers (>0 to 10 g/d).

Figure 2.11.1 Alcohol consumption and lung cancer, highest versus lowest exposure category, by study type (odds ratio/relative risk and 95% confidence intervals)



[18] Multivariate relative risks/odds ratios are presented unless otherwise stated

In the pooled analysis by Freudenheim et al (2005), an increased risk of lung cancer was observed at the highest alcohol exposure category (>30 g/d) in both men (RR 1.21, 95% CI 0.91-1.61) and women (RR 1.16, 95% CI 0.94-1.43), though confidence intervals were wide and crossed the null value, with weak evidence of a dose response trend (*p value for trend* =0.03). In two prospective cohort studies of similar size, Prescott et al (1999) and Shimizu et al (2008) reported an increased risk of lung cancer in men, drinking at the highest alcohol intake level, of similar magnitude to that reported by Freudenheim et al (2005). There was convincing evidence of an increased risk of lung cancer with increasing amount of alcohol consumed in the study by Prescott et al. (*p value for trend* =0.002), but not in the study by Shimizu et al. (*p value for trend* =0.07). In a cohort of male smokers, however, drinking at any level up to a median of 42 g/d (RR 1.0, 95% CI 0.8-1.2, *p value for trend* =0.89), was not associated with an increased risk of lung cancer (Woodson et al 1999). Benedetti et al (2006) also observed no association between low levels of alcohol consumption (<1 d/d) and risk of lung cancer in men in their population based case control study.

The small increased risk of lung cancer for women at the highest alcohol intake level, reported above by Freudenheim et al (2005), was not repeated in two prospective cohort studies; Allen et al (2009) in the largest study identified in the present review of alcohol intake and lung cancer risk in women, did not find an increased risk of lung cancer reported for women drinking approximately >20 g/d (*p value for trend* =0.20) and lung cancer and Prescott et al (1999) for women drinking >30 g/d (*p value for trend* =0.94). Allen et al (2009) did observe, however, an inverse association between three and six drinks per week (d/w) (RR 0.91, CI 95% 0.85-0.97) and risk of lung cancer in women. A possible protective effect (RR 0.78, 95% CI 0.65-0.94) of low level (>0-<5g/d) and moderate levels (5-<15g/d; RR 0.84, 95% CI 0.69-1.03) of drinking was also reported in the pooled analysis paper (Freudenheim et al 2005). Similar findings for women drinking between 1-6 d/w were reported by Prescott et al (1999) and Rohrmann et al (2006). In a Canadian case control study (Benedetti et al 2006), women drinking ≥7 d/w had a reduced risk of lung cancer (OR 0.7, 95% CI 0.5-1.1) with this protective effect stronger for women drinking 1-6 d/w (OR 0.4, 95% CI 0.2-0.5), compared to non-drinkers.

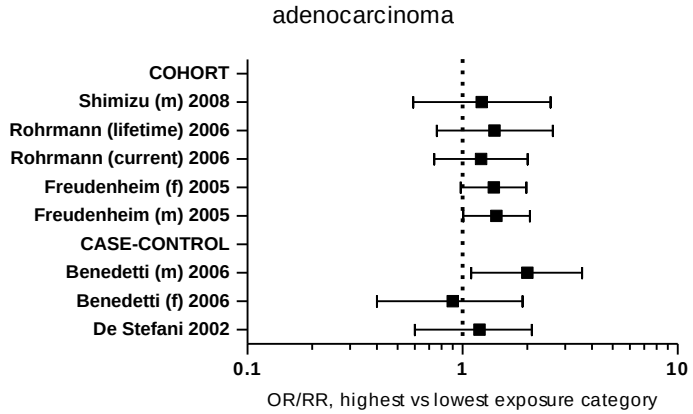
Three studies reported on the association between 'lifetime' alcohol consumption and lung cancer. In a large prospective cohort study (Rohrmann et al 2006), mean lifelong ethanol intake of >60 g/d was related to a non-statistically-significantly higher risk (RR 1.29, 95% CI 0.93-1.74) of lung cancer compared to 'low level' drinkers (0.1-4.9 g/d) whilst lifelong non-drinkers did not have an elevated risk of lung cancer. Similar odds ratios were reported in two case control studies for weekly drinking >7d/w (Benedetti et al 2009) and average weekly lifetime intake of > 3.5 d/w (Freudenheim et al 2003).

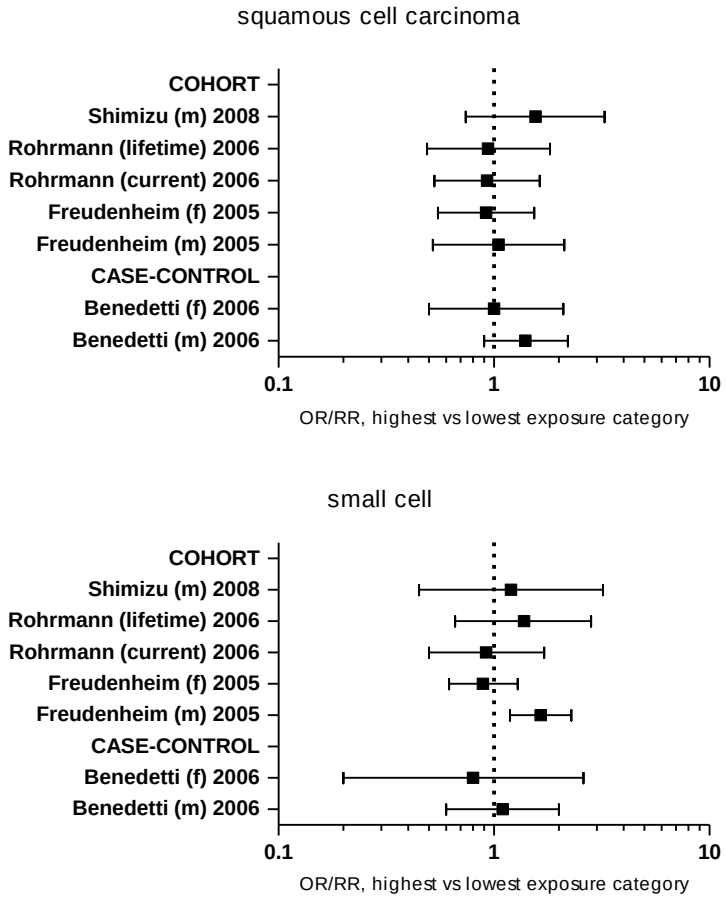
2.11.3.1 Results: alcohol and risk of lung cancer by histological subtype

Five papers reported on the association between alcohol consumption and lung cancer by histological subtype (adenocarcinoma, small cell and squamous cell). Overall, across the majority of studies, when comparing the highest alcohol exposure to the lowest exposure category, the effect of alcohol consumption was stronger and more consistent across studies for adenocarcinoma of the lung, compared to squamous cell (SCC) of the lung and small cell carcinoma. However, point estimates for all tumour types were rarely of statistical significance and with wide confidence intervals. A summary of lung cancer risk estimates, comparing the highest versus the lowest alcohol category by histological subtype, is presented in Figure 2.11.2

The pooled analysis of seven prospective cohort studies by Freudenheim et al (2005) contained the largest number of lung cancer cases for each histological subtype (approximately 600 cases). In this analysis, there was some evidence that alcohol consumption at the highest alcohol exposure (>30 g/d), compared to non-drinkers, was more strongly associated with the risk of adenocarcinoma in both men (RR 1.44, 95% CI 1.10-2.06 *p value for trend* =0.10) and women (RR 1.40, 95% CI 0.98-1.98 *p value for trend* <0.01), and with the risk of small cell tumours in men (RR 1.65, 95% CI 1.19-2.29, *p value for trend* <0.01). However, intake at lower levels was not associated with an increase in risk of any tumour type and the difference in the RRs was not significant; for men and women drinking >30 g/d category (Freudenheim et al 2005).

Figure 2.11.2 Alcohol consumption and lung cancer, highest versus lowest exposure category, by histological type (odds ratio/relative risk and 95% confidence intervals)





2.11.4 Results: drinking dimensions and risk of lung cancer

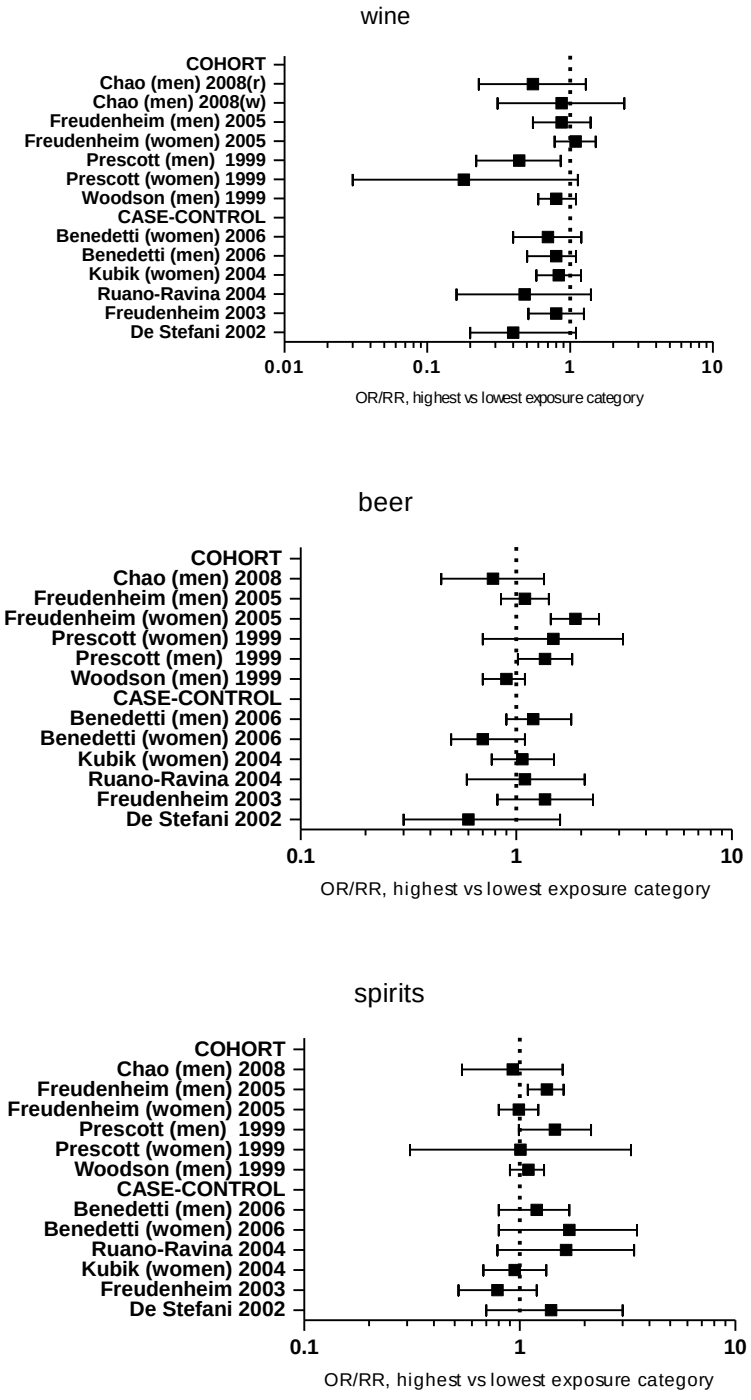
One study, from Finland, reported on the association between 'binge' drinking, defined as drinking >70 grams[19] in one drinking session, in men and risk of lung cancer (Toriola et al 2009). The RR of lung cancer among binge drinkers in the whole cohort was 1.89 (95% CI 1.10-3.20) compared to non-binge drinkers in men. In an analysis restricted to smokers alone, the RR of lung cancer among binge drinking smokers, compared with non-binge drinking smokers, was 1.79 (95% CI 1.03-3.12).

2.11.5 Results: drink type and risk of lung cancer

Nine studies reported on the risk of lung cancer by type of alcoholic drink (beer, wine and spirits). A summary of lung cancer risk estimates from all the studies comparing the highest versus the lowest alcohol category is presented in Figure 2.11.3.

[19] equivalent to the consumption of (i) six or more bottles of beer; (ii) one or more big bottle (75 cl) of mild wine;(iii) three-fourth or more of one big bottle (75 cl) of strong wine and (iv) >5 portions of hard liquor

Figure 2.11.3 Alcohol consumption and lung cancer, highest versus lowest exposure by drink type (odds ratio/relative risk and 95% confidence intervals)



In a cohort study, comprising of male teachers, Chao et al (2008) did not find any clear association between risk of lung cancer and beer, white wine, and spirit drinking. The RR estimates for consuming ≥1 d/d of beer, white wine, and liquor were 0.78 (95% CI 0.45-1.35), 0.87 (95% CI 0.31-2.40), and 0.93 (95% CI 0.54-1.58). An inverse association for red wine intake, however, was suggested by a linear model in which level of red wine intake was modelled as a continuous variable (RR 0.98; 95% CI 0.97-1.00; *p value for trend* =0.06).

2.11.6 Results: effect modification

Four studies examined the interaction between alcohol and smoking on the risk of lung cancer. In a pooled analysis, Freudenheim et al (2005) reported a statistically significant increased risk of lung cancer in men who had never smoked and who drank ≥15 g/d (RR 6.38, 95% CI 2.74-14.9; *p value for trend* <0.001), compared to non-smokers and non-drinkers. No association was observed with lung cancer for men who were current smokers and who drank up to and including ≥15 g/d. For women who were non-smokers, and drinking ≥15 g/d, the increase was more modest and the confidence interval included the null (RR 1.35, 95% CI 0.64-2.87; *p value for trend* =0.98), but the estimate was based on only 8 cases. There was no association with lung cancer among women who were current smokers and drinking up to and including ≥15 g/d.

Rohrmann et al (2006), however, in a European prospective cohort study, reported no association between lung cancer and never smokers who were non-drinkers, and or who drank between 5-60 g/d, compared to those drinking 0.1-4.9 g/d. Former and current smokers who were non-drinkers had a modest non-significant increased risk of lung cancer (45% and 27% respectively), but no association was reported at any alcohol intake level up to ≥60 g/d for former and current smokers**.** In a Japanese cohort (Shimizu et al 2008), the relative risk for male non-smokers who drank >450 g/w compared with occasional drinkers was 0.58 (95% CI 0.26-1.30, *p value for trend* =0.49). Among current smokers (defined by length of time an individual smoke), the RR of lung cancer for men who drank >450 g/w, compared with occasional drinkers, was 1.69 (95% CI 1.05–2.72, *p value for trend* =0.02).

In a Canadian case-control study, Benedetti et al (2006) observed no strong evidence of any effect modification by cigarette smoking in men or in women drinking >7 d/w, compared to those who never drank weekly. This lack of relationship was consistent across all categories of smoking; light, moderate and heavy smoking *($P_{interaction}$*=0.52 and 0.54 in men and women, respectively).

2.11.7 Summary and conclusions

This review identified 14 papers (seven prospective cohort studies, five case control studies, one pooled analysis and one meta-analysis), published between 1999 and 2009, that examined the

association between alcohol consumption and lung cancer. Studies were of moderate to high quality. Overall, there was inconsistent evidence of an association between alcohol consumption and lung cancer perhaps as a result of the strong effect of smoking on lung cancer risk, the likely weak effect of alcohol, the heterogeneity of reference groups and the different size of the studies. The large prospective cohort studies in the present review (including the pooled analysis) provided weak evidence for an association between alcohol consumption and lung cancer risk. Evidence of a dose response trend in risk was weak and confidence intervals for the risk estimates in the highest alcohol consumption category (>30 g/d) included the null. Although the evidence of a weak positive association was more consistently observed in men, too few studies reported women drinking at comparable levels to men and evidence of a gender differences in lung cancer risk associated with alcohol consumption in the pooled analysis was inconclusive. A weak association between high levels of alcohol consumption and lung cancer risk reported in the present study is consistent with the findings of other reviews (Bandera et al 2001, WCRF/AICR 2007) and that reported in a meta-analysis of twelve cohort and thirteen case control studies published before 1999 which reported that the evidence for a smoking-adjusted association between alcohol and lung cancer risk was limited to very high consumption groups (>60 g/d) in cohort and hospital-based case-control studies (Korte et al 2002).

In three prospective cohort studies, low levels of drinking were reported to be protective, against lung cancer in women, but not in men though in each study different reference groups were used; 0 grams per day (Freudenheim et al 2005), <1 d/w (Prescott et al 1999) and not drinking weekly (Benedetti et al 2006). In each study, former drinkers were also included in the reference. Boffetta (2005) observed that whilst it might be possible to provide a mechanistic interpretation for these findings e.g., by postulating a stronger reduction in C-reactive protein concentrations among female than male drinkers, as suggested in a few studies (Stewart et al 2002, Albert et al 2003), the suggestion of a protective effect should be treated with caution until replicated in other large cohort studies.

It has been previously reported that the effect by alcoholic beverage type on the risk of lung cancer is not clear, but studies seem to indicate that beer and spirits may increase risk, whereas moderate wine consumption may be protective (Bandera et al 2001). The findings of this review, based primarily on a meta-analysis of studies reporting on the association between drink type and lung cancer (Chao 2007), support the hypothesis of a protective effect of wine compared to an increased risk observed from spirit and beer drinking. Chao (2007) in a meta-analysis of cohort and case control studies published before February 2007, observed an inverse association for wine drinking and lung cancer risk when all studies (case control and cohort studies) were combined and in all subgroup analyses. The inverse association was suggested for both the average drinking level of <1 d/d (for all studies: RR 0.77, 95% CI 0.59-1.00, *p test for Heterogeneity* <0.01) and for ≥1 d/d (for all studies: RR 0.78, 95% CI, 0.60-1.02, *p test for Heterogeneity* =0.03). The meta-analysis showed a positive association (RR

1.25; 95% CI 1.06-1.48, *P* value for test of heterogeneity 0.11) between average beer drinking of ≥1 d/d and lung cancer risk. For average beer drinking of <1 d/d, an inverse association was suggested (RR 0.78; 95% CI 0.64-0.95, *p test for Heterogeneity*=0.01). This J-like pattern for the dose-specific risk estimates was found in both case-control and cohort studies. Average liquor consumption of ≥1 d/d was also found to be significantly associated with increased lung cancer risk (RR 1.25, 95% CI 1.04-1.51, *p test for Heterogeneity*= 0.02).

A protective effect from wine drinking may also support the inverse association observed for low levels of drinking and lung cancer in women who are more likely to be wine drinkers than men, though this could be mediated by the association of both wine drinking and smoking with social class Furthermore, what is not clear, is whether drinking heavy amounts of wine increase the risk of lung cancer since estimates by Chao (2007) are for low to moderate levels of drinking (>1 d/d). Studies included in this review were unable to report on this aspect since so few drinkers in their study population drank large amounts of wine.

Previously the relationship with alcohol by lung cancer cell type has been questioned due to inconsistent findings based on very small numbers with reported differences being attributed to chance (Bandera et al 2001). Overall, in this review a stronger effect for adenocarcinoma of the lung from drinking alcohol was reported, compared to SCC and small cell tumours although estimates again were based on small numbers. This effect was observed across all five prospective cohort studies reporting on this aspect of the alcohol-lung cancer association. Chance findings due to measurement bias, misclassification of tumour type or residual confounding from smoking or other risk factors may well explain the increased risk of adenocarcinoma of the lung, but the fact that this association with alcohol consumption was observed consistently across cohort studies merits further investigation.

Selection and measurement bias may contribute to some of the associations reported for overall alcohol intake, drink type and histological sub-type, but the main concern in the interpretation of these associations is residual confounding by some other factors. Boffetta (2005) observed that residual confounding by tobacco smoking is one of the main concerns in the interpretation of the increased risk among heavy drinkers. Heavy drinkers may also be more than likely to be heavy smokers and misclassification of smoking exposure at these high levels may well explain some of the associations reported (Korte et al 2002). Although all of the studies included in this review considered cigarette smoking as a confounder of this association, it was controlled for in different ways, undoubtedly resulting in varying degrees of residual confounding by smoking. Measurement error in measured aspects of smoking (i.e., smoking status, duration of smoking, and amount smoked) and variations in other unmeasured aspects (i.e., depth of inhalation and length of time that smoke is held in the lungs) may have an effect on the estimation of the risk of lung cancer from other factors correlated with

smoking, such as alcohol (Bandera et al 2001, Zang et al 2001, Freudenheim et al 2005). Recent simulations have also suggested that even a moderate misclassification of smoking status might explain most of the results reported in the literature (Korte et al 2002, Fewell et al 2007). Residual confounding from smoking may, however, only be part of the answer. Very few studies in this review fully controlled for socio-economic status (SES) despite the well established links between SES and lung cancer incidence and mortality (van Loon et al 1995a; 1995b, Brown et al 1997, Singh et al 2002). Residual confounding from SES could well explain some of the associations, positive and negative, reported between lung cancer and specific drink types. Furthermore, the effects of diet were poorly addressed in all studies included in this review and some weak evidence exists of a possible effect modification by dietary factors such as Vitamin A or vegetable intake (Bandera et al 2001).

In conclusion, there is some weak evidence of an association between alcohol consumption and risk of lung cancer though this is only apparent for consumption of more than thirty grams per day. Drink type, especially wine, may modify the effect of alcohol on the risk of lung cancer. Residual confounding from smoking, SES or diet is likely to explain these associations.

2.12 Oesophageal cancer

Oesophageal cancer: summary of evidence from previous reviews
Epidemiological studies clearly indicate that alcohol consumption is causally related to cancer of the oesophagus. There is no indication that the effect is dependent on type of beverage (IARC 1988b, WCRF/AICR 1997).

The literature search identified 26 papers from twenty three studies, published between 1999 and 2009, which examined the relationship between alcohol consumption and oesophageal cancer. There were six prospective cohort studies and 20 case control studies. Three papers, derived from two pooled case control studies carried out in Italy and Switzerland, were retained in the review because each paper reported on a different aspect of the relationship between alcohol and oesophageal cancer; risk among men (Zambon et al 2000), among women (Gallus et al 2001) and by drink type (Bosetti et al 2000a). A UK case control study contributed two papers reporting on the association between alcohol consumption and oesophageal cancer by tumour type; squamous cell carcinoma (Sharp et al 2001) and adenocarcinoma (Cheng et al 2001). Tables for each study describing the study aims, population, alcohol measurement methods and main results are provided in Appendix D.

2.12.1 Study characteristics

A summary of the general characteristics of the studies by study type is provided in Tables 2.12.1 (cohort studies) and 2.12.2 (case control studies).

Table 2.12.1 Alcohol and oesophageal cancer: general characteristics of cohort studies

Authors	Year	Country	Outcome/No outcome	Age range (M/Mdn)	Sample base	Sample selection
Allen	2009	UK (women)	773/1,274,320	>55	breast screening clinics	random selection
Fan	2008	Shanghai (men)	101/18,143	45-64	city population	representative random sample
Freedman	2007	USA	302/474,606	>50 (M=62.5)	state population registers	self-selection
Kasum	2002	USA (women)	169/34,630	55-69	state drivers licence list	representative random sample
Sakata	2005	Japan (mortality)	100/42,478	40-79	regional population	non-random sample
Tran	2005	China	1,958/29,584	40-69 (M=52)	regional population	non-random sample

Abb: n/s not specified; M=mean; Mdn= median

Five cohort studies looked at incident cases of oesophageal cancer as an outcome and Sakata et al (2005) at the association between oesophageal cancer mortality and alcohol consumption. The largest cohort study, based in China, identified approximately 2000 incident cases of oesophageal cancer (Tran et al 2005). Two cohort studies reported on the association between alcohol consumption and

oesophageal cancer in women only (Kasum et al 2002, Allen et al 2009) and one study in men only (Fan et al 2008).

Table 2.12.2 Alcohol and oesophageal cancer: general characteristics of case control studies

Authors	Year	Country	Case/control	Age range (M/Mdn)	Sample base	Sample selection
Boony'at	2002	Thailand	202/261	(M=64)	hospital	consecutive/ non-random selection
Bosetti	2000a	Italy	714/3,137	25-83 (M=60/58)	hospital	selected cases/ non-random selection
Brown	2001	USA	347/1,354	30-79	state populations/ medical insurance registers	consecutive/random sample
Cast'gue	1999	South America[1]	830/1,779	(M=64/63)	hospital	consecutive/ non-random selection
Cheng	2000	UK	74/74	<75	regional population/ health authority patient lists	consecutive/random sample
Engel	2003	USA	368/695	30-79	State cancer registry/ local neighbourhood	consecutive/random sample
Gallus	2001	Italy (women)	114/425	<79 (M=60)	*See Bosetti 2000*	
Hashibe	2007b	E&C Europe[2]	227/1,114	>18	hospital/cancer clinics	n/s
Ibiebele	2008	Australia	1,181/1,650	18-79	treatment centres/ general population	consecutive/ random selection
Lagergren	2000	Sweden	356/820	n/s	general population	consecutive/random selection
Lee	2005	Taiwan	513/818	28-89	hospital/general population	consecutive /random selection
Lindblad	2005	UK	2,128/10,000	40-84	national general practitioners research database	consecutive/random sample
Pacella	2002	South Africa	51/1,370	18-74	hospital	n/s
Sharp	2001	UK	159/159	<75	*See Cheng 2000*	
Takezaki	2000	Japan (men)	346/11,936	40-79	hospital	consecutive/ non-random selection
Vioque	2008	Spain	202/455	30-80	hospital/electoral roll	consecutive/ random selection
Wang	2007	China	355/824	>30 (M=61)	regional cancer registry/local population	consecutive/ random selection
Wu	2001	USA	222/1,289	30-74	state cancer registry/ local neighbourhood	consecutive/ non-random selection
Zambon	2000	Italy	275/593	39-77 (M=60)	*See Bosetti 2000*	
Znaor	2003	India	566/3,638	>25	hospital	not specified/non-random selection

[1] Argentina, Brazil, Paraguay and Uruguay; [2] Romania, Poland, Russia and the Czech Republic. Abb: n/s not specified; M=mean; Mdn= median

Study size was modest for the majority of case-control studies (Table 2.12.2). Of the seventeen case control studies, six studies identified more than 500 cases and controls. The largest case control study identified in this review involved 1181 cases and 1650 controls, pooled from three case control

studies across South America (Ibiebele et al 2008). Two studies identified less than 100 incident cases of oesophageal cancer (Cheng et al 2001, Pacella-Norman et al 2002).

2.12.2 Study Quality

The quality scores assessed according to the NOS are presented in Table 2.12.3. Overall, cohort studies were of a moderate to high quality with two studies achieving maximum stars (Kasum et al 2002, Fan et al 2008). Case control studies were of more mixed quality ranging from five stars (Castellsagué et al 1999, Wang et al 2008) to eight stars (Lagergren et al 2000, Vioque et al 2008).

All the cohort studies scored a maximum of four stars for sample selection. For outcome assessment, Freedman et al (2009) and Sakata et al (2005) only achieved two stars because no statement was provided on losses during follow-up in each study and Tran et al (2005) because they did not secure independent confirmation of outcome diagnosis relying instead on self-reports from the study population.

Table 2.12.3 Oesophageal cancer: assessment of study quality

	Selection* (out of 4)	**Comparability* (out of 2)**	**Outcome/Exposure[1]* (out of 3)**	**Total**
Cohort				
Allen 2009	4	2	3	9
Freedman 2007	4	2	2	8
Fan 2008	4	2	3	9
Kasum 2002	4	2	3	9
Sakata 2005	4	1	2	7
Tran 2005	4	1	2	7
Case-control				
Boonyaphiphat 2002	3	2	1	6
Bosetti 2000a, Gallus 2001, Zambon 2000	3	2	1	6
Brown 2001	3	2	2	7
Cast'gue 1999	1	2	2	5
Cheng 2000, Sharp 2001	3	2	2	7
Engel 2003	3	2	2	7
Hashibe 2007	3	2	2	7
Ibiebele 2008	3	2	1	6
Lagergren 2000	3	2	3	8
Lee 2005	2	2	1	6
Lindblad 2005	3	2	2	7
Pacella 2002	3	2	2	7
Takezaki 2000	2	2	3	7
Vioque 2008	3	2	3	8
Wang 2007	3	1	1	5
Wu 2001	3	2	2	7
Znaor 2003	3	2	1	6

* High quality characteristics within each of these items were awarded a star, up to a maximum of four stars for selection, two stars for comparability and three stars for assessment: [1] Outcome for cohort, exposure for case-control studies

For sample selection in the case control studies, the majority of studies secured three stars out of four because either they used cases and controls from a hospital or clinical setting or failed to confirm that cases of oesophageal cancer were not present in their study population. Further selection bias in recruitment of controls was addressed in four case control of studies by excluding, from their control sample, subjects admitted to hospital for alcohol or tobacco related diseases in order to avoid overrepresentation of smokers and drinkers compared to the source populations (Boonyaphipat et al 2002, Bosetti et al 2000a etc, Castellsague et al 1999, Zambon et al 2000).

Non-response bias did not appear to be a problem for the hospital based case control studies as in the four studies that reported on this aspect, all had response rates over 90% for both cases and controls. For the majority of remaining population based studies, response rates ranged from between 62%-72% for cases and 65%-75% for controls. Six case control studies, four hospital and two population based, did not report response rates. The extent of interviewer bias was not clear as the majority of case control studies did not specify blinding status in the study. In two studies that did reported on this, interviewers were not blinded to case or control status, but they were unaware of the study hypothesis (Lagergren et al 2000, Wu et al 2001). Outcome measurement was clearly defined in the majority of studies. This was done through histological confirmation of oesophageal cancer in the majority of studies. In one study, however, outcome measurement was based on a review of medical records held in a general practice database without histological confirmation (Lindblad et al 2005).

Adjustment for smoking took place in the majority of studies reporting on the association between alcohol consumption and oesophageal cancer with the exception of two prospective cohort studies (Sakata et al 2005, Tran et al 2005). There was considerable variation in how smoking was controlled for in the studies reviewed. The most common approach taken in seven studies was simply to control for smoking status (i.e. never, ever, current and former smoker). The remaining studies controlling for smoking, either adjusted for number of years smoked (Sharp et al 2000), or pack years smoked (Kasum et al 2002, Lee et al 2005, Takezaki et al 2000) or the amount of cigarettes smoked per day (Castellsagué et al 1999, Gallus et al 2001, Zambon et al 2000) or packs of cigarettes (Brown et al 2001) smoked per day. The majority of Asian based studies, with the exception of Sakata et al (2005) and Takezaki et al (2000) also controlled for betel quid chewing, a practice common in southern Asia and linked to an increased risk of oesophageal cancer. The possible protective effects of raw fruit and vegetable consumption against oesophageal cancer was controlled for in only five studies (the majority of these based in Europe), with one American cohort study (Kasum et al 2002) further adjusting for whole or refined grain intake also linked with a protective effect against oesophageal cancer. The most common proxy indicator used for socio-economic status was education, usually levels or years of schooling, and this was controlled for in eight studies. Other SES related variables controlled for included income (Brown et al 2001, Engel et al 2003), and social class (Bosetti et al 2000).

Obesity is regarded as a major risk factor for oesophageal adenocarcinoma and was controlled for in two of the four studies investigating association between this tumour type and alcohol consumption either directly in terms of body mass index measurement (Lagergren et al 2001) or indirectly through slimming practices (Cheng et al 2000). Gastroesophageal reflux was also controlled for by Lagergren et al (2001) and Lindblad et al (2005). Three of the four studies adjusted for smoking status with the exception of Cheng et al (2000).

2.12.3 Results: total alcohol intake and risk of oesophageal cancer[20]

Twenty studies, providing 23 papers, reported on total alcohol consumption and risk of oesophageal cancer either as a single entity (see below) or by tumour type: squamous cell carcinoma (see section 2.12.3.1) or adenocarcinoma (see section 2.12.3.2). Nine studies, providing 11 papers reported on the association between oesophageal cancer (including tumour type); and 'recent' alcohol intake defined as alcohol consumption in the preceding year in eight studies (Bosetti et al 2000*, Zambon et al 2000*, Gallus et al 2001*, Takezaki et al 2000, Engel et al 2003, Lee et al 2005, Tran et al 2005, Freedman et al 2008, Ibiebele et al 2008, Vioque et al 2008) and in the previous six months by Sakata et al (2005). Three studies providing four papers reported by lifetime consumption; defined as alcohol consumption 20 years before survey interview by Lagergren et al (2000) and drinking in a typical week during specific age periods (at ages 25, 40, 50 and 60) by Hashibe et al (2007). In two studies, providing three papers, the lifetime measure of alcohol consumption was not defined (Castellsague et al 1999, Cheng et al 2000** Sharp et al 2001**). In the remaining seven studies, the reference period was not specified (Brown et al 2001, Wu et al 2001, Boonyaphiphat et al 2002, Kasum et al 2002, Znaor et al 2003, Lindblad et al 2005, Fan et al 2008).

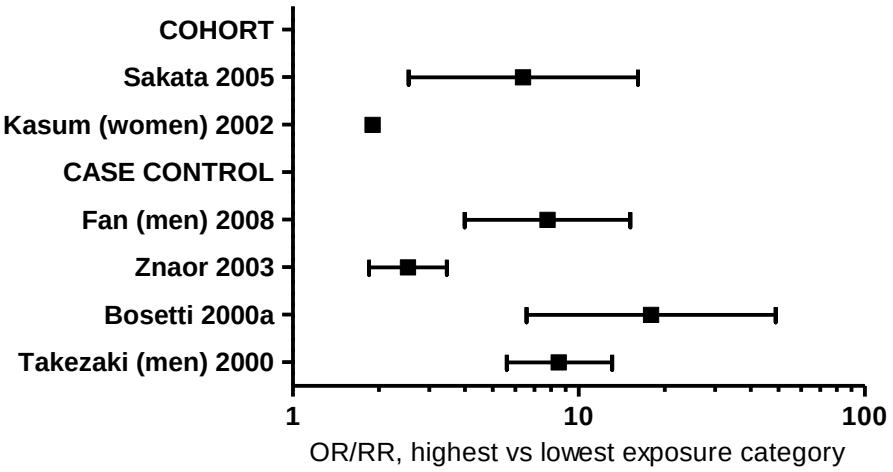
Six studies reported on association between alcohol consumption and oesophageal cancer only. A summary of oesophageal cancer risk estimates, comparing the highest versus the lowest alcohol exposure category, is presented in Figure 2.12.1.

Irrespective of study design, all studies reported a statistically significant increased risk of oesophageal cancer across a range of alcohol intake levels. In an American cohort study, women, drinking >2 drinks per day [d/d], compared to 0 d/d, had a two-fold increased risk of oesophageal cancer though no confidence intervals were reported (Kasum et al 2002). Fan et al (2008), reported that men drinking >20 grams p/d [g/d], compared to non-drinkers, were also at increased risk of oesophageal cancer, with risk increasing with amount drunk, up to the highest exposure category (≥80 g/d, *p value for trend* <0.001). A statistically significant dose response relationship between daily alcohol intake and increased risk of death from oesophageal cancer was observed in a Japanese

[20] Multivariate relative risks/odds ratios are presented unless otherwise stated
*all from the same case control study carried out in Italy (see Table 2.12.1)
** from the same UK case control study (see Table 2.12.1)

prospective cohort among daily drinkers drinking ≥3 units per day (*p value for trend* =0.028), compared to never drinkers (Sakata et al 2005). Three hospital based case control studies also identified a statistically significant increased risk of oesophageal cancer. Compared to never drinkers, Znaor et al (2003) and Takezaki et al (2000) reported positive associations between cancer of the oesophagus among those drinking >50 millilitres per day [ml/d][21] and in men drinking >5 d/d, respectively. The largest risk estimate (OR 12.35, 95% CI 8.37-18.21) was reported in an Italian hospital based case control study for those drinking ≥12 d/d compared to those <3 d/d. In the same study, even those drinking 3-4 d/d had a twofold, statistically significant, increased risk of oesophageal cancer (Bosetti et al 2000a).

Figure 2.12.1 Alcohol consumption and oesophageal cancer: highest versus lowest exposure category by study type (odds ratio/relative risk and 95% confidence intervals)



[21] 1 gram = 1.25 millilitres

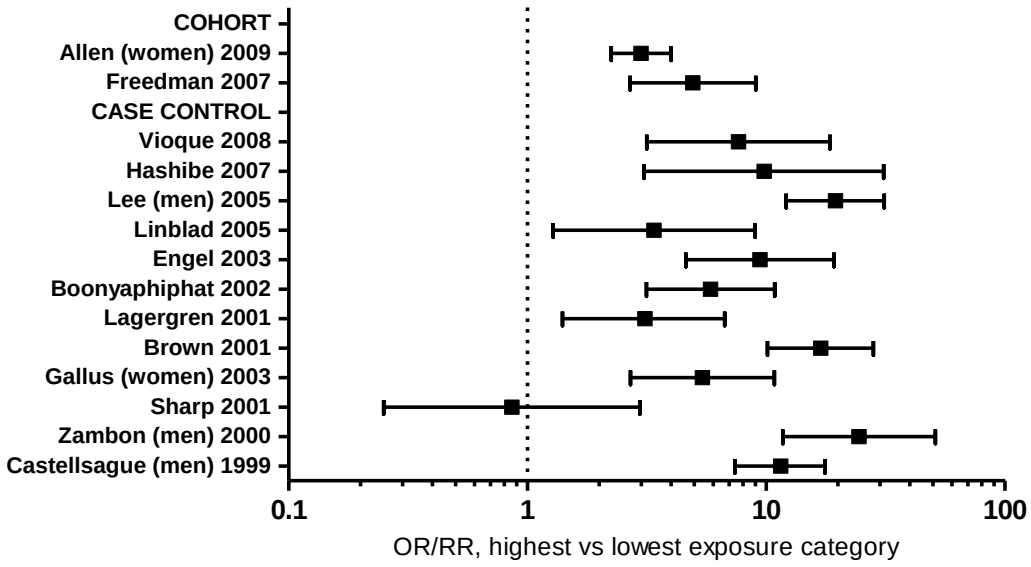
2.12.3.1 Alcohol consumption and risk of squamous cell carcinoma of the oesophagus

Fifteen papers from 14 studies reported on the association between total alcohol consumption and oesophageal squamous cell carcinoma (SCC). Of these, 13 studies reported on the dose response association between alcohol consumption and oesophageal SCC. A summary of SCC risk estimates, comparing the highest versus the lowest alcohol exposure category, is presented in Figure 2.12.2. In the remaining study, not included in Figure 2.12.2, Tran et al (2002), observed no association between current drinking status and SCC (RR 1.03, 95% CI 0.82-0.92), compared to never and former drinkers.

In a large UK prospective cohort study (Allen et al 2009), women drinking at the highest alcohol exposure category (>15 drinks per week [d/w]), compared to those drinking <2 d/w had a two-fold statistically significant increased risk of oesophageal SCC. Positive, but non-statistically significant, associations were observed at all other alcohol intake levels with a statistically significant dose response relationship (*p value for trend* =0.02). In the same study, never-drinkers had a 60% (RR 1.56, 95% CI 1.29-1.89) increased risk of oesophageal SCC, compared to the reference group (Allen et al 2009). Freedman et al (2008), in a US prospective cohort study also reported statistically significant positive associations for those drinking <1-3 and >3 d/d, compared to those drinking >0-1 d/d with strong evidence of a statistically significant dose response trend (*p value for trend* <0.0001). Non-drinkers had a two-fold increased risk (RR 2.06, 95% CI 1.16.368) of oesophageal SCC.

In the case control studies using low to moderate drinkers as a reference group, there was also clear evidence of an increased risk of SCC, from moderate to heavy alcohol consumption, with statistically significant dose response relationships. Zambon et al (2005) reported the risk of oesophageal cancer steeply rising with increasing level of alcohol consumption (>84 d/w *p value for trend* <0.001) compared to light drinkers **(**1-20 d/w). Gallus et al (2001) found a statistically significant dose response relationship (*p value for trend* <0.001) between average weekly lifetime alcohol consumption and increased SCC risk for women drinking ≥3 d/d, compared to <1 d/d. In a UK based nested case control study, Lindblad et al (2005) only reported a statistically significant association for those drinking >34 units p/w [u/w], compared to those drinking 0-2 u/w, but not for those drinking 3-15 u/w (OR 1.01, 95% CI 0.59-1.72).

Figure 2.12.2 Alcohol consumption and SCC of the oesophagus: highest versus lowest exposure category, by study type (odds ratio/relative risk and 95% confidence intervals)

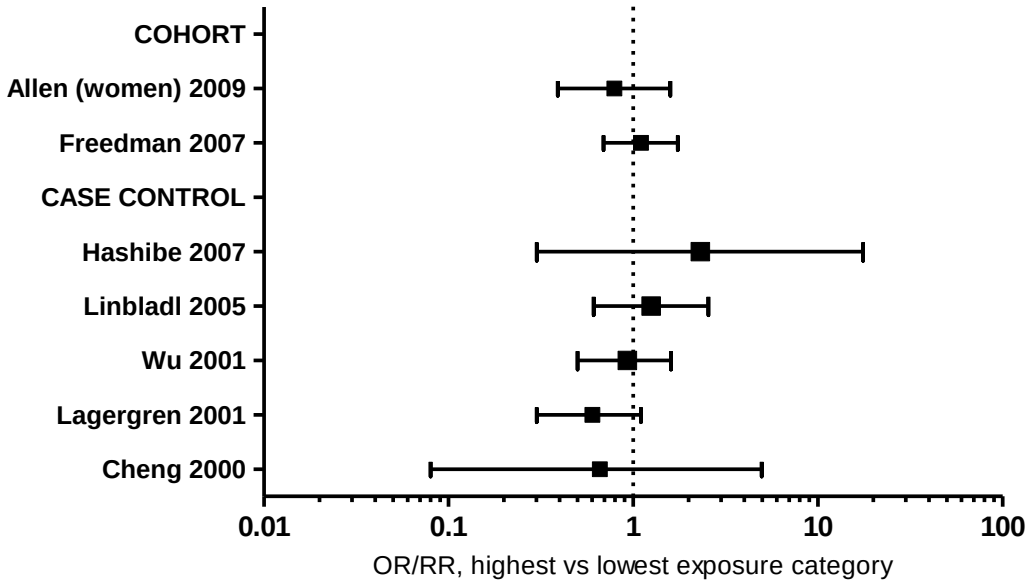


In those studies using 'abstainers' as a reference group the reported associations with SCC were less consistent. In four hospital based case control studies (Castellsagué et al 1999, Boonyaphiphat et al 2002, Lee et al 2005; *p value for trend* <0.0001, Hashibe et al 2007b; *p value for trend* =0.01), alcohol consumption at all levels was associated with an increased risk of SCC of the oesophagus. Viogue et al (2008), in a Spanish based hospital case control study reported a strong statistically significant dose response for their study population (≥75 g/d; OR 7.65, 95% CI 3.16-18.49 *p value for trend* <0.00001). In the same study drinking 1-24 g/d was associated with a small and statistically non-significant increased risk of SCC (OR 1.16, 95% CI 0.54-2.49). Similar findings were reported in two population based case control studies; Lagergren et al (2001) although observing a threefold increase in risk of SCC, for those drinking >70 u/w (OR 3.1, 95% CI 1.4-6.7) compared to abstainers, found no association for those drinking <70 u/w. Engel et al (2003) only observed a statistically significant increased risk of SCC for those drinking ≥5 d/w, compared to never drinkers. In a small nested case control study in the UK, involving less than a hundred cases and controls, Sharp et al (2001) observed a positive association between average weekly lifetime alcohol and an increased risk of SCC in women drinking ≥14 u/w; (OR 1.23 95% CI 0.44-3.37), compared to non-drinkers, but no association with SCC in women drinking <2 u/w (OR 0.80, 95% CI 0.47-1.37 or ≥2->14 u/w OR 0.75, 95% CI 0.42-1.33) over their lifetime.

2.12.3.2 Alcohol consumption and risk of oesophageal adenocarcinoma

Two cohort and five case control studies reported on the association between alcohol consumption and oesophageal adenocarcinoma. A summary of oesophageal adenocarcinoma risk estimates, comparing the highest versus the lowest alcohol exposure category, is presented in Figure 2.12.3

Figure 2.12.3 Alcohol consumption and oesophageal adenocarcinoma: highest versus lowest exposure category by study type (odds ratio/relative risk and 95% confidence intervals)



In two prospective cohort studies, alcohol consumption at any level including the highest exposure category (>3d/d), compared to moderate drinkers, was not associated with an increased risk of oesophageal adenocarcinoma with no evidence of a dose response relationship; *p value for trend* =0.2 (Allen et al 2009) and *p value for trend* =0.68 (Freedman et al 2008). Allen et al., however, observed a small statistically significant increased risk of oesophageal adenocarcinoma in never-drinkers (RR 1.28, 95% CI 1.01-1.63).

Two case control studies reported increased risks of oesophageal adenocarcinoma associated with alcohol consumption. Hashibe et al (2007b) observed a non-significant increased risk of oesophageal adenocarcinoma risk for all intake levels (maximum >420 g/w) though there were only approximately 10 cases in each intake category Lindblad et al (2005) observed a positive association between >34 u/w and an increased risk of adenocarcinoma (OR 1.25, 95% CI 0.61–2.55) though there were only nine drinkers in this category. There was no association (OR 1.06, 95% CI 0.76–1.49) with oesophageal adenocarcinoma in the category with the largest number of drinkers (3-15 u/w, n=59).

In two population based case control studies, 'lifetime' drinking was inversely associated with oesophageal adenocarcinoma. Cheng et al (2001) reported similar odds ratios for all alcohol intake levels (average >14 u/w over lifetime; OR 0.66, 95% CI 0.08-4.96, *p value for trend* =0.074),

compared to non-drinkers. Lagergren et al (2002) reported similar findings for those reporting drinking >70 u/w (OR 0.6, 95% CI 0.3-1.1) twenty years prior to the study, compared to never drinkers.

2.12.4 Results: drinking dimensions and risk of oesophageal cancer

In two studies drinking frequency was associated with an increased risk of cancer of the oesophagus. Wang et al (2007) observed an increased risk of SCC of the oesophagus in both daily (OR 2.32, 95% CI 1.53-3.53) and occasional drinkers (OR 1.99, 95% CI 1.21-3.27), compared to never drinkers. In a South African case control study, compared to non-drinkers, frequent drinking (OR 1.8, 95% CI 1.2-2.8), but not weekly (OR 0.7, 95% CI 0.4-1.3) or occasional drinking (OR 0.7, 95% CI 0.3-1.5) increased the risk of oesophageal cancer.

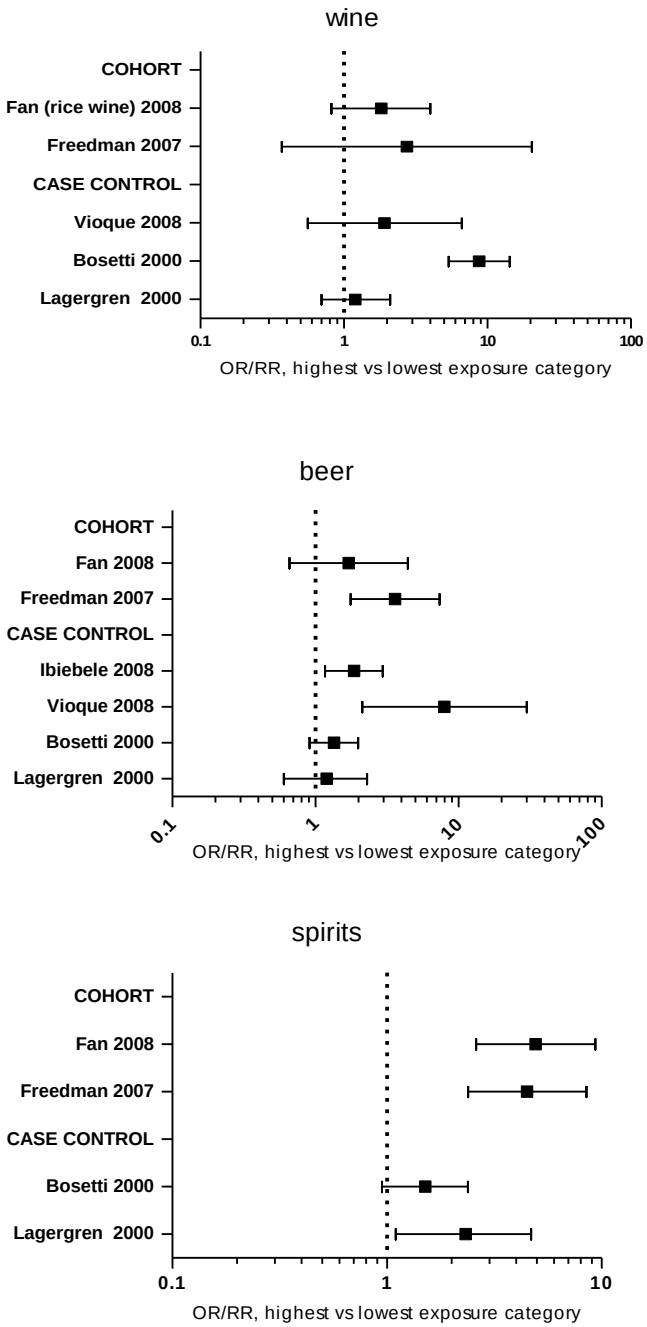
The association between drinking duration and risk of oesophageal cancer was investigated by five studies with mixed results. A Taiwanese hospital control study (Lee et al 2005) observed a statistically significant dose response relationship (*p value for trend* =0.0001) between duration of drinking and increased risk of SCC, compared to never drinkers. After further adjusting for the amount of alcohol consumed or length of time alcohol was consumed, it was found that the amount of alcohol consumed had a stronger effect (OR 2.29, 95% CI 1.69–3.08) on the development of SCC than the length of time over which it had been consumed (OR 1.84, 95% CI 1.55–2.18). Hashibe et al (2007b) and Fan (2008) both observed a statistically significant increased risk of SCC in those drinking >20 years, but no association with SCC for those drinking <20 years. Castellsagué et al (1999) and Vioque et al (2008) reported a statistically significant odds ratio for each exposure level of drinking duration among men, compared to never drinkers, though no dose response relationship was evident. There was no clear pattern among women for years of alcohol drinking and risk of oesophageal cancer. Zambon et al (2000) reported no association between duration of drinking and oesophageal cancer in men compared to those drinking less than 45 years.

2.12.5 Results: drink type and risk of oesophageal cancer

Eleven studies identified in the present review, investigated the relationship between alcohol drink type and oesophageal cancer. Six studies reported on the dose response association between drink type and oesophageal cancer and a summary of risk estimates, comparing the highest versus the lowest alcohol exposure category is presented in Figure 2.12.4. The remaining five studies reported on the association between drink type and oesophageal cancer, by drinking status. Four studies reported statistically significant associations between 'current' drinkers of wine, beer and spirits, compared to non-drinkers. The highest odds ratios were often reported for the most commonly consumed beverage in the study; arrack (Znaor et al 2003), sake and sochu (Sakata et al 2005), wine and spirits (Castellsagué et al 1999, Lee et al 2005). Hashibe et al (2007b) reported a non-significant inverse

association between current drinkers or either beer, wine or spirits, compared to a reference group comprising of drinkers of all three drink types.

Figure 2.12.4 Alcohol consumption and oesophageal cancer, by drink type (odds ratio/relative risk and 95% confidence intervals)



In four of the six studies reporting on the dose response association (Figure 2.12.4), a statistically significant increased risk of oesophageal cancer was only reported in the most frequently consumed drink type in each study irrespective of the reference group in each study; Zambon et al (2000) reported a clear trend in risk (*p value for trend* <0.001) for wine drinkers compared to abstainers;

Lagergren et al (2002) for spirit drinkers (*p*trend <0.0001) compared to never drinkers; Freedman et al (2007) for beer (*p value for trend* =0.0002) and spirit drinkers (*p value for trend* <0.0001) compared to those drinking <1 d/d and Bosetti et al (2000a) for wine drinkers at all exposure levels, with a clear trend in risk up to an including more than 12 drinks p/d compared to those drinking 1-2 d/d. In the remaining study, Ibiebele et al (2008) observed that beer consumption of >1 d/d, compared to never drinkers, had a statistically significant increased risk of oesophageal cancer, but not for those drinking <1 d/d (*p value for trend* =0.05).

Four studies reported on drink type and risk of oesophageal adenocarcinoma (Table 2.12.4). Hashibe et al (2007b) and Ibiebele et al (2008) reported no association between adenocarcinoma of the oesophagus and drink type among current drinkers. In two studies, the most commonly drunk beverage type was reported to have a statistically significant inverse association with adenocarcinoma of the oesophagus. Wu et al (2001) observed a dose response protective effect of beer drinking (*p value for trend* =0.001) and Lagergren et al (2000) for spirit drinkers consuming >30 g/w. compared to those who never drank spirits.

Table 2.12.4 Risk of oesophageal adenocarcinoma by drink type

Author	Measure/Ref. group	Drink type			
Hashibe 2007b	Current drinkers/ Beer + Wine + Spirits	**Beer** 0.88 0.16–4.91	**Liquor** 0.74 0.17–3.29		
Ibiebele 2008	Times per day/ Never drinkers of beer		**Beer**		
		Low	1.10 (0.70–1.71)		
		Moderate	0.68 (0.45–1.02)		
		High	0.74 (0.47–1.16)		
Lagergen 2000	Grams per week/Never drinker of specified drink type		**Strong beer**	**Wine**	**Spirits**
		1–5	1.3 (0.7–2.3)	0.8 (0.5–1.5)	0.6 (0.3–1.2)
		6–25	1.0 (0.6–1.9)	0.9 (0.5–1.7)	1.1 (0.5–2.2)
		>25	1.2 (0.6–2.3)	1.2 (0.7–2.1)	2.3 (1.1–4.7)
Wu 2001	never drank/ Drinks per week	*d/w*	**Beer**	**Wine**	**Spirits**
		<7	0.44 (0.3–0.7)	0.86 (0.6-1.3)	0.93 (0.6-1.4)
		7-14	0.30 (0.2-0.5)	0.72 (0.4-1.3)	1.35 (0.8-2.3)
		15+	0.57 (0.3-1.0)	1.27 (0.6-2.8)	1.34 (0.8-2.3)
		*p*trend	0.001	0.40	0.17

2.12.6 Results: effect modification

Four studies reported on the combined effect of alcohol and smoking on the risk of oesophageal cancer.

Castellsagué et al (1999) observed a strong and highly significant dose response (*p value for trend* <0.000001) relationship between an increased risk of oesophageal cancer and average number of cigarettes smoked per day and average amount of alcohol consumed per day among male patients. In this study, point estimates for even low to moderate consumers of both alcohol and cigarettes were above one though no confidence intervals were provided in data tables to determine the significance of these estimates. In a Swedish population case control study (Lagergren et al 2000), combined intake at the highest exposure level (long term smokers of >35 years and heavy alcohol users drinking

>70g/w) significantly increased the risk, compared to never users, of squamous cell oesophageal carcinoma (OR 23.1, 95% CI 9.6-56.0), but not of oesophageal adenocarcinoma (OR 2.3, 95% CI 0.9-5.7). In an Italian hospital based study, compared with never-smokers/non or light drinkers, the risk of oesophageal cancer also increased with increasing alcohol consumption in each stratum of smoking habit (Zambon et al 2000). The authors also noted that the risk increase for the highest joint level of alcohol drinking (>60 d/w) and current smoking was compatible with a multiplicative model ($P_{interaction}$=0.27). From the same case control study, Gallus et al (2001) also observed that the combined effect of low alcohol intake and smoking status increased the risk of squamous cell oesophageal cancer among women; Female patients who were current smokers and drank ≥3 d/w had an OR of 12.75 (95% CI 5.09-31.96), compared to non current smokers who were drinking <1 d/w.

2.12.7 Summary and conclusions

This review identified 26 papers from 23 studies that examined the risk of oesophageal cancer and alcohol consumption. Overall the majority of studies were consistent in reporting a statistically significant dose response relationship between alcohol consumption and risk of squamous cell carcinoma (SCC) of the oesophagus, in line with the already substantial body of evidence establishing alcohol as major risk for oesophageal SCC (IARC 1988, Corrao et al 1999, 2004, Baan et al 2007, WCRF/AICR 2007). Studies ranged in quality, but whilst issues of selection bias through poor response rates among cases and controls or recall bias may affect the size of the risk estimates they will not alter the underlying positive association between alcohol consumption and SCC of the oesophagus. In studies reporting by gender, risk estimates for men tended to be higher than those for women, but then men tend to drink more and in greater numbers than women and it is unlikely that male drinkers are necessarily at any greater relative risk of SCC than female drinkers. Specific alcoholic beverages were also shown to increase the risk of SCC though in each study this was the most obvious for the most consumed type drink in the study's country/region of origin e.g. wine in Italy (Bosetti et al 2000), arrack in India (Znaor et al 2003), sake in Japan (Sakata et al 2005) and spirits in Sweden (Lagergren et al 2001). These findings support the conclusion that ethanol is the main component of alcoholic beverages that determines the risk of oesophageal cancer, and that the most frequently consumed beverage in each area tends to be the one with the highest estimated and statistically significant relative risk (Boffetta and Hashibe 2006).

Six studies were identified in this review that reported on risk of oesophageal adenocarcinoma from alcohol consumption. In all these studies, no association was found between this tumour type and alcohol consumption which is consistent with the findings in previous case-control studies (Boffetta and Hashibe 2006). This is of particular relevance in western countries, especially in the US and UK,

where incidence rates of SCC are decreasing and those of adenocarcinoma are increasing rapidly (Takezaki et al 2005).

Average daily alcohol intake (usually within the year prior to the study commencing) and not drinking frequency or drinking duration appeared to be the relevant exposure with respect to drinking and increased risk of SCC (Lee at el 2005, Zambon et al 2000). It is not clear, however, despite consistent statistically significant dose response relationships in the majority of studies reviewed, whether low levels of drinking increased the risk of SCC. The majority of studies in this review reporting statistically significant associations at each alcohol intake level with increased risk of SCC had low level drinkers as the reference group or included in low level drinkers with never drinkers in the reference group (primarily due to the low number of abstainers/never drinkers in each of study populations). When lifelong abstainers were used as a reference group, the evidence was inconsistent on the risk of SCC from low levels of drinking (i.e. approximately 1 to 2 d/d). This may be attributed to poor study power in detecting a true association at these levels because of the small number of SCC cases identified (in those studies with never drinkers as a reference group, cases numbered between 200 and 300). Since non-response bias was an issue for many case control studies in this review this also could explain some of statistically non-significant association observed for low levels of drinking. However, this could affect risk estimates either way and heavy or excessive drinkers are more likely to be non-responders in these types of studies.

Although smoking was controlled for in nearly all studies, the measure used varied from smoking status, duration of smoking or amount smoked per day to pack years. Residual confounding is, therefore, likely to contribute to some of the excess risks observed in many of the studies though not sufficient to alter the overall association observed at moderate to heavy levels of consumption. It may, however, further, weaken the link between low levels of alcohol drinking and increased risk of SCC of the oesophagus. Equally, diet especially intake of fresh fruit and vegetables has increasingly been linked with a protective effect against both SCC and oesophageal adenocarcinoma and whilst it was adjusted for in the all studies investigating the latter tumour type, only five of the fifteen studies reporting on the association between SCC and alcohol consumption adjusted for diet.

The interaction between smoking and alcohol observed in this review is also consistent with the numerous case control and cohort studies have shown that both tobacco and alcohol increase the risk of oesophageal cancer and that their joint effect is multiplicative (Boffetta and Hashibe 2006). The small sample sizes in the analysis as well as different smoking and drinking categories used across the studies may preclude any firm conclusions being drawn about the precise size of the risk nevertheless it was evident that even at low and moderate levels, the interaction between combined smoking and drinking increased the risk of SCC.

In conclusion, the evidence from this review supports the previous findings of a statistically significant dose response relationship between alcohol consumption and increased risk of SCC of the oesophagus. The evidence is convincing for moderate to heavy levels of alcohol consumption, but at lower levels of alcohol consumption due to heterogeneous reference groups and inherent bias in cases control studies, the evidence is less convincing. There was no convincing evidence of an association between alcohol consumption and oesophageal adenocarcinoma.

2.13 Oral cancer

Oral cancer: summary of evidence from previous reviews
Epidemiological studies clearly indicate that alcohol consumption is causally related to cancers of the oral cavity and pharynx (excluding the nasopharynx). There is no indication that the effect is dependent on type of beverage (Lowenfels 1975, IARC 1988b, WCRF/AICR 1997).

The literature search identified 22 papers from 17 studies, published between 1999 and 2009, which examined the association between alcohol consumption and oral cancer. There was one prospective cohort study and sixteen case control studies.

Six papers were derived from the same pooled analysis of two case control studies carried out in northern Italy and Switzerland. All six were retained in this review because each paper reported on a different aspect of the relationship between alcohol and oral cancer; risk by total alcohol consumed and by drink type (Altieri et al 2004); risk among women (Bosetti et al 2000); among never-smokers (Fioretti et al 1999); in those aged under 46years (Rodriguez et al 2004); differences in risk when drinking with and without a meal (Maso et al 2002) and on the interaction between smoking and alcohol and risk of oral cancer (Franceschi et al 1999). Two population based case control studies came from the same Puerto Rican study population, with one examining oral cancer risk by total alcohol consumed (Hayes et al 1999) and by drink type (Huang et al 2003). Tables for each study describing the study aims, population, alcohol measurement methods and main results are provided in Appendix D.

2.13.1 Study characteristics

A summary of the general characteristics of the studies is provided in Table 2.13.1(cohort) and 12.3.2 (case control) below.

Table 2.13.1 Alcohol and oral cancer: general characteristics of cohort study reviewed

Authors	Year	Country	Outcome/No outcome	Age range (M/Mdn)	Sample base	Sample selection
Allen	2009	UK (women)	758/1,279,538	>55	breast screening clinics	random selection

Abb: n/s not specified; M=mean; Mdn= median

The largest study was provided by Allen et al (2009) who identified approximately 800 incident cases of oral cancer in a cohort of UK women attending breast screening clinics over a mean follow up period 7.2 years. Two case control studies identified more than 500 cases (Hayes 1999, Altieri et al 2004), four studies between 300-500 (Schwartz et al 2001, Sanchez et al 2003, Castellsague et al 2004, Subapriya et al 2007). The majority of the case control studies were, however, small in size, identifying approximately 100 oral cancer cases or less.

Table 2.13.2 Alcohol and oral cancer: general characteristics of case control studies reviewed

Authors	Year	Country	Cases/ Controls	Age range (M/Mdn)	Sample base	Sample selection
Altieri	2004	Italy/Swiss	749/1,772	20-78, (M=57)	hospital	selected cases/ non-random selection
Anaya-Saavedra	2008	Mexico	62/248	18+	hospital	volunteers
Balarm	2000	India (men)	309/292	18-87, (M=56/58)	hospital	all/ relatives and friends
Bosetti	2000 b	Italy/Swiss (women)	195/1,113	26-83, (M=60/58)	*See Altieri 2004*	
Castel'gue	2004	Spain	375/375	20-91, M=60	hospital	all/ non-random selection
Fioretti	1999	Italy	52/864	22-76, (M=62)	*See Altieri 2004*	
Franceschi	1999	Italy/Swiss	274/1,254	23-74, (M=57/55)	*See Altieri 2004*	
Garrote	1999	Cuba	200/200	25-91, (M=64/62)	hospital	all/non-random selection
Hayes	1999	Puerto Rico (men)	519/629	21-79	national cancer registry/ general population	all/ clustered household probability sampling
Huang	2003	Puerto Rico	286/417	21-79	*See Hayes 1999*	
Lissowska	2003	Poland	122/124	23-80	maxillofacial clinic/city hospitals	all/ n/s
Llewellyn	2004 *a*	United Kingdom	116/207	<45	regional cancer registry/GP database	all/ non-random selection
Llewellyn	2004 *b*	United Kingdom	53/91	≤45, (M=38/39)	regional hospitals (n=14)/GP database	referral/non-random selection
Maso	2002	Italy/Swiss	324/1,545	<80	*See Altieri 2004*	
Moreno	2000	Spain	75/150	M=58/61	hospital/health care centres	all/ non-random selection
Rodriguez	2004	Italy/Swiss	137/298	<46, (42/40)	*See Altieri 2004*	
Schwartz	2001	USA	407/615	18-65	state cancer registry/ population	all/random sample state households
Subapriya	2007	India	467/525	30 to 75	hospital	all/ relatives and friends
Vlajinac	2006	Serbia	100/100	37-79, (M=59)	cancer clinical centre	all/ non-random selection
Zavras	2001	Greece	110/115	22-91, (M=64/63)	hospital	selected cases/not specified
Znaor	2003	India (men)	656/3,638	>25	hospital	not specified/non-random selection

2.13.2 Study quality

The quality scores assessed according to the NOS are presented in Table 2.13.3. Overall, studies on the association between alcohol consumption and oral cancer were of moderate to high quality scoring 6-7 stars out of a possible nine.

Table 2.13.3 Oral cancer: assessment of study quality

	Selection* (out of 4)	Comparability* (out of 2)	Outcome/Exposure[1] * (out of 3)	Total
Allen 2009	3	2	2	7
Altieri 2004, Bosetti 2000b, Fioretti 1999, Franceschi 1999, Maso 2002, Rodriguez 2004	3	2	2	7
Anaya-Saavedra 2008	3	0	2	5
Balarm 2000	2	2	2	6
Castellsague 2004	2	2	2	6
Garrote 1999	3	2	2	7
Hayes 1999, Huang 2003	3	2	3	8
Llewellyn 2004b	2	1	2	5
Llewellyn 2004a	3	2	2	7
Lissowska 2003	3	2	2	7
Moreno-Lopez 2000	3	1	2	6
Schwartz 2001	3	2	2	7
Subapriya 2007	3	2	2	7
Vlajinac 2006	3	2	2	7
Zavras 2001	3	2	2	7
Znaor 2003	3	2	1	6

* High quality characteristics within each of these items were awarded a star, up to a maximum of four stars for selection, two stars for comparability and three stars for assessment [1] Outcome for cohort, exposure for case-control studies

On the basis of sample selection, three studies achieved only two stars in the selection of their sample, because either their study populations were recruited from clinical or hospital services (Balarm et al 2003), or failed to report the absence of the outcome in their control group (Bosetti et al 2002b, and did not provide an adequate case definition (Llewellyn et al 2004*b*). The majority of studies, however, scored three stars out of four, most of them failing on the selection of controls from hospital or clinic settings. A further four studies only achieved three stars because they did not specify the absence of oral cancer in their control population (Hayes et al 1999, Huang et al 2003, Llewellyn et al 2004*a*, Vlajinac et al 2006). Given the established associations between alcohol consumption, smoking and oral cancer, further selection bias in choice of controls was also dealt with in seven studies who excluded from their control population those who had been admitted to hospital with smoking and alcohol related chronic conditions (all case control studies from Italy Switzerland study, Lissowska et al 2003, Subapriya et al 2007).

Smoking and age were controlled for in the majority of studies. The most common approach taken was simply to control for smoking status (i.e. never, ever, current and former smoker though some studies controlling for smoking, by number or pack years smoked (Schwartz et al 2001, Zavras et al 2001) or the amount of cigarettes smoked per day (Altieri et al 2004, Bosetti et al 2000, Castellsagué et al 2004, Garrote et al 2001) or by "light", medium" or "heavy" smoking status (Hayes et al 1999, Huang et al 2003). A further eleven studies also controlled for education status though only three specified that this was measured by years of education (Garrote et al 1999, Sanchez et al 2000, Castellsagué et al 2004). Three studies also further adjusted for the intake of vegetables and fruit

(Franceschi et al 1999, Hayes et al 1999, Huang et al 2003). In two studies, no adjustment was made for age (Moreno-Lopez et al 2000, Llewellyn et al 2004a).

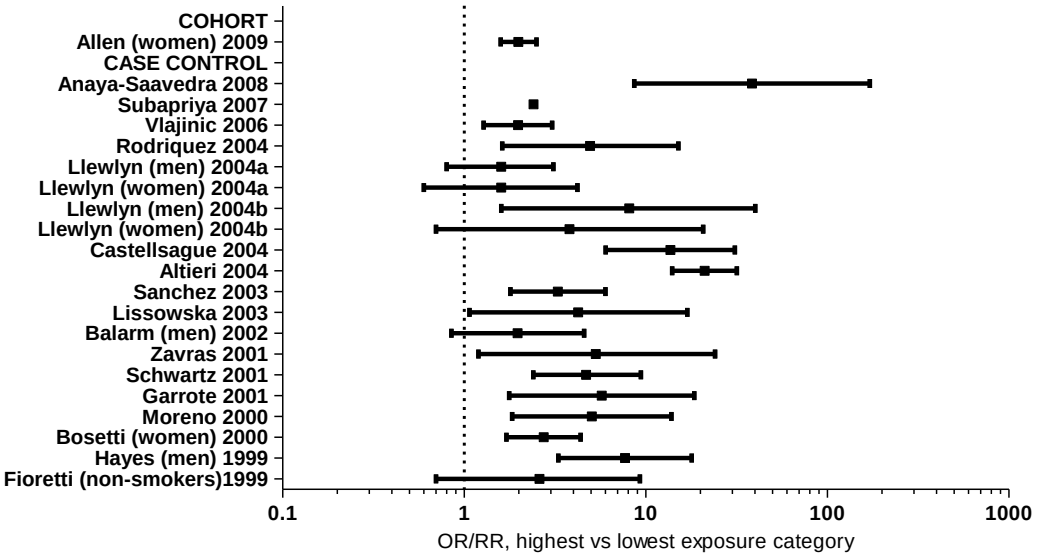
For exposure assessment, two studies scored maximum rating (Hayes et al 1999, Llewellyn 2004b), whilst the majority of studies scored two stars. Of those that only scored two, most were not awarded the third because they failed to specify if interviewers were blinded to case status. A further four studies failed because response rates were substantially different between cases (59%) and controls (>95%) and no reasons were provided for non-response (Llewellyn et al 2004a), or no response rates were specified in the paper (Castellsagué et al 2004, Rodriguez et al 2004 Vlajinac et al 2006). Participation rates across the majority of hospital based studies were very high (i.e. >90% for both cases and controls. This was not the case for the population based case control studies; response rates among cases and controls, varied from 54% and 63% respectively (Schwartz et al 2001), 60% for both cases and controls in paper by Llewellyn et al (2004b) and in two Puerto Rican studies, participation rates for cases and controls were 70% and 83% respectively (Hayes et al 1999, Huang et al 2003).

2.13.3 Results: total alcohol intake and risk of oral[22]

Sixteen studies, providing 19 papers, reported on the association between total alcohol consumption and laryngeal cancer. Of these, one study providing four papers reported on the association between oral cancer and 'recent' alcohol consumption; defined as intake in the previous year (Fioretti et al 1999, Bosetti et al 2000, Altieri et al 2004, Rodriguez et al 2004). Nine studies reported on the association between oral cancer and lifetime alcohol consumption (Hayes et al 1999, Balarm et al 2000 Moreno-Lopez et al 2000, Sanchez et al 2003, Znaor et al 2003, Castellsague et al 2004, Lissowska et al 2003, Vjajiinac et al 2006, Anaya-Saavedra et al 2008). The remaining six studies did not specify a reference period (Garrote et al 1999, Schwartz et al 2001, Zavras et al 2001, Llewellyn et al 2004a, Llewellyn et al 2004b, Allen et al 2009). A summary of oral cancer risk estimates, comparing the highest versus the lowest alcohol exposure category, is presented in Figure 2.13.1. One study reported only on the association between drinking status and oral cancer and is not included in Figure 2.13.1; Znaor et al (2003) reported a statistically significant association (OR 1.70, 95% CI 1.36–2.13) between 'ever' drinkers and oral cancer compared to never drinkers

[22] Multivariate relative risks/odds ratios are presented unless otherwise stated

Figure 2.13.1 Alcohol consumption and oral cancer: highest versus lowest exposure category, by study type (odds ratio/relative risk and 95% confidence intervals)



In a large UK prospective cohort study (Allen et al 2009), women drinking at the highest alcohol exposure category (>15 drinks per week [d/w]), compared to those drinking <2 d/w had a two-fold statistically significant increased risk of oral cancer. Positive, but non-statistically significant, associations were observed at all other alcohol intake levels, with strong evidence of statistically significant dose response relationship (p value for trend <.001). In the same study, never-drinkers had a 20% (RR 1.18, 95% CI 1.02 to 1.36) increased risk of oesophageal SCC, compared to the reference group (Allen et al 2009). In the only other study, case-control in design, reporting on the association between oral cancer and alcohol consumption in women, Bosetti et al (2000b) observed a near three-fold, statistically significant, increased risk of oral cancer in women drinking >2 drinks per day [d/d] compared to non-drinkers (p value for trend <0.0001).

Of the larger case control studies reporting on the association between alcohol consumption and oral cancer, all provided evidence of a statistically significant dose dependent association; Altieri et al (2004), in an Italian study and Castellsague et al (2004) in a Spanish study, observed a strong statistically significant dose response relationship with oral cancer (*p value for trend* 0.0001), including people who drank >11 d/d, compared to a reference group of abstainers, or light drinkers or non-drinkers. Consumption at all levels including drinking as little as 1 d/d had a small positive, statistically significant, association with oral cancer in both studies. In an American population case control study (Schwartz et al 2001), people drinking >43 d/w had an odds ratio of developing cancer of 4.7 (95% CI 2.4-9.4), compared to those drinking <1 d p/w to be at risk of oral cancer. Although there was evidence of increasing risk with amount consumed, there was no association with oral cancer for those drinking <7 d/d (OR 1.0, 95% CI 0.6-1.5). No formal test for trend was reported in

the paper. In an Indian case control study, Subapriya et al (2007) reported a statistically significant two fold increased risk or oral cancer for those drinking >7 d/w, compared to non-drinkers, with a statistically significant dose dependant association (*p value for trend* <0.0001). Lifetime alcohol consumption of >22 d/w (*p value for trend* <0.0001), compared to non-drinkers, was also associated with an increased risk of oral cancer in a population of Puerto Rican men (Hayes et al 1999), though drinking <7 d/w was did not significantly increase the risk of oral cancer (OR 0.8, 95% CI 0.3-2.1).

Smaller studies, based on less than 200 cases and controls, reported statistically significant increased risks of oral cancer at the highest alcohol exposure category ranging from >2 d/d (Balarm et al 2000, Moreno-Lopez et al 2000) to >6 d/d (Garotte et al 1999, Zavras et al 2001), compared to reference groups of lifelong abstainers (Garotte et al 1999, Lissowska et al 2003, Vlajinac et al 2006), non-weekly drinkers (Zavras et al 2001), and non-drinkers (Moreno-Lopez et al 2000). The dose response relationship was statistically significant in all these studies, though lower intake levels all showed a positive, but non-significant association with oral cancer.

In a Spanish study with a young adult population (<46 years), drinking >10 d/d was associated with a statistically significant increased risk (OR 4.94, 95% CI 1.62-15.10) of oral cancer, compared with non-drinkers (Rodriguez et al 2004). In the same study, although, a strong statistically significant dose response relationship (*p value for trend* <0.0001) was evident, drinking <6 d/d was not associated with an increased risk of oral cancer. In a UK case control study, a statistically significant increased risk of oral cancer was observed in men and women aged ≤45 years drinking above recommended weekly drinking guidelines (21 units for men and 14 units for women) compared to those drinking below the weekly guidelines (Llewellyn et al 2004a, 2004b). Among non-smokers, drinkers of <3 d/d had a statistically significant increased risk (OR 3.4, 95% CI 1.1-10.1) of oral cancer, but not for those drinking ≥3 d/d (OR 2.6, 95% CI 0.7-9.3), compared to non-drinkers (Fioretti et al 1999).

2.13.4 Results: drinking dimensions and risk of oral cancer

Seven studies reported on other dimensions of drinking behaviour and the association with oral cancer, including duration of drinking, age first started drinking, and drinking before and after meals.

Castellsagué et al (2004) reported that the odds of oral cancer risk increased steadily and markedly with longer duration of alcohol consumption with increased odds that were statistically significant after 20 years, and >51 years of alcohol consumption (*p value for trend* =0.0001), compared to abstainers. An increased risk of oral cancer still remained for ex-drinkers who had been drinking for >40 years (OR 4.53, 95% CI 2.00-10.27), whilst ex-drinkers of between 1-40 years were at considerably less risk of oral cancer (OR 1.58, 95% CI 0.82-3.07). In an Indian study, point estimates were all raised for drinking duration (up to >40 years of alcohol consumption compared to abstainers), but not for <10 years of alcohol consumption (OR 0.86) though no confidence intervals were provided

in paper to gauge precision of the estimates (Subriya et al 2007). Two studies reported no association for duration of drinking (up to >40yrs), compared to a reference group of those drinking for <20 years (Lissowska et al 2003, Vlajinac et al 2006). Age at which drinking was first started was also not associated with an increased risk of oral cancer in two studies (Balarm et al 2003, Lissowska et al 2003).

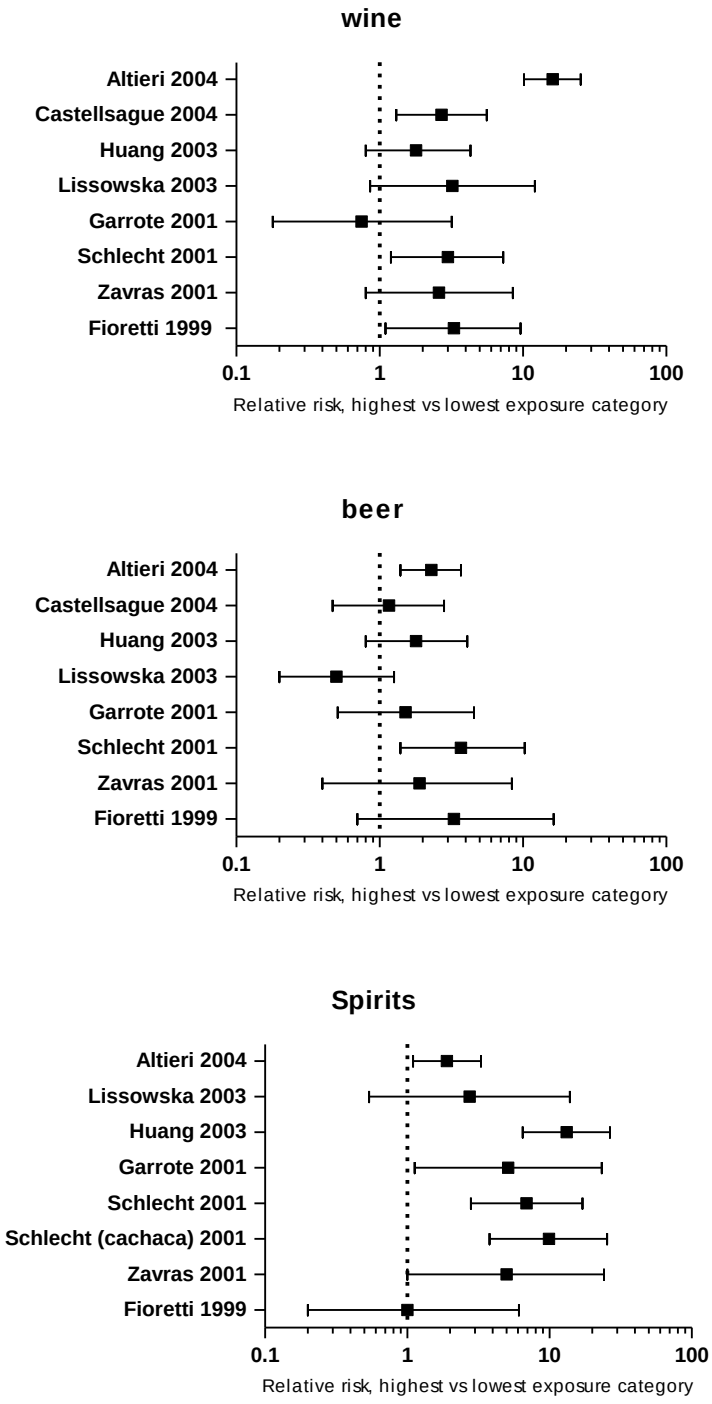
In an Italian case control study (Maso et al 2002), those who drank >56 d/w only at meals (*vs.* <20 d/w) showed an OR=10.3 (95% CI 5.3–20.1) for oral cancer and 7.1 (95% CI 3.7-13.8) for pharyngeal cancer, compared to those drinking 1-20 d/w. This pattern was also observed for those who drank between meals (>56 d/w; OR 27.6, 95% CI 7.3-103.7) and 11.3 (95% CI 4.5-28.4). However, in any alcohol-intake level, subjects also drinking between meals showed a higher risk of developing an oral and pharyngeal cancer than subjects drinking only at meals. Castellsagué et al (2004) in a Spanish study, reported that compared to abstainers, those drinking with meals only, had an OR of 2.22 (95% CI 1.18-4.15) and those drinking between meals only, an OR of 3.58 (95% CI 1.84-6.98). Drinking both with meals and in-between meals, had an OR 3.71 (95% CI 1.94-7.08), compared to never-drinkers.

2.13.5 Results: drink type and risk of oral cancer

Eight studies reported on the association between alcohol drink type and risk of oral cancer. A summary of oral cancer risk estimates, comparing the highest versus the lowest alcohol exposure category, is presented in Figure 2.13.2.

Five studies reported ORs for spirits that were consistently higher and stronger than those reported for wine and beer. In a Puerto Rican study (Huang et al 2003), the risk of oral cancer was most strongly related to heavy spirit consumption (≥43 d/w), irrespective of the quantity of beer/wine consumed, while the elevated risks associated with heavy beer/wine consumption were pronounced only among subjects who also consumed moderate to heavy quantities of spirits (≥8 d/w). Castellsagué et al (2004) reported that, drinkers of spirits (*p value for trend* <0.0001) had a consistent increase in cancer risk in each stratum of amount and duration of alcohol consumption, compared to wine and/or beer drinkers. Furthermore, although statistically significant associations were found with amount and duration within each one of the three groups of type of drink, the ORs for spirits were consistently higher and stronger than those for the other types of drinks. Zavras et al (2001) reported that drinking ouzo (or tsipouro), a local clear spirit of a high (40%) ethanol concentration, was more strongly associated with an increased risk of oral cancer than comparable amounts of wine or beer, e.g., drinking 1-13 drinks of ouzo per week, compared with 1-13 drinks of other types of alcohol, was associated with a 17.4-fold increased risk (95% CI 1.9-162.5), compared to a two-fold increase in risk for those drinking comparable amounts of wine, or beer.

Figure 2.13.2 Alcohol consumption and risk of oral cancer, by drink type (relative risk and 95% confidence intervals)



In a Brazilian study, Schlecht et al (2001) observed increasing risk effects of oral cancer, for wine, beer, hard 'liquor' and cachaca (spirit based drink and predominant choice of alcoholic beverage in southern Brazil) drinkers, though odds ratios were higher for drinkers of cachaca compared to other drink types. Similar findings were also observed for spirit drinkers, compared to wine or beer drinkers, in a small Cuban case control study (Garrote et al 1999).

In contrast, Altieri et al (2004) reported a strong statistically significant positive association for wine drinkers drinking >3 d/w up to >12 drinks p/w, compared to non-wine drinkers. Beer and spirit drinkers of more than >3 d/w also had a statistically significant increased risk (OR 2.3, 95% CI 1.4-3.7) of oral cancer, compared to non-beer and spirit drinkers respectively. The trends in risk with the dose were significant for wine (*p value for trend* <0.0001) and beer (*p value for trend* =0.02), but not for spirits (*p value for trend* =0.29). Lissowska et al (2003) observed a fourfold, non-significant increase in risk for wine drinkers, but only at the highest level of consumption (>5 d/w, OR 3.9, 95% CI 0.94-16.39). No associations were observed between beer and spirit consumption and increased risk of oral cancer. In an Italian population of non-smokers, where wine was the most popular drink type consumed, wine and not beer or spirits was associated with an increased risk of oral cancer, compared to abstainers (Fioretti et al 1999).

2.13.6 Results: effect modification

Three small case control studies examined the interaction between alcohol and smoking on the risk of oral cancer.

Castellsagué et al (2004) found that simultaneous exposure to both smoking and drinking at the highest exposure levels (>6 d/d and ≥21 cigarettes p/d) increased oral cancer risk by almost 50-fold (OR 50.65, 95% CI 19.11-134.24), compared to never drinkers and never smokers. Drinking 1-2 d/d combined with smoking ≥21 cigarettes p/d had a OR of 8.20 (95% CI 2.93-22.94), and never drinkers who smoked >21 cigarettes p/d had a OR of 1.85 (95% CI 0.31-11.13). Castellsagué et al (2004) concluded that the combined effects of smoking and drinking amounts were compatible with a synergistic model of borderline statistical significance ($P_{interaction}$=0.1), but did not state if an additive or multiplicative model was used.

Hayes et al (1999) also reported an increased risk of oral cancer in men at all joint exposure levels, compared to non-smokers and non-drinkers, but risk estimates only reached statistical significance in men smoking >10 cigarettes p/d and who drank >21 d/w. Male non-smokers who drank ≥42 d/w had a OR of 6.4 (95% CI 1.3-31.9), whilst men who did not drink and who smoked >40 cigarettes p/d had a OR of 2.4 (95% CI 0.2-27.2). Heavy drinkers (≥42 d/w) and heavy smokers (>40 p/d), however, had a OR of 38.7 (95% CI 13.6-110.0). Garrotte et al (2001) reported a similar pattern in their Cuban case control study; OR of 111 (95% CI 22.7-543.7), at the highest levels of both exposures (>30 cigarettes p/d and >21 d/w), compared to non-drinkers and non-smokers. Both Hayes (1999) and Garotte (2001) concluded that the joint exposure to alcohol and tobacco resulted in risks 'consistent with independent effects on a multiplicative scale', though no formal test for interaction was reported in either paper.

2.13.7 Summary and conclusions

This review appraised 24 papers from 18 studies (17 case-control and one prospective cohort) that examined the association between alcohol and oral cancer. The majority of studies were consistent in reporting a statistically significant dose response relationship between total alcohol consumption and increased risk of oral cancer irrespective of study size or study design The findings from this review are in line with the already substantial body of evidence establishing total alcohol consumption as a major risk factor for oral cancer (IARC 1988, Corrao et al 2004, WCRF/AICR 2007). There are, however, persisting uncertainties concerning the risk of oral cancer and variation in risk by drink type, duration of use, age and gender, and in relation to the interaction between smoking and alcohol on risk of oral cancer.

Study quality was of a moderate to high standard. The majority of studies recruited cases and controls from hospital settings and were subject to selection bias though in itself unlikely to alter the consistent positive association with oral cancer at the highest alcohol intake levels reported across these studies Smoking and age were controlled for across the majority of studies though residual confounding from smoking is still likely due to imprecise measurements of smoking. The well-established link between socio-economic status (SES) and risk of oral cancer (IARC 2004, Conway et al 2006) was insufficiently dealt with in all studies; although, levels of education were controlled for in eleven of the studies, this is an imprecise measure of SES and further residual confounding from SES is therefore likely though it would only alter the size of the effect and not the direction of the relationship between alcohol intake and risk of oral cancer risk.

To date, little has been published on the effect of drinking on the risk of oral cancer in women though it has been hypothesised that women may be more susceptible than men to alcohol carcinogens as a result of alcohol exposure due to the potential differences in alcohol metabolism (Blume 1986, Corrao et al, 1999; 2000). Two large well designed studies, included in this review both observed an increased risk of oral cancer in women drinking more than two drinks per day (Bosetti et al 2000, Allen et al 2009). The use of low-drinkers as a reference group in a UK study (Allen et al 2009) may have also underestimated the risk of oral cancer in women by using a reference group of light drinkers. Effect sizes in these studies were broadly comparable to those reported for men and for combined populations suggesting very little difference in oral cancer risk by gender. A meta-analysis recently reported no statistically significant effects of gender in modifying the effect of alcohol intake (up to and including more than 100 grams per day) on oral cancer risk (Bagnardi et al 2001).

The association between drink type and risk of oral cancer was investigated by eight studies with inconsistent findings. The ORs for spirits were consistently higher and stronger than those for the other types of drinks in four studies, and wine higher than other drink types in two studies, but these analyses were based on small subgroups of drinkers and estimates lacked precision with wide

confidence intervals. Huang et al (2003) hypothesised that the stronger effect of spirits observed in their study suggested that, alcohol concentration per se is an important risk factor for oral cancer independent of the total quantity of alcohol consumed. However, the differences between drink types in this study were only observed at the highest exposure category where there were three to four times more spirit drinkers than beer or wine drinkers. This pattern was repeated across the majority of studies where the most popular drink type consumed tended to have the highest ORs: spirits (Garrote et al 1999, Castellsagué et al 2004), ouzo (Zavras et al 2003), cachaca (Schlecht et al 2001), and wine (Altieri et al 2004). This would suggest the effects of alcohol per se are perhaps more important than drink type in determining the risk of oral cancer risk.

A number of recent studies have observed the rising incidence of oral cancer cases in younger ages particularly in the UK (Conway et al 2007). Three studies in this review reported on risk of oral cancer in young adults; heavy levels of alcohol consumption associated with non-significant six fold increase in risk in two UK studies and one Spanish study. Studies, however, were small (approximately 100 cases) and estimates lacked precision and in the case of the UK studies, low response rates among cases and controls) make any conclusion about an increased risk in younger people difficult.

The interaction between smoking and alcohol observed in this review is consistent with the numerous case control and cohort studies that have shown that both tobacco and alcohol increase the risk of oral cancer and that their joint effect is multiplicative. The small sample sizes in the analysis as well as different smoking and drinking categories used across the studies may preclude any firm conclusions being drawn about the precise nature of the interaction between smoking and oropharyngeal cancer risk. Previous studies on the interaction between alcohol consumption and smoking and risk of upper aero-digestive tract cancers (UADT) have indicated that in the absence of tobacco use, the association between alcohol consumption and the risk of head and neck cancer is weak and is apparent only at high doses and only for pharyngeal and laryngeal cancers (Hashibe et al 2007). Allen et al's UK study also reported that moderate alcohol intake, compared to those drinking less than 2 drinks per day was only associated with an increased risk of UADT cancers among current smokers. However, in common with all studies included in this review Allen et al (2009) did not report on the risk separately for oral and pharyngeal cancer. Furthermore the inclusion of people drinking at low levels and moderate levels of consumption in a studies reference group ignores the increased risk of oral cancer posed by even low levels of alcohol consumption and this will be particularly marked in light drinkers who smoke low to moderate amounts per day.

Overall, despite weakness inherent in study design, the small size of many of the studies included in the review and the potential for residual confounding from insufficient control for smoking habit and socio-economic status, studies consistently observed a strong association between alcohol

consumption and risk of oral cancer. Effects of drink type were inconclusive though the weight of evidence would suggest that alcohol itself and not the type of drink is the most important factor in determining risk of oropharyngeal cancer.

2.14 Ovarian cancer

Ovarian cancer: summary of evidence from previous reviews
Overall, studies on cancers of ovary show no association with consumption of alcoholic beverages (IARC1988b, WCRF/AICR 1997). Webb et al (2004) in a meta-analysis of seven population based case control studies, published between 1966 and 2003 observed an inverse association between ovarian cancer and the highest compared to the lowest alcohol exposure category (OR 0.72 95% CI 0.54-0.97).

This literature review identified 14 studies, published between 1999 and 2009, that examined the association between alcohol consumption and ovarian cancer. There were seven prospective cohort studies and seven case control studies. Tables for each study describing the study aims, population, alcohol measurement methods and main results are provided in Appendix D.

2.14.1 Study characteristics

A summary of the general characteristics of the studies is provided in Table 2.14.1 below.

Table 2.14.1 Alcohol and ovarian cancer: general characteristics of studies reviewed

Authors	Year	Country	Outcome/No outcome Case/Control	Age range (M/Mdn)	Sample selection	Sample selection
Cohort studies						
Allen	2009	UK	3,559/ 1,280,296	>55	breast screening clinics	random selection
Chang	2007	USA	253/90,478	(M=50)	state teachers retirement system	random selection
Keleman	2004	USA	147/27,008	55-69	Iowa driver's license registry	random sample
Lagiou	2001	Sweden	76/36,856	(M=42.7)	national hospital database	consecutive
Larsson	2004	Sweden	266/61,084	39-76	regional population	random-selection
Schouten	2004	Netherlands	214/2,412	55-69	general population	random sample
Tworoger	2008	USA	507/79,646	30-55	female registered nurses	volunteers
Case control studies						
Fujita	2008	Japan	141/2,016	>30	hospital	consecutive/
Goodman	2003	USA	558/607	n/s	regional population	consecutive /random sample
Modugno	2003	USA	767/1,367	20-69	hospital/local population	consecutive/random sample
Peterson	2006	USA	762/6,271	40-79 (M=58)	regional population	consecutive/random selection
Riman	2004	Sweden	655/3,899	50-74	regional population	consecutive/random sample
Tavani	2001	Italy	1,031/2,411	18-79 (M=56)	hospital	not specified
Webb	2004	Australia	696/768	18-79	hospital/ electoral rolls	consecutive/random sample

Abb: n/s not specified; M=mean; Mdn= median

The largest prospective cohort study was carried out by Allen et al (2009) with seven times as many incident ovarian cancer cases as the next largest study (Tworoger et al 2008). The remaining cohort

studies identified approximately 200 ovarian cancer cases. The majority of case control studies were also moderate in size ranging between 650-750 cases. The largest case control study identified in this review was carried out by Tavani et al (2001), recruiting approximately 1031 cases and 2411 controls to their study population

2.14.2 Study quality

The quality scores assessed according to the NOS are presented in Table 2.14.2. Overall, studies were of a moderate to high quality, scoring between 5-8 stars.

Table 2.14.2 Ovarian cancer: assessment of study quality

	Selection* (out of 4)	Comparability* (out of 2)	Outcome/Exposure[1]* (out of 3)	Total
Cohort				
Allen 2009	3	2	2	7
Chang 2008	3	2	3	8
Kelemen 2004	4	2	1	7
Larsson 2004	4	1	2	7
Lagiou 2001	3	0	2	5
Schouten 2004	4	1	3	8
Tworoger 2008	3	1	3	7
Case control				
Fujita 2008	3	1	2	6
Goodman 2003	4	1	2	7
Modugno 2003	3	1	1	5
Petersen 2006	3	1	2	6
Riman 2004	4	1	2	7
Tavani 2001	3	1	3	7
Webb 2004	4	1	2	7

* High quality characteristics within each of these items were awarded a star, up to a maximum of four stars for selection, two stars for comparability and three stars for assessment; [1] Outcome for cohort, exposure for case-control studies.

On the basis of sample selection, cohort studies scored highly with either three or four stars out of four. A number of studies failed in this item because of the potential selection bias introduced by their choice of study populations i.e. groups of nurses and health professionals (Tworoger et al 2008), and teachers (Chang et al 2008).

Attempts to address selection bias varied across the case control studies. The majority of studies were consistent in excluding subjects reporting a history of ovarian cancer or previous bilateral oophorectomy. Only one study excluded patients admitted to the hospital for chronic conditions or digestive tract diseases related to alcohol intake (Tavani et al 2001). In one study, no exclusion criteria were specified (Modungo et al 2003). For many of the studies there was, therefore, the possibility that conditions related to known or potential risk factors for ovarian cancer or alcohol consumption were included in the study populations. The extent of interviewer bias among the case control studies was unclear. Only one study specified the interviewers were blinded to case and control subject status (Peterson et al 2006). Non response bias was generally not a problem for the

majority of case control studies with four reporting participation rates for cases and controls of approximately 75%-85%. However, in one American case control study response rates were only 60% and 65% for cases and controls, respectively (Goodman and Tung et al 2003). A lack of detail in the study on reasons for non-participation makes it difficult to determine what effect these low rates may have on the risk estimates. In one study response rates were not specified (Tavani et al 2001). The potential for recall bias and measurement error varied across the case control studies. Consumption in the last month was used as the reference period by Riman et al (2004) and in the preceding year by Webb et al (2004). In contrast, Goodman and Tung (2003) examined lifetime history of alcohol use and Peterson et al (2006) defined their reference period as intake in early adulthood (20-30 years of age) and 1 or 5 years before study commenced.

Many of the established risk factors for ovarian cancer and possible confounders of the alcohol-ovarian cancer association such as parity, oral contraceptive use and hormone replacement therapy (HRT), were controlled for in all the studies. For comparability purposes, therefore, studies were only awarded an extra star if they controlled for HRT. All studies controlled for age and a further two for HRT (Keleman et al 2004, Chang et al 2008). The remaining studies all received one star though in the majority of these adjustment was made for other risk factors associated with ovarian cancer (and alcohol consumption), but where the evidence was less consistent e.g. measures of BMI (controlled for in eight studies), or diet and in particular folate intake (Larsson et al 2004). Petersen et al (2004) did not adjust their estimates for the established ovarian cancer risk factors and only controlled for age. In the record linkage cohort study by Terry et al (2001), no adjustment for the aforementioned risk factors since no lifestyle information was collected as part of their study.

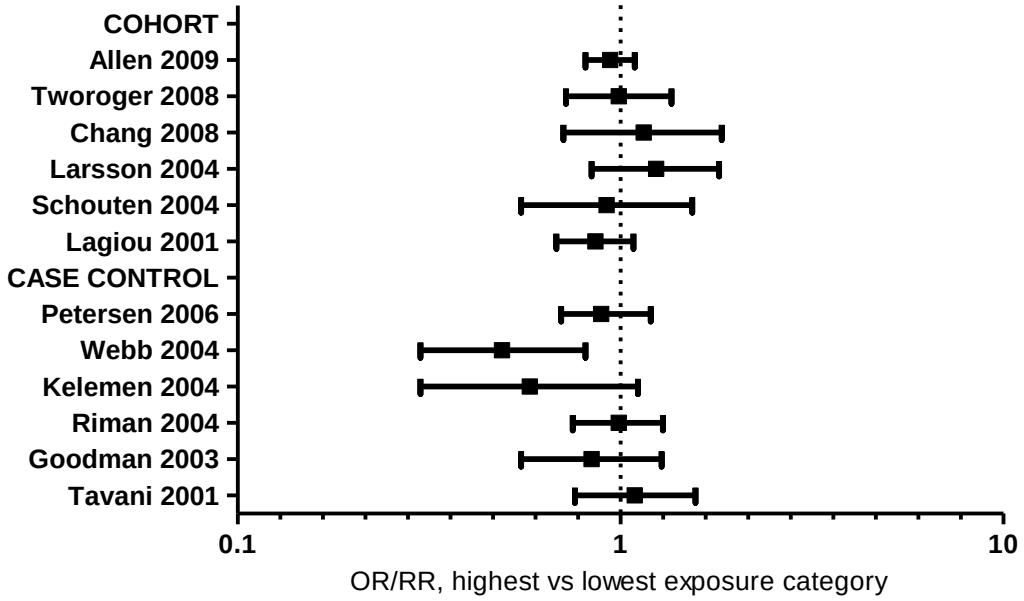
2.14.3 Results: alcohol intake and risk of ovarian cancer[23]

Thirteen of the 14 studies reported on the dose response association between alcohol consumption and ovarian cancer. Six studies reported on the association between ovarian cancer and 'recent' alcohol intake defined as alcohol consumption in the preceding year in five studies (Kelemen et al 2004, Schouten et al 2004, Chang et al 2007, Fujita et al 2008, Tworoger et al 2008) and in the previous month (Riman et al 2004). Goodman and Tung (2003) examined lifetime history of alcohol use defined as drinking any type of alcoholic beverage at least once a week for 6 months or more and Peterson et al (2006) defined their reference period as intake in early adulthood (20-30 years of age) and 1 or 5 years before study commenced. In the remaining five studies, the reference period was not specified (Tavani et al 2001 Modugno et al 2003, Larsson and Wolk 2004, Webb et al 2004, Allen et al 2009). A summary of ovarian cancer risk estimates, comparing the highest versus the lowest alcohol exposure category, is presented in Figure 2.14.2. In the remaining study, Fujita et al (2008)

[23] Multivariate relative risks/odds ratios are presented unless otherwise stated

reported a statistically significant inverse association (OR 0.58, 95% CI 0.35-0.96) between 'current' drinkers and ovarian cancer, compared to abstainers.

Figure 2.14.1 Alcohol consumption and ovarian cancer, highest versus lowest exposure category, by study type (odds ratio/relative risk and 95% confidence intervals)



In an Australian case control study, increasing of alcohol consumption of ≥2 drinks per day [d/d] was associated with a 50% decreased risk of ovarian cancer (*p value for trend* =0.003), compared to non-drinkers (Webb et al 2004). Goodman and Tung et al (2003) also reported an inverse association for women drinking <7 d/w and ≥14 d/w, compared to non-drinkers, but women drinking 7-<14 d/w had an increased risk (OR 1.14 95% CI 0.76-1.72, *p value for trend* =0.70) of ovarian cancer. Two case control studies, however, found no association between ovarian cancer and alcohol consumption. In a Swedish study, women drinking ≥5 g/d had an OR of 0.99 (95% CI 0.75-1.29, *p value for trend* =0.80), compared to non-drinkers (Riman et al 2004). Tavani et al (2001), in an Italian hospital based case control study, observed no association between alcohol and ovarian cancer for women drinking 36 g/d, compared to lifelong abstainers.

2.14.3.1 Results: total alcohol intake and risk of ovarian cancer by histological type

Four studies investigated risk of ovarian cancer associated with alcohol consumption based on histological subtype. Three studies, one cohort (Riman et al 2004) and two case control studies (Goodman and Tung 2003, Petersen et al 2006) found no association between mucinous ovarian tumours and alcohol consumption. In contrast, Modugno et al (2003) reported a significant increase in

risk for mucinous tumours among current drinkers (but not former drinkers), drinking >24 grams per week [g/w] (OR 1.93, 95% CI 1.02-3.65), compared to never drinkers.

Goodman and Tung (2003) reported a significant inverse association between current drinkers and risk of non-mucinous (i.e. serous, endometrioid, or clear cell tumours) ovarian cancer (OR 0.69, 95% CI 0.48-0.98). Riman et al (2004), however, observed no association for endometrioid, serous, and clear cell tumours among women drinking >5 g/d compared to non-drinkers. Petersen et al (2006) found that for serous tumours, risk was significantly elevated in women consuming >1d/d aged between 20-30 years (OR 1.72, 95% CI 1.16-2.56), compared to non-drinkers, though a more modest and non-significant association was obtained for recent consumption (OR 1.19, 95% CI 0.82-1.73).

2.14.4 Results: drinking dimensions and risk of ovarian cancer

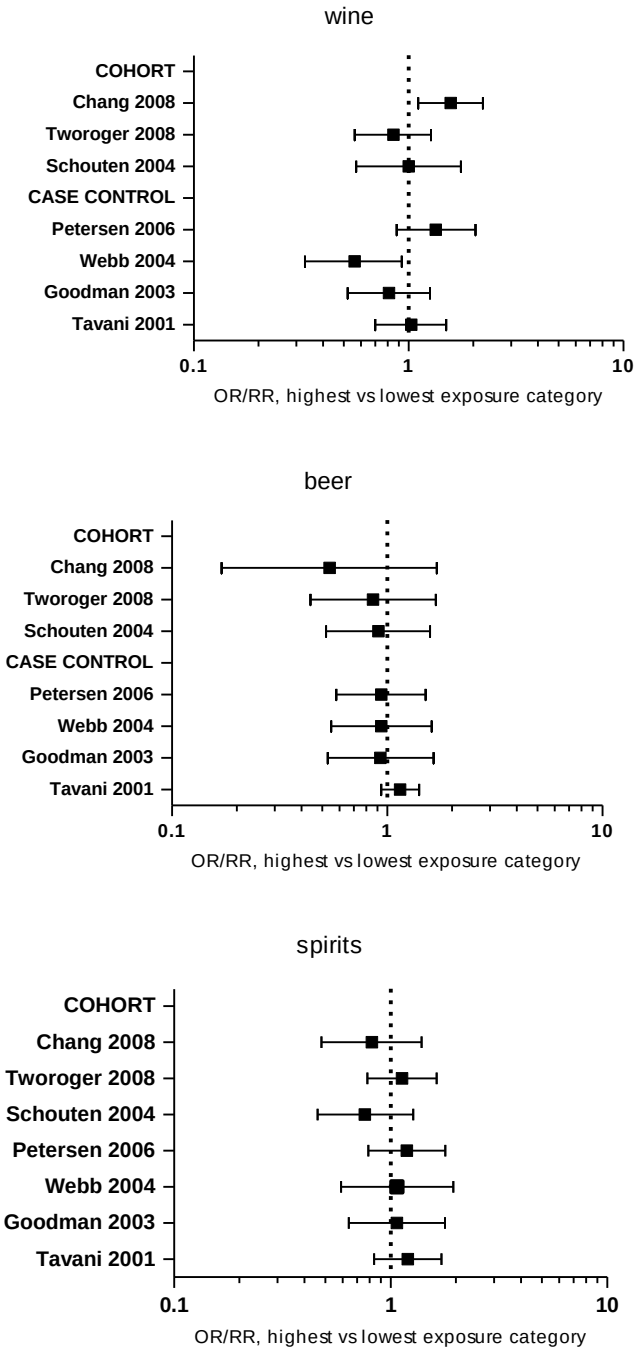
Chang et al (2008) found no association between drinking at ages 18-22 years and 30-35 years and risk of ovarian cancer in a cohort of American teachers. Further**,** in an American population case control study (Peterson et al 2006), compared to non-drinkers, ever drinking at ages 20-30 (OR 1.27, 95% CI 0.96-1.68, *p value for trend* =0.11) or drinking >1 d/d in the recent past was not associated with an altered risk of ovarian cancer (OR 0.89, 95% CI 0.70-1.20, *p value for trend* =0.77).

2.14.5 Results: drink type and risk of ovarian cancer

Eight studies examined whether risk of ovarian cancer varied by type of alcoholic beverage. A summary of risk estimates, comparing the highest versus the lowest alcohol exposure category, is presented in Figure 2.14.2.

Three prospective cohort studies reported no association between wine, spirits or beer, and risk of ovarian cancer (Keleman et al 2004, Schouten et al 2004, Tworoger et al 2008). In the remaining cohort study, Chang et al (2008) observed a statistically significant increased risk of ovarian cancer associated with wine consumption, but not beer or spirits in their cohort of teachers.

Figure 2.14.2 Alcohol consumption and risk of ovarian cancer, highest versus lowest exposure, by drink type (odds ratio/relative risk and 95% confidence intervals)



Of the four case control studies to look at the risk of ovarian cancer by drink type, Goodman and Tung (2003) found a modest reduction in risk, but not statistically significant, associated with wine and beer drinking, but no association with spirits drinking. Webb et al (2004) also reported that wine drinkers had a lower risk of ovarian cancer than both self-reported non-drinkers and women who reported drinking only beer or spirits. There was also a statistically significant trend toward lower risk with increasing wine consumption (*p value for trend* =0.01 excluding non-drinkers). In both these

studies, wine was the most consumed alcoholic beverage among cases and controls. In the hospital case control study by Tavani et al (2001), consumption of wine, which accounted for 95% of the total alcohol consumption in their study population, closely resembled the total alcohol drinking pattern, with a slight increase in risk of ovarian cancer from wine drinking, but no trend in risk with dose. In the remaining study, no association was found between wine or beer consumption and risk of ovarian cancer, compared to never drinkers (Peterson et al 2004).

2.14.6 Results: effect modification

Three studies, two prospective and one case control, reported on the interaction between alcohol and other risk factors in increasing or decreasing the risk of ovarian cancer.

Keleman et al (2004) examined whether the relation of folate with ovarian cancer would depend on the level of alcohol intake in a population of post-menopausal women. They reported that women drinking ≥4 g/d with a total folate intake of ≥331 μg/day had a non-significant decreased risk (RR 0.46, 95% CI 0.16–1.32) of ovarian cancer compared to those drinking with a folate intake of <331 μg/day. On the other hand, women drinking <4g/d with a folate intake of ≥331 μg/day, had a small, non-significant, increased risk of ovarian cancer (RR 1.19, 95% CI 0.76–1.88). The test for interaction between total folate and alcohol consumption and ovarian cancer risk was statistically significant ($P_{interaction}$=0.04).

Schouten et al (2004) examined the effect modification on the association between alcohol consumption and ovarian cancer by use of oral contraceptives, parity and body mass index (BMI) and found little evidence of a statistically significant interaction with any of the risk factors. Among women who had never used oral contraceptives, there was no association between ovarian cancer and alcohol consumption (RR 0.99, 95% CI 0.69-1.42), while the risk among ever users of oral contraceptives was only slightly and non-significantly increased (RR 1.22, 95% CI 0.51-2.91). The interaction with BMI, however, appeared to show a trend; in women of normal weight (BMI < 25 kg/m^2) alcohol consumption was associated with a non-significantly increased relative risk of 1.33 (95% CI 0.82- 2.14). In overweight (BMI 25-<30 kg/m^2) and obese (BMI ≥30 kg/m^2) women, alcohol consumption was associated with non-significantly decreased relative risks of 0.95 (95% CI 0.54-1.67) and 0.52 (95% CI 0.20-1.34), respectively, but there was no evidence of a statistically significant interaction ($P_{interaction}$=0.21). There was no also statistically significant interaction between parity ($P_{interaction}$=0.22) and energy intake ($P_{interaction}$=0.23) on the relationship between alcohol consumption and ovarian cancer (Schouten et al 2004). It was not clear from this paper whether the additive or multiplicative model had been used to test for interaction.

In an Italian case control study, there was no significant consistent heterogeneity with ovarian cancer risk for alcohol intake in any subgroup of age at diagnosis, education, parity, oral contraceptive use, family history of ovarian/breast cancer, body mass index, and calorie intake (Tavani et al 2001).

2.14.7 Summary and conclusion

This review identified 14 studies which examined the association between alcohol consumption and risk of ovarian cancer. In summary, the findings of this review furnish an inconsistent picture regarding an association between total alcohol consumption and ovarian cancer. Cohort studies reported both positive and inverse associations between drinking alcohol and ovarian cancer and the two largest cohort studies in the present review found no association between alcohol consumption and ovarian cancer. Evidence from previous reviews is also inconsistent. Webb et al (2004) in a meta-analysis of seven population based case control studies observed an inverse association between ovarian cancer and the highest compared to the lowest alcohol exposure category (pooled OR 0.72 95% CI 0.54-0.97, *p heterogeneity among studies* =0.09). In the same paper, a meta-analysis of seven hospital based case control studies reported an OR of 1.10 (95% CI 0.83-.44, *p heterogeneity among studies* =0.20) for the highest intake versus the lowest alcohol intake level (Webb et al 2004). In a pooled analysis of 10 prospective cohort studies (published between 1997 and 2004), which included 2001 ovarian cancer cases, alcohol consumption was not associated with ovarian cancer risk (pooled RR (PRR) 1.12, 95% CI 0.86-1.44, *p value for trend* =0.72, *p heterogeneity among studies* =0.50) comparing >30g/d to 0 g/d (Genkinger et al 2006).

In the present review an association between drink type and ovarian cancer was observed for wine drinkers, but not beer or spirit drinkers, compared to never drinkers. The findings reported for wine drinkers were, however, contradictory. One study reported an inverse association between approximately one glass of wine a day and ovarian cancer (Webb et al 2004) whilst two studies reported an increased risk of ovarian cancer at similar levels of drinking (Tavani et al 2001, Chang et al 2008). Socio-economic status was not controlled for in these studies and this may explain the associations observed between wine drinkers and ovarian cancer in the present review. In addition, many of the studies suffered from small numbers of cases within strata and subsequently results of variations in ovarian cancer risk, by drink type should interpreted cautiously. Genkinger et al (2006) in pooled analyses that simultaneously adjusted for intakes of alcohol from wine, beer, and spirits as continuous variables (increment 15 g/d) reported no association of alcohol from wine (pooled multivariate RR (PRR) 1.07, 95% CI 0.95-1.21), beer (PRR 1.02, 95% CI 0.84-1.24) and spirits (PRR 1.03, 95% CI 0.93-1.14) with ovarian cancer risk (P-value for the test of difference=0.83).

There was little evidence, in the present review, of a modifying effect of other risk factors on the association between alcohol consumption and ovarian cancer. Only a small number of studies

reported on this aspect and no evidence was provided of a significant interaction of parity, oral contraceptive use, folate intake or weight on the association between alcohol consumption and ovarian cancer. Genkinger et al (2006), in their pooled analysis of 10 cohort studies, also reported that the association between total alcohol intake (15 g/d increment) and ovarian cancer risk was not significantly modified by a range of hormonal, environmental and nutritional factors including folate intake ($P_{interaction}$=0.18), BMI ($P_{interaction}$=0.74), parity ($P_{interaction}$>0.99) and oral contraceptive use ($P_{interaction}$=0.41).

Overall a strong association between alcohol consumption and ovarian cancer seems unlikely. However, only observations can be made about low to moderate levels of consumption since most studies contained few heavy drinkers. Further studies looking at this aspect of drinking are therefore required. Additional studies of risk factor for epithelial ovarian cancer by histological type are also warranted with some consistency required in histological classification.

2.15 Pancreatic Cancer

Pancreatic cancer: summary of evidence from previous reviews
Earlier systematic reviews have concluded that alcohol consumption is unlikely to be causally related to cancer of the pancreas. IARC1988b, WCRF/AICR 1997). A meta-analysis of 17 studies (including 4 cohort and 13 case control studies published between 1966-1999) reported no increased risk of pancreatic cancer in those drinking 25 g/d (RR) 0.98, 95% CI 0.90-1.05) and a small non-significant, increased risk in those drinking 50 g/d (RR 1.05, 95% CI 093-1.18) and 100 g/d (RR 1.18 95% CI 0.94-1.49, P Het <0.05) (Bagnardi et al 2001).

This literature review identified 12 studies, published between 1999 and 2009, which examined the association between alcohol consumption and pancreatic cancer. There were eight cohort studies and four case control studies, including one nested case control study. Tables for each study, describing the study aims, population, alcohol measurement methods and main results, are provided in Appendix D.

2.15.1 Study characteristics

Ten studies reported on the association between alcohol drinking and incident pancreatic cancer and the remaining two (prospective cohort) studies investigated the association between alcohol consumption and pancreatic cancer mortality (Coughlin et al 2000, Lin et al 2002). Three papers were based on established prospective cohort studies described in described in section 2.4; Netherlands Cohort Study on diet and cancer (Heinen et al 2009); the European Prospective Investigation into Cancer and Nutrition (Rohrmann et al 2009) and the US Nurses' Health Study and Health Professional follow up study (Michaud et al 2001). A summary of the general characteristics of the studies is provided in Table 2.15.1 below.

The largest study included in the present review, a US prospective mortality study, identified approximately 3,500 pancreatic cancer deaths (Coughlin et al 2000). A further two cohort studies, investigating the association between incident pancreatic cancer and alcohol consumption, identified over 1,000 cases; the UK Million Women Study (Steven et al 2009, see Allen et al in section 2.3.1.) and the US National Institutes of Health (NIH)-AARP Diet and Health Study (Jiao et al 2009). In general, however, the majority of studies were of a small to moderate size, with the number of pancreatic cancer cases identified ranging between 200 and 600.

Table 2.15.1 Alcohol and pancreatic cancer: general characteristics of studies reviewed

Authors	Year	Country	Sample size	Age range (M/Mdn)	Sample base	Sample selection
Cohort studies						
Coughlin[1]	2000	USA	3,751/1.2m	≥30 (Mdn=57)	general population	volunteers
Heinen	2009	Netherlands	447/120,405	55–69	general population	random sample
Jiao	2009	US	1,149/ 566,020	50-71	regional pop. in 6 states & members of retirement scheme	random selection
Lin[1]	2002	Japan	225/110,567	40–79 (M=57.3)	general population	random selection
Michaud	2001	US	288/136,305	30-75	female nurses and male health professionals	volunteers
Rohrmann	2009	Europe	555/477,845	n/s	various	random selection
Stevens	2009	UK women	1,338/1.3m	>55 (M=55.9)	breast screening clinics	random selection
Ye	2002	Sweden	305/178,383	(M=44)	national database of hospital patients	non-random selection
Case control studies					**cases/controls**	
Hassan	2007	US	808/808	(M=61/62)	hospital	consecutive/ random selection
De Martel	2008	US	104/262	(M=49/52)	general population	random sample
Talamini	1999	Italy	630/700	(M=52/50)	regional hospitals /electoral lists	consecutive/random selection
Villeneuve	2000	Canada	583/4,813	(M=61.5/58)	state cancer registry /health insurance plan holders	consecutive /random sample

Abb: n/s not specified; M=mean; Mdn= median [1] Outcome is pancreatic cancer mortality

Eleven of the 12 cohort studies were prospective in design. In the remaining study, women hospitalised in any Swedish hospital between 1965 and 1994, with a diagnosis of 'alcoholism' based on ICD-9 classification, were identified and retrospectively followed up for an average of 10 years (Ye et al 2002). De Martel et al (2008) conducted a nested case control study among 128,992 adult subscribers to a Medical Care Program; cases were randomly selected from newly diagnosed cases of pancreatic cancer and matched to controls from the same source as the cases. In an Italian hospital based case control study, Talamini et al (1999) created two groups from their pancreatic cancer cases – patients with pancreatic cancer without a history of chronic pancreatitis and those without a history of chronic pancreatitis. Of the chronic pancreatitis cases, 80% were estimated to have alcohol-induced chronic pancreatitis.

2.15.2 Study quality

The quality scores assessed according to NOS are presented in Table 2.15.2. Overall, cohort studies were of a high quality, scoring between 7-9 stars. Case control study quality was of a moderate to high quality scoring between 5-8 stars.

Six cohort studies achieved maximum rating on the NOS. One prospective study achieved three stars failing because of possible selection choice of study population i.e. health professionals (Heinen et al 2008), whilst Ye et al (2002) in their retrospective hospital based record linkage study did not control for any of the established confounding risk factors of the alcohol and pancreatic cancer association. On the basis of sample selection, two case-control studies scored highly four stars out of four. Hassan et al (2008) failed because their control group was selected from a small group of relatives and friends attending the same hospital as cases. Villeneuve et al (2000) did not demonstrate that cancer was absent from their control group. Hassan et al (2008) also excluded from their control group, people with tobacco-related cancers from their control group, but no case-control study specified the exclusion of alcohol related cancers or diseases from their control group.

Table 2.15.2 Pancreas cancer: assessment of study quality

	Selection* (out of 4)	**Comparability* (out of 2)**	**Outcome/Exposure[1]* (out of 3)**	**Total**
Cohort				
Coughlin	4	2	3	9
Heinen	4	2	3	9
Jiao	4	2	2	9
Lin	4	2	3	9
Michaud	3	2	2	7
Rohrmann	4	2	3	9
Stevens	4	2	2	8
Ye	3	0	3	6
Case control				
De Martel	4	0	2	6
Hassan	3	2	3	8
Talamini	4	1	2	7
Villeneuve	3	2	2	7

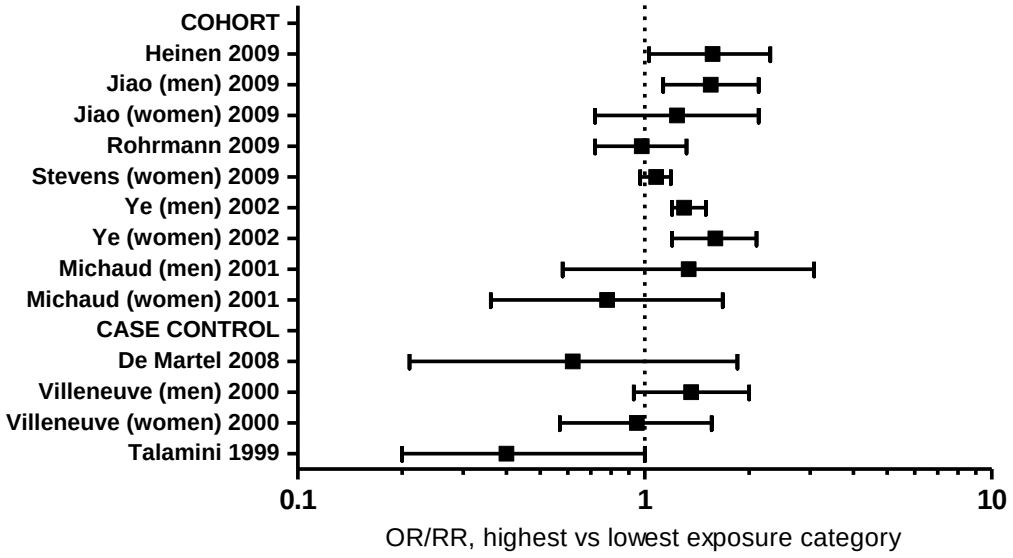
* High quality characteristics within each of these items were awarded a star, up to a maximum of four stars for selection, two stars for comparability and three stars for assessment; [1] Outcome for cohort, exposure for case-control studies

Two studies failed to achieve any stars for comparability, since unadjusted estimates were presented in their paper (Ye et al 2002, De Martel et al 2008). Age and smoking were controlled for in the remaining studies. Smoking terms generally consisted of current smoking status, amount (per day) and duration smoked (pack-years). Villeneuve et al (2000) did not control for weight (BMI). Five studies controlled for a 'history' of diabetes (Coughlin et al 2001, Michaud et al 2001, Lin et al 2002, Hassan et al 2007, Jiao et al 2009). Diet and nutritional status was controlled for in a number of ways from measures of 'energy intake' (Michaud et al 2001, Rohrmann et al 2009) to measures of total energy intake, energy-adjusted saturated fat, red meat, and total folate intake (Jiao et al 2009). Talamini, et al (1999) stratified their analysis by pancreatic cancer patients, with and without a history of chronic pancreatitis.

2.15.3 Results: total alcohol intake and risk of incident pancreatic cancer [24]

Nine studies, six cohort and three case-control studies, investigated the association between incident pancreatic cancer and 'recent' alcohol consumption. A summary of pancreatic cancer risk estimates, comparing the highest versus the lowest alcohol exposure category, is presented in Figure 2.15.1.

Figure 2.15.1 Alcohol consumption and incident pancreatic cancer, highest versus lowest exposure category, by study type (odds ratio/relative risk and 95% confidence intervals)



In one of the larger cohort studies, Jiao et al (2009) observed an increased risk of pancreatic cancer in only those drinking ≥3 drinks per day [d/d] compared with light drinkers; those who drank ≥3 d/d (approximately 39-42 grams per day [g/d]) had a relative risk of 1.45 (95% CI 1.17-1.80, *p value for trend* =0.002). Men (RR 1.50, 95% CI 1.18-1.90, *p value for trend* =0.001) were at higher risk of pancreatic cancer than women (RR 1.24, 95% CI 0.72, 2.13, *p value for trend* =0.75) though the differences were not statistically significant ($P_{interaction}$=0.50). Male and female non-drinkers had a non-significant 12% and 21%, respectively, increased risk of pancreatic cancer, compared to 'light drinkers' (Jiao et al 2009). Heinen et al (2009) observed a modest borderline statistically significant 70% increased risk of pancreatic cancer, in their Dutch cohort, for those drinking >30 g/day, compared to abstainers, but not at lower levels of intake and there was no evidence of a dose response relationship (*p value for trend* =0.12). Michaud et al (2001) also observed a non-significant 20-40% increased risk (*p value for trend* =0.55) of pancreatic cancer in male health professionals across all alcohol intake levels (highest intake level of (≥30 g/d) compared to non-drinkers, but no association between alcohol and pancreatic cancer in female nurses (≥30 g/d; RR 0.78, 95% CI 0.36-1.68, *p value for trend* =0.49). In a Swedish retrospective cohort study, a modest and unadjusted, statistically

[24] Multivariate relative risks/odds ratios are presented unless otherwise stated

significant, excess risk in pancreatic cancer of 30% and 60% was also observed among men and women, respectively, who had been admitted to hospital with a diagnosis of 'alcoholism', compared to the Swedish general population (Ye et al 2002).

In contrast, in a multi-centre European based cohort study, drinking 30 to 59.9 g/d (RR 1.03, 95% CI 0.88-1.21) and ≥60 g/d (RR 0.88, 95% CI 0.72-1.08), compared to those drinking 0.1 to 4.9 g/d, was not associated with an increased risk of pancreatic cancer. Non-drinkers were also not at an increased risk (RR 0.95, 95% CI 0.81-1.12) of pancreatic cancer, compared to light drinkers (Rohrmann et al 2008). Stevens et al (2009), in a large cohort study, reported that the risk of incident pancreatic cancer did not vary significantly for women across categories of alcohol consumption (≥14 units per week [u/w]; RR 1.08, 95% CI 0.11, *p value for trend* =0.2), compared to women drinking 1-2 u/w. Non-drinkers had a similar risk of pancreatic cancer as drinkers in highest alcohol exposure category (RR 1.07, 95% CI 0.06).

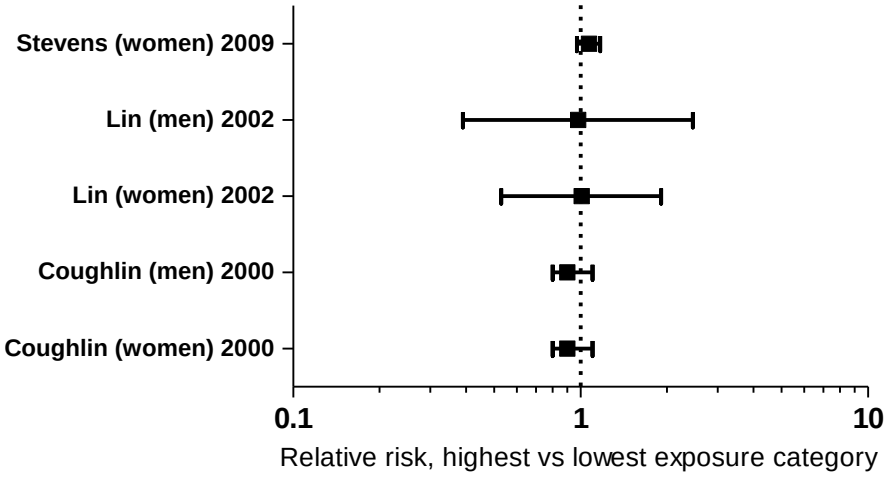
Villeneuve et al (2000) reported a modest and non-significant increased risk of pancreatic cancer in men drinking >7 drinks per week, compared to non-drinkers. There was no increased risk of pancreatic cancer in women drinking at similar levels. In a nested case control study reporting only unadjusted odds ratios, drinking ≥2 d/d did not increase the odds of pancreatic cancer occurring, compared to non-drinkers (De Martel et al 2008). In an Italian hospital based case control study, Talamini et al (1999) reported a six-fold increase in the odds of pancreatic cancer in men with chronic pancreatitis, drinking >80 g/d (OR 6.7, 95% CI 1.2-36), compared to those drinking 0-40 g/d. In contrast, they reported a weak statistically significant inverse association in men without a history of chronic pancreatitis who drank >80 g/d (OR 0.4, 95% CI 0.2-1.0), compared to non-drinkers without a history of chronic pancreatitis. Male cases with chronic pancreatitis and without cancer, had a two-fold, statistically significant, increased risk of pancreatic cancer (OR 2.2, 95% CI 1.5-3.3), compared to men drinking >40 g/d.

Two studies reported on the association between lifetime drinking and increased risk of pancreatic cancer; Hassan et al (2007), in a US hospital case control study, reported that for average lifetime alcohol consumption of >60millilitres (ml) per day compared to those drinking <60 ml/d (approx. <40 g/d) there was no increased risk of pancreatic cancer. Rohrmann et al 2009 also observed that an average lifetime intake of ≥30 g/d did not significantly increase risk of pancreatic cancer.

Three prospective cohort studies reported on the association between pancreatic cancer mortality and alcohol consumption (see Figure 2.15.2). In a large American cohort study, alcohol consumption was not associated with an increased risk of pancreatic cancer mortality in men and women who drank >1 d/d (Coughlin et al 2002) and for women drinking up to and including >14 u/w in a UK study

(Stevens et al 2009). In a Japanese cohort, heavy alcohol consumption (>60 g/d for men and >30 g/d for women) was also not associated with an increased risk of fatal pancreatic cancer (Lin et al 2002).

Figure 2.15.2 Alcohol consumption and pancreatic cancer mortality, highest versus lowest exposure category in prospective cohort studies (relative risk and 95% confidence intervals)



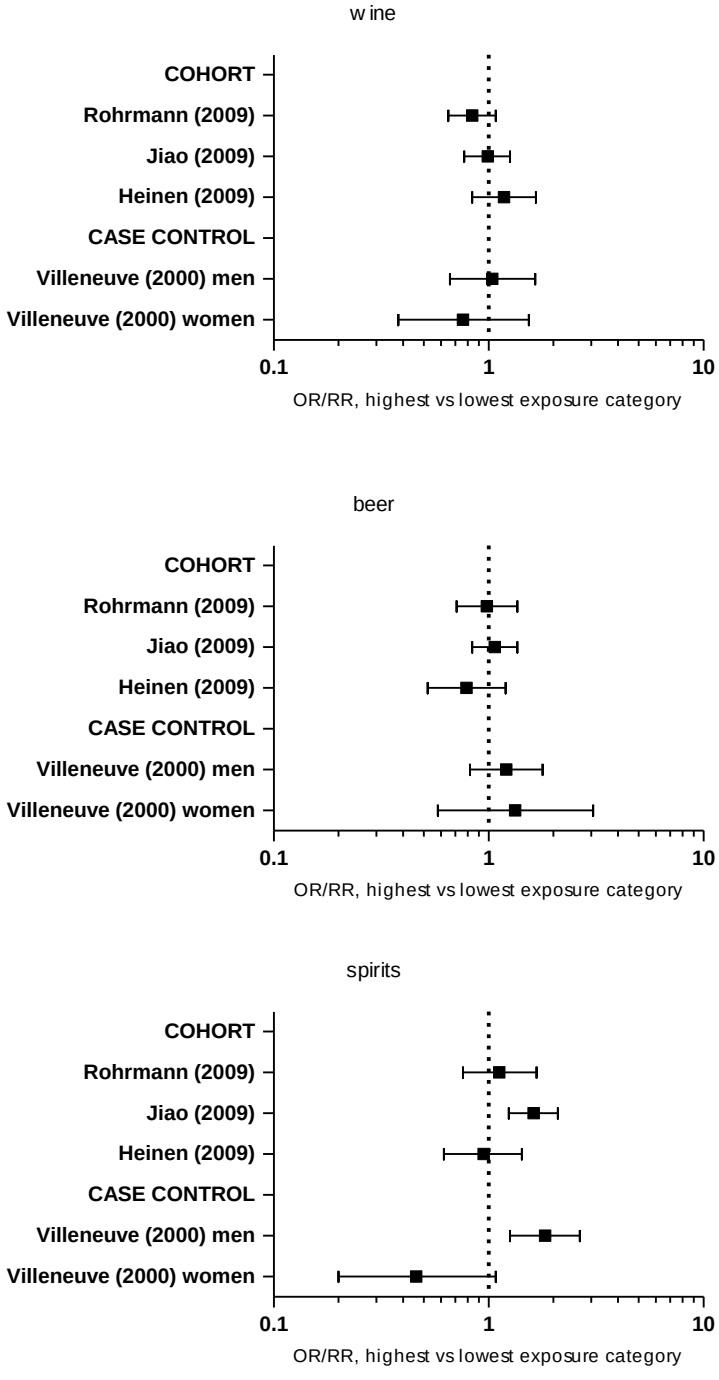
2.15.4 Results: drinking dimensions and risk of pancreatic cancer

There were no studies identified in this review investigating the associations between drinking dimensions (e.g. duration, frequency and pattern) and risk of pancreatic cancer.

2.15.5 Results: drink type and risk of pancreatic cancer

Four studies examined whether risk of pancreatic cancer varied by type of alcoholic beverage. A summary of risk estimates, comparing the highest versus the lowest alcohol exposure category, is presented in Figure 2.15.3.

Figure 2.15.3 Alcohol consumption and risk of pancreatic cancer, highest versus lowest exposure category; by drink type (odds ratio/relative risk and 95% confidence intervals



In two prospective cohort studies, which reported on low levels of drinking only (approximately one drink per day), beer, wine or spirit consumption was not associated with either an increased risk of pancreatic cancer among current drinkers i.e. those drinking in the previous year (Heinen et al 2009) or among current and lifetime drinkers (Rohrmann et al 2009). Jiao et al (2009) observed an increased risk, of statistical significance, in their cohort of Dutch spirit drinkers, drinking >3 d/d. Similar

findings were reported by Villeneuve et al (2000) for men drinking >1 spirit d/d, but not in women. Neither beer nor wine was associated with an increased risk of pancreatic cancer in these studies.

2.15.6 Results: effect modification

Three studies assessed the interaction between smoking and alcohol consumption on the risk of pancreatic cancer. Jiao et al (2009), in a large US cohort study reported, that there were no statistically significant interactions of alcohol use on risk of pancreatic cancer, by lifelong smoking status ($P_{interaction=}$0.25), the number of years since quit smoking ($P_{interaction=}$0.61), or folate intake ($P_{interaction=}$0.50). The authors further evaluated the risk of pancreatic cancer among participants with self-reported diabetes based on 161 cases and found that heavy total alcohol use (> 6 d/d) was not associated with risk. The association of alcohol use with risk did not vary by diabetes status ($P_{interaction=}$=0.30).

Heinen et al (2009) reported that current smokers drinking >30 g/d had a two-fold (RR 2.40, 95% CI 1.06-1.41) statistically significant increased risk of pancreatic cancer, compared to never-smokers and abstainers. Non-smokers drinking >30 g/d had a non-significant increased risk of pancreatic cancer (RR1.77, 95% CI 0.58-5.33). There was no evidence of significant interaction ($P_{interaction=}$0.97) of alcohol consumption and smoking on the risk of pancreatic cancer.

In a cohort of nurses and health professionals, Michaud et al (2001) reported that male current smokers, who drank >5 g/d had an increased risk of pancreatic cancer, but these associations were statistically non-significant (compared with <5 g/d, the RRs, for male current smokers drinking between 5-14.9 g/d and ≥15 g/d, were 3.98, 95% CI 0.8-18.9 and 2.14, 95% CI 0.4-10.5 respectively). The alcohol intake and pancreatic cancer associations were similar for never-smokers and past smokers with both not associated with an increased risk of pancreatic cancer. Michaud et al (2001) also assessed the interaction between weight (measured by BMI) and alcohol consumption on the risk of pancreatic cancer; those with a BMI ≥25 kg/m^2 did not have an increased risk of pancreatic cancer at any alcohol intake level (>15 g/d, RR 0.97, 95% CI 0.54-1.76), compared to non-drinkers with a BMI ≥25 kg/m$^{2.}$ In contrast, a BMI of <25kg/m^2 and drinking >15g/d was associated with a non-significant increased risk of pancreatic cancer compared to non-drinkers with a BMI of <25kg/m^2. Michaud et al (2001) reported that these differences were not statistically significant, and that no trend was apparent for the increased risk among those in the low BMI stratum, but no data was provided in the paper to demonstrate this.

2.15.7 Summary and conclusions

Twelve studies, eight cohort and four case-control, published between 1999 and 2009, were appraised

and which considered the association between alcohol consumption and pancreatic cancer. Drinking ≥30 g/d was associated with an increased risk of pancreatic cancer in most, but not all, of the cohort studies. Risk estimates were generally higher for men than for women, but differences were not statistically significant. There was no convincing evidence that drinking <30 g/d was associated with an increased risk of pancreatic cancer. The association between drink type and risk of pancreatic cancer was inconsistent across studies and these analyses were limited by very small sample sizes and risk estimates lacked precision. Alcohol consumption was not associated with an increased risk of pancreatic cancer mortality.

Studies in the present review were generally of a moderate to high quality. In general, studies adjusted for the main confounders of the alcohol and pancreatic cancer association including age, smoking and weight (BMI). Some studies controlled for history of diabetes mellitus thought the nature of the association between alcohol consumption and diabetes is still uncertain. Residual confounding from smoking may explain some of the inconsistent results reported for the association between low to moderate levels of alcohol consumption, and pancreatic cancer risk. Diabetes mellitus and chronic pancreatitis, however, may have a modifying effect on the association between alcohol consumption and increased risk of pancreatic cancer. The potential effect of chronic pancreatitis was demonstrated in the paper by Talamini et al (1999) where a small number of pancreatic cancer cases (n=69) without a history of chronic pancreatitis, drinking >40 g/d, had a 50% reduced risk of pancreatic cancer compared to a two-fold increased risk for chronic pancreatitis cases without cancer, the vast majority of which were alcohol related. Heavy alcohol consumption has also been known to be a risk factor for type 2 diabetes mellitus, which is also linked to pancreatic cancer (Go et al 2005). The various metabolic effects of alcohol through heavy consumption can also lead to or interact with other risk factors (genetic, dietary, environmental, and lifestyle factors) that result in acute and chronic pancreatitis and diabetes mellitus and, ultimately, affect the multi-step process of carcinogenesis toward the development of pancreatic cancer (Go et al 2005).

The findings of the present review are consistent with those in the published literature. The recent WCRF/AICR (2007) review concluded that low to moderate levels of drinking were unlikely to have an effect of the risk of pancreatic cancer, but the effects of heavy (approximately 30-40 g/d) drinking on the risk of pancreatic cancer could not be excluded. A meta-analysis of 17 studies (including 4 cohort and 13 case control studies published between 1966-1999) reported no increased risk of pancreatic cancer in those drinking 25 g/d (pooled relative risk (PRR) 0.98, 95% CI 0.90-1.05) and a small non-significant, increased risk in those drinking 50 g/d (pooled PRR 1.05, 95% CI 093-1.18) and 100 g/d (pooled PRR 1.18 95% CI 0.94-1.49, *P* Het <0.05) (Bagnardi et al 2001). In a recent pooled analysis of 14 cohort studies (including data from the Michaud et al (2001) paper identified in the present review), only drinking ≥30 g/d, compared to drinking 0 g/d, was associated with a modest increase in the risk of pancreatic cancer (PRR 1.36, 95% CI 1.15-1.60, *p value for trend* =0.05, *P* Het

=0.80) (Genkinger et al 2009). The PRRs were consistently higher for women than for men, but differences were not statistically different (*P* Het =0.19).

Overall the evidence for an association between low and moderate alcohol consumption and increased pancreatic cancer is weak. Heavy alcohol consumption may increase the risk of pancreatic cancer either directly or by causing chronic pancreatitis. Further studies are required, to clarify the possibility of an increased risk of pancreatic cancer at heavy levels of alcohol consumption and which take into account major risk factors such as smoking, and the modifying effect of diabetes mellitus and chronic pancreatitis.

2.16 Prostate Cancer

Prostate cancer: summary of evidence from previous reviews
Overall, studies on cancers of the prostate show no association with consumption of alcoholic beverages. IARC1988b, WCRF/AICR 1997). The lack of association between total (current) alcohol consumption and prostate cancer risk was also reported in a review of studies conducted between 1971 and 1996 (Breslow and Weed 1998) and a meta-analysis (Dennis and Hayes 2001).

The literature search identified 18 papers from 17 studies, published between 1999 and 2009, which examined the relationship between alcohol consumption and prostate cancer. There were nine cohort studies and eight case control studies. Two cohort studies reported on the same cohort of male health professionals in America and both have been retained in the review as they report on different aspects of the relationship between alcohol and prostate cancer; from baseline and average lifetime alcohol intake (Sutcliffe et al 2007), and by drinking frequency and prostate tumour type (Platz et al 2004). Of the cohort studies, eight were prospective and one was retrospective in design (Putnam et al 2000). Tables for each study, describing the study aims, population, alcohol measurement methods and main results, are provided in Appendix D.

2.16.1 Study characteristics

A summary of the general characteristics of the studies is provided in Table 2.16.1 below.

Five papers were based on four established prospective cohort studies described in Box 2, section 2.2 (p28); Netherlands Cohort Study on Diet and Cancer (Schuurman et al (1999); European Prospective Investigation into Cancer and Nutrition Rohrmann et al (2008); the Health Professional follow up study (Platz et al 2004, Sutcliffe et al 2007) and the Copenhagen Centre for Prospective Population Studies (Albertsen et al 2001). In a small retrospective cohort study, the study population consisted of cancer-free controls who participated in a population-based case-control study conducted between 1986 and 1989 (Putnam et al 2000). Controls were randomly selected from a regional population identified through driver's license records and health insurance plans.

Cohort and cases control studies varied in size. The largest cohort study identified in the present review included approximately 3,348 prostate cancer cases (Sutcliffe et al 2007). Other large cohort studies by Rohrmann et al (2008) and Platz et al (2004) identified 2655 and 2,479 prostate cancer cases, respectively. The length of follow up in the majority of cohort studies ranged from between ten to twenty years though in three studies the duration of follow up was between five and six years (Schuurman et al 1999, Putnam et al 2000, Sesso et al 2001), whilst Rohrmann et al (2008) reported an average follow up of 8.7 years.

Three case control studies identified approximately 1500 cases and controls (Villeneuve et al 1999, Crispo et al 2004, Chang et al 2005). One case control study recruited less than 100 cases and controls to their study population (Barba et al 2004).

Table 2.16.1 Alcohol and prostate cancer: general characteristics of studies reviewed

Authors	Year	Country	Sample size	Age range (M/Mdn)	Sample base	Sample selection
Cohort studies						
Albertsen	2001	Denmark	233/26,496	(M=52)	city population	random sample
Breslow	1999	USA	386/5,766	25 -75	general population	representative sample
Ellison	2000	Canada	154/3,400	50-84	10 Canadian provinces	random sample
Lund Nilsen	2000	Norway	644/22,895	>40	regional population	representative sample
Platz*	*2004*	*USA*	*2,479/47,843*	40-75	*male health professionals*	*volunteers*
Sutcliffe*	*2007*		*3,348/45,433*			
Putnam	2001	USA	101/1,577	(M=69.4)	state population	random sample
Rohrmann	2008	Europe	2,655/ 142,607	40-65	various	random selection
Schuurman	1999	Holland	680/58,279,	55-69	general population	random sample
Sesso	2001	USA	366/12,805	(M=66.6)	Harvard university alumni	volunteers
Case control studies			**cases/controls**			
Barba	2004	USA	88/304	35-85	hospital/state driver licence list	consecutive/random sample
Chang	2005	Sweden	1,499/1,130	45-79	regional population	consecutive/non-random selection
Crispo	2004	Italy	1,294/1,451	(M=66)	hospital	consecutive/non-random selection
Hodge	2004	Australia	858/905	<70	regional population	random sample
Hsieh	1999	Greece	372/308	>60	hospital	consecutive/non-random selection
Schoonen	2005	USA	753/703	40-64	cancer registry/state population	random sample
Sharpe	2001	Canada	399/476	(M=63)	hospital/regional electoral list	consecutive/random sample
Villeneuve	1999	Canada	1623/1623	50-74	regional population	consecutive/random sample

* papers from the same study. Abb: n/s not specified; M=mean; Mdn= median

2.16.2 Study quality

The quality scores assessed according to the NOS are presented in Table 2.16.2. Overall, studies were of a moderate to high quality, scoring between 6-8 stars.

On the basis of sample selection, cohort and case control studies scored highly with either three or four stars out of four. Seven studies scored four stars, and all the other studies that scored three failed either because their study cohort could not be considered truly representative of the general population (Schuurman et al 1999, Sesso et al 2001, Sutcliffe et al 2007), for not specifying that the outcome was absent prior to baseline entry into cohort (Albertsen et al 2002) or from the study control group (Schoonen et al 2005, Chang et al 2005). All studies scored either two or three stars for

exposure assessment in cases control studies and for outcome assessment in cohort studies. Of those that only scored two, most were not awarded the third because of the potential response bias in their study due to low and contrasting response rates among cases and controls (Barba et al 2004, Hodge et al 2004 Chang et al 2005) or for failing to provide a statement of the completeness of follow-up in cohort studies (Breslow et al 1999, Ellison et al 2000, Llund-Nilsen et al 2000, Albertsen et al 2002, Rohrmann et al 2008).

Table 2.16.2 Prostate cancer: assessment of study quality

	Selection* (out of 4)	**Comparability* (out of 2)**	**Outcome/Exposure[1]* (out of 3)**	**Total**
Cohort				
Albertsen 2002	3	2	2	7
Breslow 1999	4	1	2	7
Ellison 2000	4	1	2	7
Llund-Nilsen 2000	4	1	2	7
Platz 2004 Sutcliffe 2007	3	1	3	7
Putnam 2000	3	1	3	7
Rohrmann 2008	4	1	2	7
Schuurman 1999	3	2	3	8
Sesso 2001	3	1	2	6
Case-control				
Barba 2004	3	2	2	7
Chang 2005	3	1	2	6
Crispo 2004	3	2	2	7
Hodge 2004	4	2	2	8
Hsieh 1999	1	1	2	4
Schoonen 2005	3	1	2	6
Sharpe 2001	4	2	3	9
Villeneuve 1999	4	2	3	9

* High quality characteristics within each of these items were awarded a star, up to a maximum of four stars for selection, two stars for comparability and three stars for assessment; [1] Outcome for cohort, exposure for case-control studies

Since the aetiology of prostate cancer is poorly understood, adjusting for confounding factors in studies on alcohol consumption and prostate cancer is problematic which explains the variation in comparability scores. Only six studies scored two stars and the remaining studies only one star principally because they controlled for age. Of the six studies with two stars, the second star was awarded because each study attempted to control for the possible confounding effects of socio-economic status (SES) on the association between alcohol consumption and prostate cancer. Measures of SES used, however, varied across studies from years of education (Albertsen et al 2002, Barba et al 2004), to levels of family incomes (Villeneuve et al 1999, Sharpe et al 2001). A further two studies did not define their measure of SES (Schuurman et al 1999, Hodge et al 2004).

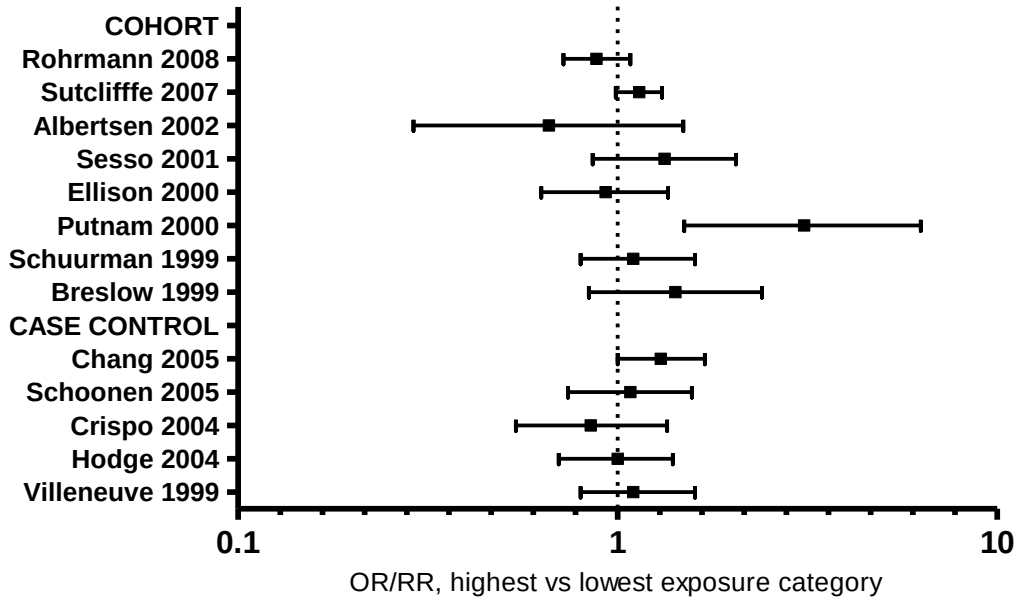
2.16.3 Results: total alcohol intake and risk of prostate cancer[25]

Eight cohort and five case-control studies, reported on the association between total 'recent' alcohol

[25] Multivariate relative risks/odds ratios are presented unless otherwise stated

consumption and prostate cancer. A summary of prostate cancer risk estimates, comparing the highest versus the lowest alcohol exposure category, is presented in Figure 2.16.1.

Figure 2.16.1 Alcohol consumption and prostate cancer, highest versus lowest exposure category, by study type (odds ratio/relative risk and 95% confidence intervals)



Of the larger cohort studies, Rohrmann et al (2008) did not find an association between alcohol consumption and an increased risk of prostate cancer (≥60 grams per day [g/d]; RR 0.88, 95% CI 0.72-1.08, compared to 0.1-4.9 g/d). For each additional 10 g/d of alcohol the relative risk was 1.00 (95% CI, 0.98-1.02). Non-drinkers were not at an increased risk of prostate cancer. 0.95 (95% CI 0.81-1.12). Sutcliffe et al (2007) reported a modest, non-significant, increased risk of prostate cancer across all alcohol intake categories, with strong evidence of a statistically significant dose response relationship (≥16.5 g/d; RR 1.14, 95% CI 0.96-1.34, *p value for trend* =0.0034).

Schuurman et al (1999) observed a small increased risk of prostate cancer associated with alcohol consumption, but none of the point estimates were statistically significant and there was no evidence of a dose response association (≥30 g/d; RR 1.1, 95% CI 0.8 95% CI 0.8-1.6, *p value for trend* =0.74, compared to non-drinkers). Sesso et al (2001) reported similar findings in a cohort of American university alumni (>36 g/d; RR, 1.33 95% CI 0.86-2.05, *p value for trend* =0.40, compared to 'almost never' drinkers).

In a small retrospective cohort study, Putnam et al (2000), reported a threefold increased risk of prostate cancer in men drinking >13 g/d (RR 3.1, 95% CI 1.5-6.3), compared to non-drinkers, with strong evidence of a statistically significant dose response relationship (*p value for trend* =0.001). Breslow et al (1999) reported a 40% non-significant increased risk of prostate cancer in men drinking

≥22 drinks per/week [d/w], but drinking <22 d/w was not associated with an increased risk of prostate cancer, compared to non-drinkers. In a Danish cohort study (Albertsen and Grønbaek 2004), men drinking >70 g/d, compared to those drinking <1.5 g/d (including non-drinkers), had a relative risk of 0.68 (95% CI 0.31-1.52). There was no association between prostate cancer and men drinking <30 g/d and no strong evidence of statistically significant dose response relationship (*p value for trend* =0.48).

Of the larger case control studies, Chang et al (2005) observed a weak statistically significant dose response relationship (>22 g/d OR 1.2, 95% CI 1.0-1.7, *p value for trend* =0.06, compared to non-drinkers) between 'recent' alcohol consumption and prostate cancer. In the remaining case control studies there was no evidence of an association between alcohol consumption and an increased risk of prostate cancer (Villeneuve et al 1999, Crispo et al 2004, Hodge et al 2004, Schoonen et al 2005).

Three studies reported on the association between lifetime drinking and an increased risk of prostate cancer. In a large European cohort study Rohrmann et al (2008) did not find an association between lifetime alcohol consumption and prostate cancer (≥60 g/d; RR 1.09, 95% CI 0.86-1.39). Cumulative drinking levels over a person's lifetime also did not increase the risk of prostate cancer in an American population based control study (≥24,000 grams; OR 1.29, 95% CI 0.84–1.97, *p value for trend* =0.33, compared to non-drinkers) (Schoonen et al 2005) or in an Italian case control study (>11048 ounces; OR 0.83, 95% CI 0.43-1.6, compared to drinking<2647 ounces) (Barba et al 2004).

2.16.3.1 Results: total alcohol intake and risk of prostate cancer by tumour type

Five studies investigated the association between alcohol consumption and risk of prostate cancer, by tumour type. In three prospective cohort studies, there was no association between advanced or localised tumours and alcohol consumption, and risk estimates were similar for both tumour types across all alcohol intake levels in each study (Schuurman et al 1999, Platz et al 2004, Rohrmann et al 2008). In a large Swedish case control study, Chang et al (2005) reported an increased risk of localised tumours across all alcohol intake levels (>22 g/d; OR 1.4, 95% CI 1.0-2.0, *p value for trend* =0.34), compared to non-drinkers, but not of advanced tumours (>22 g/d; OR 0.9 0.7-1.2, *p value for trend* =0.50). Differences between tumour types were, however, not statistically significant (*p value for test of heterogeneity* =0.78).

2.16.4 Results: drinking dimensions and risk of prostate cancer

Six studies investigated the association between prostate cancer and other aspects of drinking behaviour including drinking frequency, patterns and duration of drinking. Daily drinking was not associated with an increased risk of prostate cancer in Norwegian cohort study (Llund-Nilsen et al

2000) and in a cohort of American health professionals (Platz et al 2004). However, a moderate, statistically significant, increased risk of prostate cancer was observed in a Canadian case control study, for both weekly (OR 1.6, 95% CI 1.1-2.4) and daily (OR 1.6, 95% CI 1.1-2.3) drinkers compared to those reported 'never drinking weekly' (Sharpe and Siemiatycki 2001).

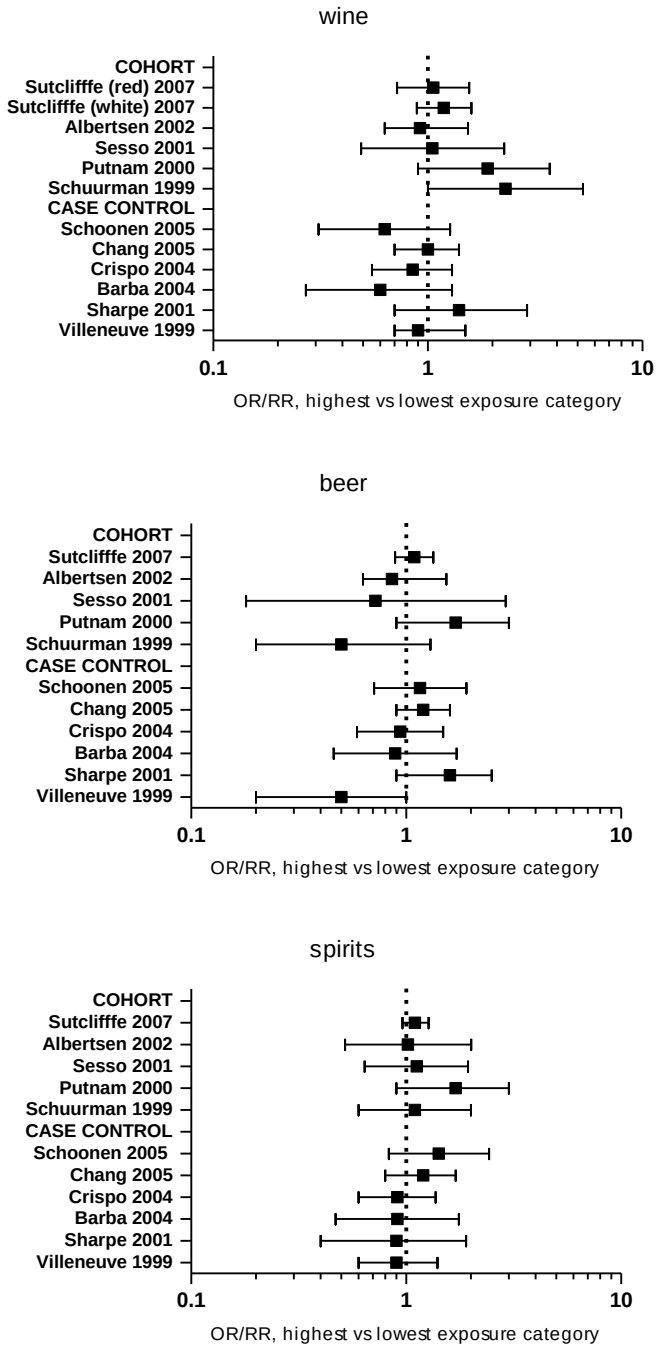
Duration of drinking was also not associated with prostate cancer in three case control studies (Barba et al 2004; Crispo et al 2004; Schoonen et al 2005) though Sharpe and Siemiatycki (2001) reported, as they did with drinking frequency, that men drinking for more than 39 years were four times more likely to get prostate cancer than non-drinkers. Men who started drinking between the ages of 17-19 years had a small, but statistically significant increased risk of cancer of the prostate (OR 1.36, 95% CI 1.05-1.75) compared to those who started drinking at 16 years and under. This increase in risk was not evident for those who started drinking between ages 20-22 years and >23 years (Crispo et al 2004).

2.16.5 Results: drink type and risk of prostate cancer

Eleven studies reported on the association between alcoholic beverage type and risk of prostate cancer. A summary of risk estimates, comparing the highest versus the lowest alcohol exposure category, is presented in Figure 2.16.2.

Five cohort studies reported on the association between drink type and prostate cancer. In a large European prospective cohort study, wine (red or white), beer and spirits were not associated with an increased risk of prostate cancer (Sutcliffe et al 2007). Similar findings were reported by Albersten and Grønbaek (2002). Putnam et al (1999) reported non positive associations, in their retrospective cohort study, between prostate cancer and drinking of wine, beer or spirits, compared to non-drinkers. Point estimates at each alcohol intake level were broadly comparable across all drink types.

Figure 2.16.2 Current and lifetime alcohol consumption and risk of prostate cancer, highest versus lowest exposure category; by drink type (odds ratio/relative risk and 95% confidence intervals)



In contrast to findings reported in their paper on the association between total alcohol consumption and prostate cancer, Schuurman et al (1999) observed a twofold increase in risk (RR 2.3, 1.0-5.3, *p value for trend* =0.67) of prostate cancer among men drinking ≥30 g/d of wine. Men drinking equivalent amounts of beer, however, had a reduced risk of prostate cancer (RR 0.5, 95% CI 0.2-1.3, *p value for trend* =0.48), compared to non-drinkers, but no association with prostate cancer was reported at lower intake levels. There was no association between spirits and prostate cancer. Sesso et

al (2001), in a cohort of university alumni, also reported an inverse association between prostate cancer and men drinking >3 'units' p/d of beer, but no association between wine or spirit drinkers and prostate cancer.

Of the large case control studies, Crispo et al (2004) reported that wine beer and spirits were not associated with an increased risk of prostate cancer. In the paper by Chang et al (2005), results for drink type were similar across all intake levels and were comparable to those reported for total alcohol consumption and risk of prostate cancer. Villeneuve et al (1999), however, observed a reduced risk of prostate cancer among men drinking >1/d/d of beer (OR 0.5, 95% CI 0.2-1.0), compared to non-beer drinkers. In contrast spirit intake of ≥4 d/d was associated with a non-significant 80% (OR 1.8, 95% CI 0.9-3.8, *p value for trend* =0.52) increased risk of prostate cancer. No association was reported between wine and prostate cancer.

Two case control studies reported on the association between lifetime drinking and prostate cancer by drink type. Barba et al (2004) observed a non-significant 10-40% decreased risk of prostate cancer at the highest alcohol lifetime exposure category, compared to abstainers, for all three drink types. A similar decrease in the odds of getting prostate cancer, was observed by Schoonen et al (2005), for lifetime wine drinkers; ≥15 d/w, OR 0.63, 95% CI 0.31-1.27, *p value for trend* =0.41, compared to non-drinkers. Beer and spirit drinkers however, drinking at comparable amounts, had ORs of 1.16 (95% CI 0.71-1.91) and 1.42 (95% CI 0.83–2.43), respectively.

2.16.6 Results: effect modification

Two studies reported on the effect modification of other risk factors on the association between alcohol consumption and prostate cancer. In both papers, details of these interactions where only provided in the main text with no supporting data tables.

Rohrmann et al (2008) reported that the associations between baseline or average lifetime alcohol consumption and prostate cancer risk were not modified by age at baseline ($P_{interaction}$ =0.34 and 0.82, respectively) or body mass index ($P_{interaction}$ =0.92 and 0.87, respectively). Platz et al (2004) reported that the association between alcohol intake and prostate cancer did not vary by age at diagnosis or by intake of folic acid, vitamin E, or tomato sauce. However, the association of alcohol with advanced and metastatic/fatal disease was stronger in men who were younger (<60 years old) at diagnosis ($P_{interaction}$=0.03 and 0.07, respectively). Risk of prostate cancer associated with alcohol consumption was greater among men with type 2 diabetes mellitus ($P_{interaction}$= 0.08). Among men with diabetes, in comparison with non-drinkers, the hazard ratios were 1.09 for 0.1-4.9 g/d, 1.27 for 5.0-14.9 g/d, 1.92 for 15.0-29.9 g/d, 1.37 for 30-49.9 g/d, and 2.48 for ≥50 g/d (p-trend = 0.05). For men without diabetes, the association was similar to the overall association.

2.16.7 Summary and conclusion

This review identified 18 papers from 17 studies that examined the association between prostate cancer and alcohol consumption. Overall the majority of cohort and case control studies observed an increased risk of prostate cancer at the highest alcohol exposure category (range 16-30g/d), compared to reference groups mainly consisting of non-drinkers, but rarely reported a statistically significant dose response relationship. Residual confounding from socio-economic status or unknown or less well established risk factors may explain the observed increased risk. Weiss et al (2003) for example have argued that the screening history for prostate cancer may affect disease incidence and act as confounder. Schoonen et al (2005) in their case control study did observe a strong association between screening history and disease and found that screening history differed across levels of alcohol intake among controls. The lack of association between total (current) alcohol consumption and prostate cancer risk has been reported elsewhere: in a comprehensive review of studies conducted between 1971 and 1996 (Breslow and Weed 1998) and a meta-analysis (Dennis and Hayes 2001).

There was no convincing evidence that drink type modified the association between alcohol consumption and prostate cancer. The larger and better designed studies, both cohort (Sutcliffe et al 2002, Sutcliffe et al 2007) and case-control (Crispo et al 2004 and Chang et al 2005) reported no variation in the association for prostate cancer by beer, wine or spirits. Overall, the reported associations between drink type and prostate cancer were similar to those reported for total alcohol consumption and risk of prostate cancer. The inconsistency of results of the association between prostate cancer and wine or beer drinking could be explained by the different reference groups used across studies varied which consisted in some studies of 'abstainers' and in others of 'non-drinkers of specific drink types'.

Five studies examined this aspect of the relationship between alcohol consumption and prostate cancer. In each of the studies alcohol intake showed stronger associations with localized prostate tumours than with advanced prostate tumours or distant and familial tumours though these were of borderline statistical significance and were often based on less than 100 cases. It may be that these are chance findings because of small sample sizes and inconsistencies in defining tumour type outcomes, however, the consistent reporting of an increased association between alcohol consumption and risk of localised prostate tumours cannot be ignored.

Other aspects of drinking behaviour may have a role in the aetiology of prostate cancer. Whereas traditionally alcohol and prostate cancer risk studies have assessed usual alcohol consumption over the previous year (as is the case in the studies reviewed here), clinical and epidemiological evidence suggests that prostate carcinogenesis may span decades (Issacs 1994). Drinking duration or distant past alcohol intake may, therefore, be more relevant to prostate cancer risk and/or very different from

recent intake. Evidence from this review would suggest however that this type of drinking behaviour, as with current drinking, has no relationship with the development of prostate. Five of the studies in this review explored this aspect of the alcohol and prostate cancer relationship and in each study drinking duration showed no association with prostate cancer including a large high quality cohort study (Rohrmann et al 2008). Furthermore in Schoonen et al's (2005) study, a rigorous approach to measuring this aspect of drinking behaviour was taken whereby men were allowed to change their drinking pattern over time without standardized consumption periods, enabling short periods of heavy drinking to be recorded in addition to the typical adult drinking habits. In this study duration of drinking years, lifetime total intake and average lifetime intake per week were not associated with increased risk of prostate cancer. Interestingly two studies, both population based case-control studies, did observe a statistically significant dose response relationship for those who had first started drinking alcohol aged <16 years when they were sixteen years or younger was reported (Sharpe & Siemiatycki 2001, Crispo et al 2004) though it was not clear if those in this age-group continued to drink throughout their adult life and for how long. Distant past exposures are also problematic to ascertain because they depend on participants' memory of exposure history leaving considerable room for misclassification error.

In conclusion, although alcohol consumption is unlikely to increase the risk of prostate cancer, a positive effect of high intakes of alcohol cannot be excluded, since the majority of studies reviewed here were only able to look at effects of low to moderate drinking. The positive associations between age related exposure and drinking frequency are interesting, but due to the small number of studies looking at this aspect, inconclusive. The long latency period of prostate carcinogenesis certainly requires past alcohol consumption to be considered as much an important dimension to prostate cancer risk as total alcohol consumption and future cohort and case control studies should look at these previously ignored areas of drinking behaviour and risk of prostate cancer. The inconclusive nature of prostate cancer risk by drink type needs further research and in particular studies would look to recruit sufficient numbers of people drinking each drink type to fully explore the range of alcohol intake levels. Further studies are also needed to explore alcohol consumption and risk of localized or advanced tumours of the prostate.

2.17 Discussion

2.17.1 Summary of evidence

The aim of the current systematic literature review was to provide a summary of the evidence relating to the relationship between alcohol consumption and cancer for

1. total alcohol consumption ('recent' and lifetime)
2. drinking patterns (e.g. daily/weekly drinking, 'binge' drinking)
3. alcohol beverage type (e.g. wine, beer, spirits)

2.17.1.1 Total alcohol consumption

Table 2.17.1 summarises the current state of evidence for the association between alcohol consumption and risk of cancer at specific sites, based on the data presented in sections 2.3 to 2.16.

Table 2.17.1 Summary of evidence for a link between alcohol and cancer

Cancer site	Evidence base: relationship between alcohol and cancer
Bladder	No relationship
Breast	Increased risk, irrespective of menopausal status, at moderate to heavy consumption, cannot rule out residual confounding
Colon	Increased risk with heavy consumption
Endometrium	No relationship
Gastric (stomach)	No association with low to moderate consumption, possible increased risk with heavy consumption and variation by tumour type (cardia and non-cardia)
Kidney (renal cell)	Evidence of decreased risk
Larynx	Increased risk, even with moderate consumption,
Liver	Increased risk at heavy consumption, possible threshold effect
Lung	Possibly increased risk at heavy levels of alcohol consumption, heavily confounded by smoking
Rectum	Increased risk with heavy consumption
Oesophagus	Increased risk, even with moderate consumption for SCC, but not adenocarcinoma
Oral	Increased risk, even with moderate consumption
Ovary	Conflicting and inconsistent evidence
Pancreas	Increased risk with heavy consumption
Prostate	No relationship with low-moderate consumption, cannot rule out effect of heavy alcohol consumption or lifetime consumption

NOTE: Moderate consumption is defined as up to 2 alcoholic drinks per day (24-30 grams per day), Heavy consumption > 30 grams per day (WCRF/AICR 2007)

There is convincing evidence that alcohol consumption increases the risk of upper aero-digestive tract cancers (oral, pharynx, larynx and oesophagus). Strong evidence exists that alcohol consumption increases the risk of oesophageal squamous cell carcinoma, but not oesophageal adenocarcinoma. The evidence would also suggest that the association between alcohol consumption and laryngeal cancer risk may differ by tumour type (larynx and hypopharynx). For these cancer sites, there is a dose-

response relationship with alcohol consumption that persists after adjustment for potential confounders such as age tobacco smoking and diet. These results appear to hold for both men and women, though many studies suffered from limited numbers of women drinkers, compared to men, especially those drinking heavily to totally rule out a gender effect.

There is sufficient evidence that moderate to heavy alcohol consumption (≥30g/d) is associated with an increased risk of liver and colorectal cancer. For liver cancer there is evidence of a threshold effect whereby drinking ≥40 g/d increases the risk of liver cancer. Positive associations between 'current' alcohol consumption and an increased risk of breast cancer were in general only associated with alcohol consumption of approximately >15 g/d (i.e. approximately >1 'standard' drink or >2 UK 'units per day). For cancers of the breast and colorectal cancer, there is insufficient evidence of an effect at low levels of alcohol consumption due to residual confounding, particularly from diet and folate intake (Klatsky 2001). Alcohol is known to modestly suppress blood folate levels (Barak 1993, Chiuve 2005) and in some, but not all, studies of alcohol and breast cancer the elevated risk attributed to alcohol is attenuated among women with high dietary folate intake (Zhang 1999, Baglietto 2005, Beasely 2010).

Low to moderate levels of drinking are unlikely to have an effect of the risk of pancreatic and prostate cancer, but the effects of heavy alcohol consumption (approximately 30-40 g/d) drinking on the risk of these cancers cannot be ruled out. The latency period of prostate carcinogenesis almost certainly requires past alcohol consumption to be considered as much an important dimension to prostate cancer risk as total recent alcohol consumption and too few studies in this review reported on this aspect to completely rule out an effect of lifetime alcohol consumption increasing the risk of prostate cancer.

The evidence is inconsistent or insufficient for cancers of the lung, bladder, ovary, kidney, endometrium, and bladder. The association between alcohol and lung cancer is heavily confounded by tobacco smoking, to the extent that it is difficult to reliably determine the independent effect of alcohol consumption. Evidence of a decreased risk for kidney cancer was evident in the review, but the association is based on too few studies to be convincing.

Overall, studies published since 2009 support the findings of the present systematic literature review. Tramacere et al (2010a), in a recent meta-analysis of alcohol consumption and risk of oral and pharyngeal cancers (45 studies including 17,085 cases), reported that "light alcohol drinking" (≤1 drink per day), compared to non-drinkers, was associated with a statistically significant 20% (RR 1.21, 95% CI 1.10-1.33, p value for heterogeneity (P) =0.01), increase in risk of oral and pharyngeal cancer. The corresponding estimate for heavy alcohol drinking (≥4 drinks per day (approximately 7.5 units), compared to non-drinkers, was 5.24 (95% CI 4.36-6.30, P =0.01). Further evidence of alcohol's weak association with adenocarcinoma of the oesophagus is provided by Freedman et al

(2011). In a pooled analysis of two cohort and nine case control studies, including 1821 cases of oesophageal adenocarcinoma (OA), drinking >98 grams per day (approx. 12 units), compared to non-drinkers, was not associated with an increased risk of OA (OR 0.97, 95% CI 0.68-1.36, p trend 0.21). The authors also reported that 'moderate' alcohol intake (7->14 grams per day or 1-2 units) was associated with a decreased risk of OA (OR 0.63, 95% CI 0.41-0.99). Seitz et al (2012) reported that a significant increase of the order of 4% in the risk of breast cancer associated with up to on drink per day. Heavy alcohol consumption, defined as three drinks or more a day was associated with an increased risk by 40-50%. In the most recent published meta-analysis of 23 cohort and 34 case control studies, Fedriko et al (2011) reported a 7% increase (95% CI 4-10%) in risk of colorectal cancer per 10 grams of alcohol consumed per day and a 38% (95% CI 28-50%) increase in risk per 50 grams per day. In categorical analysis, "light drinkers" (<12.5 grams per day), were, however, not at increased risk of colorectal cancer; RR 1.01 0.97-1.05, compared to non- and occasional drinkers. On the other hand, moderate (≥12.6 to 49.9 g/day) and heavy drinkers (≥50g/day) had a 20% (95% CI 20-30%) and 42% (95% CI 13-80%) statistically significant increased risk of colorectal cancer.

Fillmore et al (2009) performed a meta-analysis (21 cohort and 14 case control studies) finding evidence to suggest that prostate incidence is positively linearly associated with heavier alcohol use. This finding was largely due to the contribution of population case-control studies and those measuring men recruited before age 60. Thus, for population case-control studies, "heavier" drinking among younger samples at recruitment increased the likelihood of prostate cancer incidence. The point at which statistical significance was reached was around 2 'standard drinks' per day (approx. 4 units) for the younger population case-control samples No relationship between alcohol consumption and prostate cancer was found for cohort and hospital case-control studies. Fillmore et al. also carried out analyses of study design effects and found that population case-control studies were probably better suited to identify potential alcohol-prostate cancer relationships due to the close temporal proximity of the measurement of level of alcohol consumption to diagnosis. It is also possible that other variables not measured in the meta-analyses and in many individual cohort and case control studies may have an important role to play. One such variable might be the degree to which the populations sampled by the various studies were exposed to prostate cancer screening. In a meta-analysis of seven prospective cohort studies, including 6086 endometrial cancer cases (Friberg et al 2010), compared with non-drinkers, women drinking less than 1 'drink' of alcohol (=13g) per day had a lower risk for endometrial cancer; this risk was lower by 4% (95% CI: 0.93-1.00) for consumption up to 0.5 drink per day and by 7% (95% CI: 0.85-1.02) for consumption up to 1 drink. However, there was no evidence of a statistically significant increased risk for endometrial cancer for drinking ≥2 drinks per day: compared with non-drinkers, the risk was higher by 14% (95% CI: 0.95-1.36) for 2-2.5 drinks per day and by 25% (95% CI: 0.98-1.58) for >2.5 drinks per day. In a pooled analyses (of 12 prospective cohort studies and one case control study) with 1530 pancreatic cancer cases (Michaud

et al 2010), there was no significant overall association between total alcohol intake and pancreatic cancer (OR=1.38, 95% CI 0.86-2.23.for ≥60 grams per day compared to those drinking <5 grams per day). A statistically significant increase in risk was reported, however, for men drinking ≥45 grams of alcohol from spirits per day (OR 2.23 95% CI 1.02-4.87). In a recent meta-analysis of 24, 557 gastric cancer cases from 15 cohort and 44 case control studies, Tramacere et al (2011) reported there was no dose response association observed for those drinking an increment of 10 grams (RR 0.95,95% CI 0.91-0.99) and 25 grams (RR 1.01 95% CI 0.96-1.06) per day of alcohol but those drinking an increment of 50 grams per day had a statistically significant increased risk of gastric cancer (RR 1.14,95% CI 1.08-1.21).

2.17.1.2 Drinking frequency, patterns

Evidence that other dimensions of drinking behaviour such as 'age first started drinking' and duration of drinking increase cancer risk was mixed and largely came from case control studies and therefore subject to selection bias and recall bias. Where reported, evidence suggested a stronger effect for daily drinking compared to infrequent or occasional drinking though estimates were broadly similar to those reported for total alcohol intake. A few studies concluded that average daily alcohol intake, usually within the year prior to the study commencing and not drinking frequency appeared to be the relevant exposure index with respect to drinking and increased risk of cancer (Lee at el 2005, Zambon et al 2000). Less than 10% of papers in this review, however, reported on the risk of cancer by drinking frequency and many of the estimates were based on small numbers, different definitions of what constituted 'daily' 'weekly' and 'occasional' drinkers and therefore an association between drinking frequency and an increased risk of cancer cannot be ruled out.

The finding of a different effect on the alcohol-breast cancer association, depending on whether alcohol is drunk with meals or between meals reported by Dal Maso et al (2002), is intriguing. Unfortunately this was the only study to investigate this aspect of the relationship between alcohol consumption and cancer. This may be of significance in understanding risk estimates provided in studies depending on the study's country of origin and each country's drinking patterns. Sieri et al (2002) observed that, across countries in Europe, the distribution of alcohol consumption varied during the week and whether or not it was consumed mainly at mealtimes; in Italy, most alcohol is consumed with meals, whereas in most other countries more alcohol was drunk outside main meals, especially in Germany and the Netherlands. The consumption pattern was not very different in the majority of countries when weekdays and weekends were considered separately. However, in Spain, and in Norway the proportion of alcohol consumed outside mealtimes increased during the weekend; while among women in the UK the proportion of alcohol drunk outside mealtimes decreased during the weekend (Sieri et al 2002). The study by Sieri et al suggests large variation in drinking patterns among European countries, especially if alcohol was drunk with meals or outside mealtimes. There are, however a number of limitations in their study design (Riboli and Kaaks 1997); Alcohol

consumption is measured by a 2-hour recall interview which provides an incomplete estimated of regular consumption and cannot distinguish, occasional drinkers, non and former drinkers. The selected study cohorts were also from restricted regions in each individual country included in the study; for example in the UK, the cohort was drawn from a sample of GP practices in Oxford and Cambridge. The overall figures for alcohol consumption may therefore not accurately reflect consumption at the country level. These limitations aside the findings by Sieri et al form a useful basis for future prospective studies on association between alcohol consumption and cancer.

It is reasonable to assume that the effects of a given volume are more pronounced in heavy episodic drinkers than in persons who do not drink large amounts per occasion (Rehm et al 2003). However, demonstration of such interaction requires a large sample size. For example, a study with a 1000 participants is probably too small. Once the sample is stratified by, for example, gender, age and binge drinking, the individual cells become too small for meaningful analyses of interactions. The misclassification of alcohol intake would obscure further the underlying associations (Bobak 2005). Some time ago, Peto (1982) suggested that most clinical trials are too small to be useful. The same may apply to alcohol-related research: there is now a need for large studies and good measurements to disentangle the effects of drinking volume and patterns and their interaction in relation to cancer outcomes.

2.17.1.3 Types of alcoholic drink

Analysis of cancer risk by type of alcoholic beverage has not provided consistent results. Some of the evidence reviewed in chapters 2.3 to 2.16 does appear to show that some types of drink seem to have different effects. A few studies have shown a more protective effect from wine and a more harmful effect from beer and spirit For example, for cancers of the mouth, pharynx, and larynx, the evidence that alcohol causes cancer, is stronger for consumption of beer and spirits than for wine. Here is the possibility of residual confounding: wine drinkers in many countries tend to have healthier ways of life than beer or spirit drinkers. Apparent discrepancies in the strength of evidence may also be due partly to variation in the amounts of different types of alcoholic drinks consumed. Equally the presence of resveratrol, a polyphenol specifically present in red wine, may contribute to the cancer preventive effects. Resveratrol in fact inhibits the metabolic activation of carcinogens, has antioxidant and anti-inflammatory properties, decreases cell proliferation and induces apoptosis. Data on the availability of resveratrol in vivo are however still lacking. Bianchini and Vainio (2003) argue that in order to establish a causal relationship between consumption of wine or resveratrol and prevention of disease, a beneficial effect should be demonstrated in intervention studies, in which known doses of wine and/ or resveratrol are given for a precise duration.

One difficulty in determining an independent effect of a particular alcohol type is that people who drink alcohol tend to drink a variety of alcohol-containing beverages. It is widely accepted that, in

general, the beverage associated with the greatest risk of cancer is the most frequently consumed type of alcoholic beverage in each population (Bagnardi 2001, Burger et al 2004, Altieri et al 2005, Garavello et al 2006), suggesting that no meaningful difference exists for different types of alcoholic beverages. This finding could potentially be the result of inadequate power to assess uncommon drinks, under-reporting, or misclassification of consumption (Brennan & Boffetta 2004). In general, the evidence to date suggests that alcoholic drinks are or may be associated with increased risk of various cancers, irrespective of the type of alcoholic drink, though an effect of drink type cannot be completely ruled out.

2.17.2 Limitations of current research base

The evidence considered in this review exhibited methodological limitations which are summarised below. These limitations can be divided into two categories: limitations of the research included in the review and limitations of the review process.

2.17.3.1 Limitations of research

The quality of studies included in this review was assessed using the NOS developed by Wells et al (2005) for assessing the quality (i.e. internal validity) of non-randomized trials in met-analyses. Overall the cohort studies included in this review were of a moderate to high quality scoring an average of 7.7/9 stars and case control studies of a moderate quality scoring an average of 6.6/9 stars though there was variation in the average scores awarded to each study design by cancer type (Table 2.17.2).

Table 2.17.2 NOS scores by cancer and study type

	COHORT		CASE CONTROL		
	No of studies	Average score	No of studies	Average score	
Bladder	3	8.7	5	5.2	6.1
Breast	24	7.7	17	7.1	7.4
Colorectal	7	8.3	7	6.4	7.4
Larynx	0	-	12	6.8	6.8
Liver	1	8.0	8	6.5	6.7
Gastric	9	7.6	10	6.5	6.3
Endometrial	4	7.5	3	6.3	7.0
Pancreas	8	8.1	4	7.0	7.8
Prostate	10	6.9	9	7.0	6.9
Oral	0	-	22	6.4	6.4
Oesophagus	5	7.8	20	6.3	6.6
Ovary	6	7.0	7	6.4	6.7
Renal	4	8.0	5	7.0	7.4
Lung	7	8.3	5	5.2	6.1
All	88	7.7	134	6.6	6.9

Case control studies were characterised by susceptibility to selection bias and recall bias. Recall bias would be expected to result in over-estimation of the true level of association between the specific risk factor and risk of cancer. Some of the case control studies were more likely to suffer from selection bias than others due to variation in the methods of control selection. The magnitude and direction of this source of bias is more difficult to estimate. Cohort studies were also susceptible to bias, including selection bias (due to low participation and follow-up rates) and information bias (due to misclassification of exposure or outcome). Misclassification of exposure is most likely to be non-differential, thus diluting the level of association with cancer**.**

Although the NOS has been considered easy to use and suitable for systematic reviews (Deeks et al 2003), it still remains un-validated and there are a number of serious limitations both for the items selected as a measure of internal validity and the gaps in bias measurement not covered by the scale. The NOS assigns a higher score to cohort studies with community representativeness of the exposed cohort. Established prospective cohort studies providing multiple papers in this review, such as the Nurses Health Study, the Health Professionals Follow-Up Study, received a lower quality score as their cohorts are not representative of the general population. However as Stang et al (2010) observe, 'representative' cohort studies frequently suffer from low baseline response resulting in questionable generalisibility of the study findings whilst unrepresentative cohorts may have the advantage of higher baseline response, better exposure assessment and better follow-up response that may result in higher internal validity of the study. The NOS gives a higher score to case-control studies that had blinded exposure assessment, but blinding is sometimes impossible as the case control status can be easily discerned due to visual or acoustic signs of the disease which is particularly true for many of the cancers included in this review (Stang et al 2010). The NOS also gives a higher score to case-control studies with comparable non-response rates among cases and controls than case control studies with different response proportions, but does not take into account different non-response rates with exposed and non-exposed controls. Identical response proportions, of the case control group, are therefore no safeguard against selection bias.

Another weakness of the NOS in relation to alcohol consumption and cancer outcomes concerns its approach to managing data on risk factors that may confound the alcohol-cancer association. A higher score is awarded on the NOS which control for the most 'important factor' by design (matching) or by analysis (adjustment) and an even higher score if adjustment for a second 'important' factor takes place. However, matching in case-control studies is undertaken in the vast majority of studies included in this review and in the general epidemiological literature (Miettinen 1985). Therefore, the quality items on NOS have little discriminatory effect on the vast majority of case-control studies. Furthermore, the meaning of important factor is undefined and therefore arbitrary. Confounding is specific to individual research questions and the importance of confounding (e.g. change in estimate, multiple confounding risk factors) of the NOS remains undefined. In this review, the vast majority of

studies received the maximum stars in this category as they controlled for age and one of the main risk factors that confound the alcohol-cancer association e.g., smoking diet, weight. A more robust system would award for complete confounding of all possible important risk factors. For example, many of the studies in this review that reported on the alcohol-gastric cancer association controlled for dietary factors, but only a few for *H* pylori infection and dietary factors yet the absence of control for *H* pylori infection could result in a substantial influence on the estimated level of association. Overall, the NOS provides at best a quality score that has unknown validity or that includes quality items that may be even invalid for both cohort and case-control studies.

A further issue concerning the quality of the studies in this review concerns the measurement of alcohol consumption itself. The NOS does not look this in any detail with only one item regarding whether questionnaire used was self-completed or administered by a structured interview. Yet the construction of questions on alcohol consumption and how are they are reported may have a significant impact on the risk estimates produced in epidemiological studies. There are longstanding concerns about the measurement and reporting of alcohol consumption in cohort and case control studies regarding the type of questions used to elicit drinking information, the use of reference and recall periods, the choice of reference groups and the variation contributed by different measures of ethanol content used in studies to estimate volume consumed (Turner 1990, Correa et al 1994, White et al 1994, Greenfield and Kerr 2008) These issues will now be briefly discussed with reference to the studies included in the present review.

Survey questionnaires

Many epidemiological studies, particularly those focused on alcohol-related health outcomes, have relied on the type of food frequency questionnaires (FFQ) commonly used in nutrition and other medical research. In many cases all alcohol, or beer, wine and spirits separately, would be assessed in the course of obtaining rates of consuming other beverages such as milk, soda and coffee. These questions typically include several frequency categories for less than daily drinking and quantity levels for daily drinkers. This discrepancy highlights the main problem with this type of measure, which is that it is not suited for populations that typically drink on a weekly or monthly basis and often have more than one drink per occasion (Rehm and Gmel 2000, Greenfield and Kerr 2008). Use of FFQ measures in epidemiological research may therefore underestimate true levels of alcohol consumption in study populations In survey research, new instruments have been developed such as the quantity frequency and graduated frequency approach to better identify different patterns of drinking (these are discussed in more detail in chapter 3) and have been shown to more sensitive than food frequency measures in identifying risky/high risk drinkers (Rehm et al 1999, Clemens and Matthews 2008).

Overall, it was difficult to ascertain the exact method of alcohol data collection used by studies due to poor reporting of this aspect in many of the papers included in this review with 42% not specifying their method or simply stating they used a structured questionnaire. Over one in ten (14%) reported devising a questionnaire specific to the study, but did not provide details of any validation of these questionnaires. Food frequency questionnaire were used in over a third of studies (38.7%) compared to 4.1% using the quantity frequency method. It is difficult not to conclude that alcohol consumption is under-reported in many studies and therefore the true association with cancer outcomes may be underestimated.

Another issue relevant to exposure assessment is change in exposure status during the follow-up period in cohort studies. In general, unless the exposure status is not subject to modification, it should be reassessed periodically to account for any changes. As far as possible, each exposure should be characterized as to when it began, when it ended (if at all), and how it was distributed during the intervening period (was it periodic or continuous? did the dose vary over time?). Similar details should also be obtained for any behaviour that may protect against the exposure. There is thought to be a restricted period, the critical time window, during which the exposure could have caused cancer. Unfortunately, the beginning and end of this critical time window are not known, and its length is likely to vary between individuals (Dos Santos Silva 1999). Collecting data on the timing of exposure allows the possible extent of this window to be estimated. The frequency of reassessment will depend to some extent on the likelihood of change and the costs of reassessment. Exposure to alcohol is measured typically among participants at baseline and health outcomes are tracked during the follow-up period (which may be several decades).

The majority of studies (38/46) in the present literature review have used single measurements of alcohol use and hence have not assessed the importance of updating alcohol intake or the effect of changes in consumption over time. despite evidence from descriptive alcohol studies that consumption levels change throughout the life course (Fillmore et al 1987, Midanik et al 1990, Mulder et al 1998, Britton et al 2009). This could be a limitation if people vary their alcohol intake substantially during follow-up (Willet et al 1987, Emberson et al 2005) because random measurement error of long-term intake based on one measure may bias the association toward the null (Willet et al 1987). Also, repeated measures of exposure are useful for studying latency (time from exposure to cancer) (Thomas 1988). Of the eight studies (providing 27 papers) identified in the present review that did collect follow up alcohol exposure information, the majority used a weighted average of alcohol consumption from the baseline examination until the examination preceding the occurrence of cancer. Previous prospective studies of use of baseline and updated information on risk factors for cardiovascular disease showed that the strongest risk estimates were for updated information (Emberson et al 2003; 2005). This has been ascribed to increasing non-differential misclassification of baseline information on risk factors with longer follow-up (MacMahon et al 1990). Willett and

Stampfer (1997) proposed that the association for example between alcohol intake and breast cancer might be underestimated by at least 50% when based on a single assessment of alcohol intake. In two papers from the Copenhagen Heart Study, however, it was reported that results for baseline, updated, and cumulative average alcohol intake in relation to breast (Thygesen et al 2008a) and colorectal (Thygesen et al 2008b) cancer were relatively consistent which the authors argued implied that the timing of alcohol exposure during follow-up was not important because of a pronounced effect of latency; Thygesen et al (2008b) reported that for higher alcohol intake and risk of colorectal cancer, the suggestive lower consistency may reflect the influence of timing - a possibility that was supported by the weak attenuation of risk estimates for longer latency times, especially for alcohol intake above 30 g/d. The consistency for alcohol intake <20 g/d could also be because alcohol intake was rather stable during follow-up for persons with low and moderate intake. Recent studies support this supposition; adult abstainers and moderate drinkers had more stable alcohol intake over time than heavy drinkers (Kerr et al 2002, Britton et al 2009). For higher alcohol intake, the suggestive lower consistency may therefore be explained by higher intra-individual intake variation during follow-up; thus, repeated measures of alcohol intake may be important for persons with high alcohol intake.

Previous studies have suggested that updated exposure information is more precise and therefore superior to baseline information however one conclusion of papers from the Copenhagen Heart Study is that this may not apply in cancer epidemiology, because of a pronounced effect of latency. If the latency is long, variations in alcohol intake during follow-up may equate to non-differential misclassification. The effect will be strong if the variation in exposure during follow-up is large and independent of previous exposure. Despite these considerations, the overall conclusion of minor differences between the approaches indicates that other studies based on only one measurement well characterize alcohol intake for at least 16 years of follow-up (Thygesen et al 2008a), a finding that may have impact on the planning on future prospective cohort studies.

Reference period

It is crucial to provide a reference period - the period over which the respondent is instructed to provide summary information - such as 12 months or 30 days. When reference period is not explicit (e.g., “how often do you usually drink alcohol” rather than “During the last 12 months, how often...”), it has been shown that respondents assume periods ranging from a week to several years when describing their recent drinking (Greenfield 2000, Midanik and Greenfield 2003). Monthly or weekly thirty day measures can easily omit both infrequent light and intermittently heavy drinkers, which is better captured by 12-month measures which in addition also minimize seasonal variability.

Approximately a third of studies (32.8%) included in this review specified a reference period of drinking within the previous year and a further 5% used a reference period of drinking within the last 2 years. Only a small number of studies (5.9%) looked at drinking in the prior month or week. Approximately, one in five (17.7%) of studies investigated consumption over a respondent's lifetime, with a further 5% of studies using other to be less reliable than assessments of current drinking patterns, because they are subject to recall bias (Schottenfield 1979, Greenfield and Kerr 2008). Generally the farther in the past that the behaviour occurred the stronger this effect will be. There is also some evidence that the respondent's current drinking behaviour will influence their retrospective reports (Lemmens et al 1997). This generally means a downward bias because drinking often decreases with age. Lifetime measures were used by approximately one in five of studies and there was no consistency in the approach used, resulting in between-study differences in drinking distributions making results non comparable. Only three studies specified using established techniques to assist recall such as calendar of life events (Li et al 2003, Berstad et al 2008) or the Skinner Alcohol Use Inventory (Marrero et al 2005).

The reference period used in studies also, implicitly defines current drinkers; and by implication this also establishes the study's definition of non-current drinker or abstainers (Midanik and Greenfield 2003). Therefore the lack of detail in the majority of the studies on this aspect is reflected by the variation in reference groups used across studies in this review. The majority of studies (52.9%) in the review specified a reference group of 'non-drinkers), but did not define this group, over one in ten (13.7%) used a reference group of lifelong abstainers (excluding ex-drinkers) whilst one in four (25.5%) included in their reference group light drinkers (and even moderate drinkers in some studies). There is a potential source of bias if light, infrequent, or ex-drinkers are classified as non-drinkers, and the risk associated with alcohol consumption is estimated relative to this group (odds ratio/relative risk 1.0). The inclusion of former drinkers within the 'non-drinker' reference category is subject to misclassification bias. If ex-drinkers are grouped into the reference category with never drinkers then the risk for current drinkers will be underestimated (Wakai et al 2007). Fillmore et al (2006) observed that this approach will inevitably include more individuals with some pre-existing illness i.e. the "sick quitter" hypothesis, as proposed by Shaper et al (1988) in the United Kingdom; this states that the pool of abstainers includes many former drinkers who quit drinking because of illness or because alcohol interacts with prescription drugs they are taking. Obviously, comparisons of healthy drinkers with abstainers who take prescription drugs or who have underlying illnesses that raise one's risk for heart disease will produce a biased result in favour of the alcohol-consuming subjects. Prospective cohort studies in which alcohol intake is assessed at different times (rather than having "changes" based only on recall at one point in time) usually indicate that subjects who decrease their intake are more likely to subsequently develop adverse health outcomes, especially related to cardiovascular disease, than those who continue moderate drinking (Liang and Chikritzhs

2010). Future prospective cohort studies should consider multiple repeated measures to establish the heterogeneity of the 'non-drinking' group.

Units of measurement: the ethanol content of drinks

It has recently become apparent that the variation contributed by this source of measurement may of equal importance to all the other influences discussed above from the perspective of accuracy of consumption and drinking pattern measurement (WCRF/AICR 2007, Greenfield and Kerr 2008, Turner et al 2009).

Studies included in these reviews frequently analyzed the effect of alcohol as quantified by a 'standard drink.' The standard drink concept suggests that there is a serving size of alcohol that is typical of a particular country. However the use of the standard drink concept is complicated by different standards across countries and even within countries (WHO 2000). This was evident across studies included in this review. In the U.S., Canada, and Denmark for example, both 12 grams and 14 grams and in Italy both 13 grams and 15 grams were commonly cited as standard drink amounts. Some countries use a smaller standard such as 8-10 grams in the UK, 8-13 grams in the Netherlands or 10 grams in Australia and Greece, while others use a larger standard, the highest being reported to between 23-29 grams in Japan.

In practice, one standard will be taken by researchers to apply to all beverage types while in reality the typical serving sizes and ethanol contents tend to differ by beverage type, leading to non-equivalence. A number of factors are potentially associated with variation in drink ethanol content including beverage type and brand, glass size and shape, cultural and historical factors, the context in which drinking takes place, the specific drink recipe used (in the case of mixed drinks), the percentage alcohol content of the beverage/s used, and the type of measuring device or other pouring method involved. Variation in strength of beers commonly consumed complicates this further. In recent years, the strength and serving size of some alcoholic drinks have also increased. For example, in the UK, wine is commonly served in 250 ml glasses as opposed to the standard 125 or 175 ml glass. Studies that measure consumption in terms of number of drinks may therefore be referring to very different amounts of alcohol therefore making the syntheses of the alcohol-cancer association from international studies more challenging.

Reporting of alcohol consumption as a categorical variable

Due to the way that questionnaires ask about alcohol consumption, studies that relate the risk of cancer to levels of alcohol consumption summarize alcohol consumption within discrete categories, whereas the distribution between individuals is, in fact, continuous. Categorizing the alcohol intake has several disadvantages: high and low risk individuals could be merged (e.g., for highest alcohol

consumption group), and thereby dilute the estimated influence; and the number and placement of category boundaries may affect the estimates and thereby the level of alcohol consumption with the lowest risk of ill-health (Greenland 1995, Weinberg 1995, Polesel et al 2004)

2.17.3.2 Limitations of review

There are also limitations in the review process used. The review has been limited by restriction to English language articles and to articles that were published over restricted time period (1999-2009). Both of these factors may have resulted in bias. Publication bias may also have resulted from restriction to the published literature. Published literature is more likely to have identified an association with the outcome of interest though there was an extensive search of the grey literature, the results of which did not differ from those in the published literature. There was no double selection of relevant research and double extraction of data was not used. This increases the chance of missing relevant literature and incorrectly extracting data.

Considering the size of the topic, a limited timeframe was available to conduct the review. This meant that the search strategy had to be restricted to a specified number of cancers that have been linked with alcohol consumption in the literature prior to 1999. There were, therefore, a number of cancers (e.g. nasopharynx, cervix, gallbladder, small intestine, thyroid and non-Hodgkin's lymphoma) not included in this review, but which potentially may be associated with alcohol consumption.

It should also be noted that the review did not include the role of various genetic polymorphisms and their effect on the alcohol-cancer association. Individuals differ in their ability to metabolize alcohol through genetic differences in alcohol dehydrogenase (*ADH*), the enzyme that catalyzes the oxidation of approximately 80% of ethanol to acetaldehyde, a known carcinogen (Lachenmeier et al 2009). There is a growing body of evidence that suggests that for many of the alcohol related cancers, the relationship is potentially modified by genotype. A recent review concluded that there is evidence for a role of the ADH1B and ALDH2 polymorphisms on risk of cancer of the upper aero-digestive tract (Druesne-Pecolla et al 2009). Terry et al (2006) demonstrated in US based study and Stürmer et al (2002) in a German study, that fast metabolisers of alcohol as measured by the $ADH_3^{1\text{-}1}$ genotype have a higher risk of breast cancer risk, from alcohol intake than slow metabolisers. Hong et al (2005) also demonstrated that polymorphisms in the XRCC1 genes may contribute to colorectal cancer susceptibility in their Korean study population with evidence of a genetic modification for the relationship between alcohol intake and colorectal cancer. It is therefore possible that the overall small increased risk in association seen between alcohol and breast, colorectal and even gastric cancer in this review may not be explained by bias in study design, but reflects the effect of genetic polymorphisms.

The present review also did not consider the role of ethnicity and the relationship with alcohol consumption on cancers. Striking variations by ethnic group and incidence of cancer have been reported in the US (Miller et al 1993, Zahm and Fraumeni 1995) and a recent report by Cancer Research UK/National Cancer Intelligence Network (2009) observed that males and females in the Asian, Chinese and Mixed ethnic groups in England all had significantly lower risk of getting cancer than whites when the all malignancies combined group was examined. Across both age groups and for all ages, people from these three ethnic groups were between 20% and 60% less likely to get cancer than those from the White ethnic group. Overall the report concluded that generally, people from the Black and Minority Ethnic groups examined were at a significantly lower risk of getting cancer than the White ethnic group and there was no evidence for an overall inequality in cancer incidence. The report did observe, however, that for certain alcohol related cancers, e.g. liver and oral, Asian ethnic group had significantly higher rates for three specific sites of cancer in comparison with the White ethnic group (Cancer Research UK/National Cancer Intelligence Network (2009). The contribution of alcohol consumption to these disparities is unclear. Studies have shown that the prevalence of certain variations of genes for the alcohol-metabolizing enzymes alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) can vary across Asian ethnic groups and may cause some groups to have higher rates of alcohol dependence than others. For example, relatively high rates of alcohol dependence have been determined among Koreans and Korean Americans, whereas relatively low rates have been found in Chinese and Chinese Americans (Eng et al 2007). Tramacere et al (2011) also found that the effect of heavy drinking was stronger and of statistical significance in non-Asian countries explained by higher presence of ADH and ALDH in Asian populations, subjects with these mutant alleles cannot be heavy drinkers and which reduces prevalence of heavy drinking in Asia. Moles et al (2010) observed in a UK study that the positive trend in oral and pharyngeal cancer risks with socioeconomic status in non-South Asians in their study was consistent with the socioeconomic differences in the consumption of tobacco, but not alcohol, reported by the 1999 English Health Survey. Similarly, the ethnic differences in risk in females in our study do not parallel differences in their alcohol consumption but are, to a certain extent, consistent with their higher prevalence of tobacco chewing, particularly among Bangladeshi women. This would accord with tobacco chewing being associated with higher risks of oral than pharyngeal cancers (Dikshit and Kanhere, 2000), the former effect being stronger in females (Balaram et al 2002). More descriptive and analytic and comparative studies are needed to identify and explain variations in cancer risk associated with alcohol consumption among population subgroups. Especially important are studies to clarify the role of differential exposures, susceptibility, and diagnostic factors and the effect of genotype in cancer incidence.

2.17.3 Research gaps and scope for further research

Based on the current review of alcohol consumption and cancer risk, a number of research gaps have been identified that warrant further investigation so that a clearer understanding can be gained of the link between alcohol intake and risk of specific cancers, and the mechanisms underlying such risks. The following areas warrant further investigation:

- Alcohol consumption and risk of cancers of the bladder lung, pancreas, ovary, and kidney (Note that the evidence base for these cancers is currently inconsistent and often insufficient)
- Role of folate and other effect modifiers in breast and other cancers (such as colorectal and gastric cancer)
- Cancer risks associated with lifetime alcohol consumption versus consumption during specific periods
- The combined effect of latency and alcohol exposure on the association between alcohol and cancer
- Patterns of drinking on risk of cancer e.g., drinking with meals versus between meals, heavy irregular (binge) drinking
- Role of age at starting and stopping drinking (and starting and stopping smoking for those cancers confounded by tobacco)
- Risk in different sub-sites of the upper aero-digestive tract (oral vs. pharynx, larynx vs. hypopharynx
- Potential mechanisms by which alcohol may affect cancer risk and the role of genetic polymorphisms

2.17.4 Conclusion

The evidence that alcoholic drinks are a cause of cancers of the oral cavity, pharynx, and larynx, SCC of the oesophagus, and are a probable cause of colorectal, breast and liver cancer is convincing. There is insufficient evidence for an effect on cancers of the ovary, bladder, lung and endometrium. There is little evidence to suggest that alcohol is a risk factor for pancreatic and prostate cancer though an effect of heavy alcohol consumption cannot be ruled out. There is some evidence, based on a small number of studies, that alcohol is protective against cancer of the kidney. Confounding for risk factors especially socio-economic status, diet and folate intake may affect these estimates.

Associations between alcohol and cancer are however based on imprecise measurements that vary by type of assessment method used as well as the different alcohol content and strength of alcohol drinks in individual countries which makes it difficult to generalise the findings from the international literature to specific countries. Country specific research is therefore required to support or dispute these associations particularly in countries such as Scotland which are associated with high levels of

both alcohol consumption and incidence of alcohol related cancers. In the next two chapters the epidemiology of alcohol consumption and alcohol related cancers in Scotland will be briefly described.

Chapter 3 Trends in alcohol consumption in Scotland

This chapter will describe trends in population and individual levels of drinking in Scotland, using the two common approaches to measuring alcohol consumption (Midanik & Room 1992);

1. analyzing production and distribution statistics for alcoholic beverages as market commodities (aggregate population alcohol consumption) and
2. asking samples of the population questions about their drinking behaviour

Specifically, the chapter will describe trends in the weekly and daily alcohol consumption reported by national population surveys in Scotland and trends in the production and sales of alcohol at national level in Scotland. Variation by gender, age, deprivation and internationally will be examined. The strengths and limitations of these approaches to measuring alcohol consumption will be assessed.

3.1 Aggregate alcohol consumption

The oldest and most widely available measures of drinking behaviour in the United Kingdom (UK) are social statistics on the production and sales of alcohol drinks. These are commonly described as 'per capita' consumption figures. Series of such statistics are available in the United Kingdom, back to the beginning of the twentieth century. Her Majesty's Customs and Excise (HMCE) publish annual estimates, based on excise duty return, of the amount of pure ethanol in litres of total alcohol, and separately, beer, wine and spirits released for sale per adult (capita) in the country during a calendar year. The primary motivation behind the collection of such statistics was of course not a concern with alcohol problems, but rather the fiscal interest of the state in alcohol as a vehicle for taxation (Room 1979, Midanik and Room 1992).

Aggregate 'per capita alcohol consumption' statistics tell us something about levels of drinking at a societal level. Trends in per capita consumption are available over a longer period of time than trends obtained from series of population surveys. Due to the nature of reporting on excise duty returns, per capita alcohol consumption estimates have been traditionally published for the UK as a whole, with no disaggregation of the data to the constituent areas of the UK, Scotland England and Wales and Northern Ireland, and these data do not indicate whether alcohol consumption levels differ across the UK. It is only recently that separate per capita alcohol consumption data for Scotland and England/Wales have been reported (Robinson et al 2010). These data are not directly comparable with HMCE figures; they are based upon industry sales data derived from a sample of on-trade outlets (which allow the consumption of alcohol on the premises e.g. pubs, restaurants) and off-trade outlets (where alcohol must be removed from the vendor's premises and drunk elsewhere e.g. supermarkets)

across the United Kingdom, as opposed to HMCE figures which are based on alcohol production statistics (Robinson et al 2010).

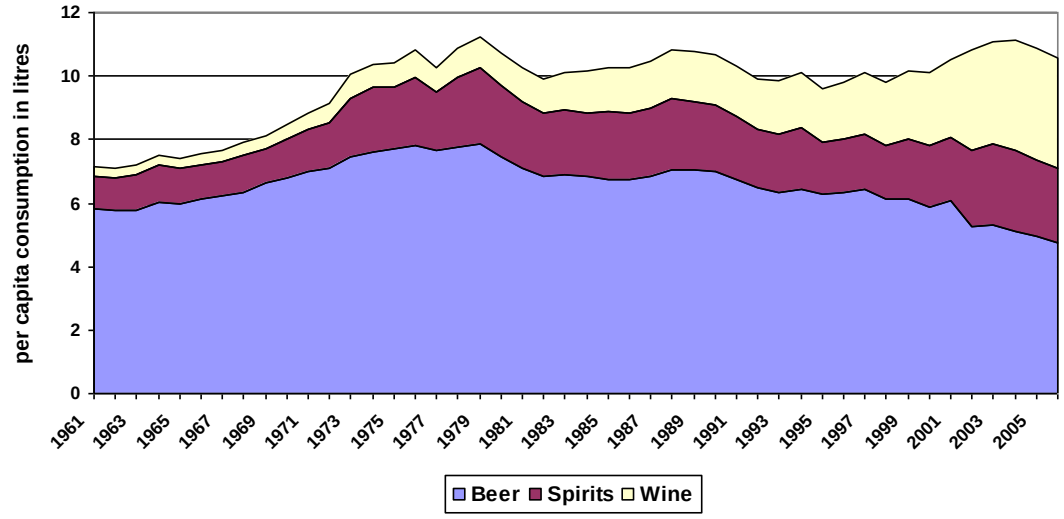
From the WHO Global Information System on Alcohol and Health (GISAH), it is also possible to compare international trends in 'per capita alcohol consumption' over a forty year period (Gliksman and Rylett 2009). GISAH provides estimates of pure ethanol in litres of total alcohol, and separately, for beer, wine and spirits consumed per adult (15 years and older[26]) in each country during a calendar year, as calculated from official statistics on production, sales, import and export. In order to make the conversion into litres of pure alcohol, the alcohol content of beer, wine, and spirits is considered to be 5%, 12% and 40% respectively. Specific conversion factors are used for other, less common types of alcoholic beverages (WHO 2004). GISAH estimates are based on either FAO (Food and Agriculture Organization of the United Nations) or alcohol industry (e.g. World Drink Trends) data, except for a few countries in Europe where the data come directly from governments (e.g. United Kingdom).

3.1.1 Trends in 'per capita alcohol consumption'

Since the middle of the last century, 'per capita alcohol consumption' i.e. alcohol released for sale in the UK market, has been rising; from 7.14 litres per capita in 1961 to 11.39 litres per capita in 2006 (Figure 3.1). Most of this increase has been due to growing consumption of wine, which increased eight-fold from 0.28 litres per head in 1961 to 3.48 in 2000. Spirit consumption doubled over the same period (from 1.04 litres per capita in 1961 to 2.35 litres per capita in 2000) whilst beer consumption has been in decline since the early 1980s (Figure 3.1). These figures will also be an underestimate of actual aggregate consumption since the data do not account for unrecorded alcohol consumption, resulting from home-made production and cross-border shopping and smuggling. Unrecorded per capita alcohol consumption is estimated to equate to approximately 2 litres per person per annum for the years after 1995 (Leifman 2001), though the peak of cross-border shopping and smuggling in the UK occurred between 1997 and 2000 (IAS 2010).

[26]WHO uses adult (people 15 years and older) per capita to measure alcohol consumption, instead of per capita for the whole population. This is to balance the fact that population distributions in developing countries are quite different from developed countries, i.e. they have a much larger proportion of children and young people. Using per capita would mean that countries with many young people will underestimate the consumption among adults, if it is assumed that most young people below 15 do not consume significant quantities of alcohol (WHO 2000).

Figure 3.1 Pure alcohol consumption, litres per capita aged 15 plus, United Kingdom, 1961 to 2006 by drink type (Source WH



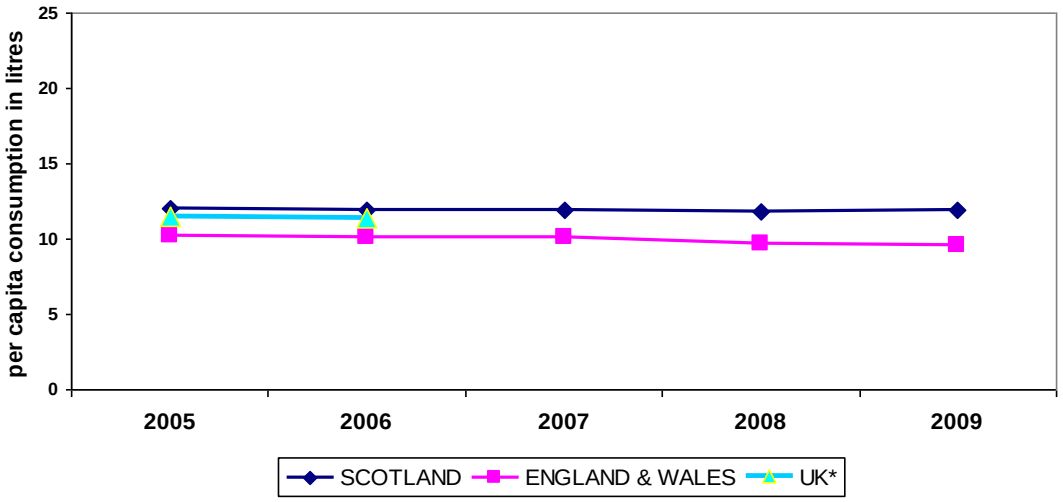
O

GISAH)

Using a methodology based on alcohol sales data[27] (as opposed to HMCE alcohol production statistics), Robinson et al (2010) have estimated per capita alcohol consumption levels in Scotland and, England and Wales, from 2005-2009 (Figure 3.2). The volume of pure alcohol sold per person (aged 16 and over), in Scotland, has remained broadly stable over the past five years (2005 = 12.0 litres; 2009 = 11.9 litres). In contrast, the volume of pure alcohol sold per person (aged 16 and over) in England and Wales has decreased slightly every year between 2005 and 2009 (2005 = 10.2 litres; 2009 = 9.6 litres). The gap between Scotland and the rest of Great Britain has, therefore, widened (2005 = 1.8 litres; 2009 = 2.3 litres). Differences in per capita consumption are accounted for by the consumption of spirits which is twice as high in Scotland, than in England and Wales (Robinson et al 2010).

[27]Data obtained from The Nielsen Company based on their continuous retail measurement system, which captures actual sales from scanned readings at Electronic Points of Sale. Weekly data are obtained from (a) all large multiple retailers which provide data from all of their stores, and (b) a stratified random sample of independent and smaller multiple retailers (Catto et al 2010).

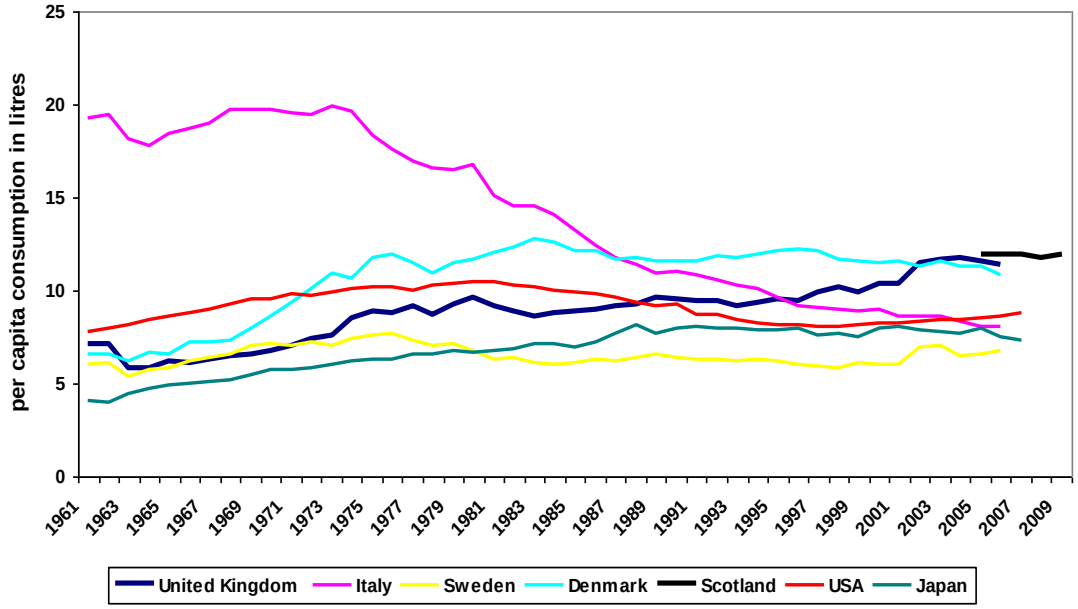
Figure 3.2 Sales of pure alcohol per person (aged 16+) in Scotland and England & Wales, 2005-2009 (Source Robinson et al 2010)



** GISAH UK per capita consumption data only available up to 2006*

'Per capita alcohol consumption' data allow a direct comparison to be made between UK or Scotland with countries (i.e. USA, Japan, Sweden, Denmark, and Italy) in which the majority of studies on the association of alcohol consumption and cancer (described in Chapter 2) were conducted. In the early 1960s, per capita alcohol consumption in the UK was roughly equivalent to that found in Sweden, Denmark, the US and Japan (Figure 3.3), though per capita alcohol consumption in Italy was approximately three times higher than that in the UK. By 2006, UK per capita alcohol consumption data was the highest among the selected countries at 11.4 litres per head having steadily increased from 7.1 litres per head in 1961. Consumption in Denmark was at comparable levels (10.8 litres per head) to the UK in 2006 and has been at this level since the late 1980s. Japanese per capita consumption has increased the most in relative terms, rising from 4 litres per head in 1991 to 7.3 litres per head in 2007. On the other hand per capita alcohol consumption in Italy has fallen dramatically, from a high of 19.7 litres per head in 1970 to 8.0 litre per head in 2006. In Sweden and the US, per capita consumption changed very little between 1961 and 2007 (approximately 6 litres and 8 litres per head, respectively). Analysis of alcohol sales data for Scotland shows a widening gap with alcohol sales data in England and Wales (Figure 3.2), and they demonstrate that the population of Scotland is continuing to drink more alcohol than most of those countries where much of the epidemiological evidence of the alcohol-cancer association originates from.

Figure 3.3 Pure alcohol consumption, litres per capita aged 15 plus, Trends in selected countries, 1961 to 2009 (Source: WHO GISAH)



3.1.2 Limitations of per capita alcohol consumption

'Per capita alcohol consumption' data have, however, some limitations. Alcohol production statistics collected at the wholesale level, or sales data collected at the retail level, do not take account of the fact that goods may not actually be consumed in the year in which they are recorded as having been shipped or sold. Taxes collected at the producer or wholesal**e** level may also introduce a variable time lag into the data, since they do not reflect actual retail sales. Alcohol sales data also assume that all alcohol sold is consumed, but this is not necessarily the case (WHO 2000). Generally sales data from the alcohol industry at a retail level are considered more accurate than statistics on alcohol production or taxes raised at a wholesale level provided that sales of alcoholic beverages are separated from the sales of other items sold at the location and that sales data are beverage specific (WHO 2000, Gmel and Rehm 2004). In reality, however, differences between the various methods are marginal; recent figures for alcohol 'sales' data in Scotland and England, were 11.9 and 10.1 litres per head respectively(Robinson et al 2010) compared to HMCE statistics on alcohol produced and released for sale, of 11.4 litres per head (WHO GISAH 2010).

'Per capita alcohol consumption' data also do not take into account or adjust for tourist consumption. Hospitality and tourism is one of the largest industries in Scotland, employing over 200,000 people, or about 9% of the total number of people employed in Scotland and contributing between £2-4 billion to the economy (5% of Gross Domestic Product). Consequently tourism is a significant factor in high alcohol sales and consumption in Scotland (British Hospitality Association 2008, Scottish Beer and Pub Association 2008, Scottish Parliament 2008) and may make a larger contribution to sales data

than in other countries. There is also some uncertainty as to whether changes in per capita consumption are necessarily correlated with changes in individual drinking levels. A longitudinal survey of Finnish drinkers found no increase in individual levels of self-reported alcohol consumption among respondents between 1999 and 2002, despite an increase in 'per capita alcohol consumption' as a result of excise duty reductions (Makela et al 2007, Mustonen et al 2007).

In principle, although per capita alcohol consumption statistics reflect the total volume of consumption by the population of a particular geographic area, by their nature, they offer few clues as to the structure of drinking within the geographically defined populations they are derived from (Room 1979, Midanik & Room 1992, Stimson 2006). In theory, a per capita consumption of 52 litres a year could represent a population where everyone is drinking 1 litre a year, or, on the other hand, a population where 90% are abstainers and the other 10% are each consuming 10 litres a year. Survey data certainly support the common sense observation that there is considerable variation between different populations in the proportion of abstainers and in the frequency of drinking (Room 1979). Lemmens (2001) observes that even though individual alcohol consumption is the result of a complex combination of personal, social or environmental factors resulting in considerable variability in individual drinking, it is remarkable that per capita consumption in societies in general is relatively stable (which has been the case in the United Kingdom in recent years). Research has shown that not only is per capita consumption relatively stable, but so also is the way consumption is distributed among drinkers. Many researchers, following the lead of Ledermann (1964), have observed an empirical regularity in the distribution of alcohol consumption among drinkers in a variety of cultures (Room 1979, Skög 1985, Lemmens et al 1990, Skög1995). It is generally acknowledged that the population distribution is skewed with a mean higher than the median which again is higher than the mode (Lemmens 2001). This implies that the heaviest drinkers account for a disproportionately large part of the total alcohol consumption in a population. Since it is estimated that one-tenth of the adult population is responsible for between 30-60% of the alcohol consumed, it is argued that trends in per capita alcohol consumption can generally be regarded as an indicator of trends in very heavy drinking (Room 1970, Room 1979, Midanik and Room 1992, Lemmens 2001).

Lemmens (2001) argues that although undoubtedly one can speak of a certain regularity in the way alcohol consumption is distributed in a population, what is seen at the aggregate level should be regarded with caution. A stable distribution does not imply stable consumption patterns of individuals. What Lemmens describes, as 'chronicity of heavy drinking', has been found to vary across (sub) populations and over time. Similarly, a particular consumption level can be attained in different ways. Lederman's theory on the regularity of alcohol consumption has been further developed by Skög's (1995) social interaction model where people's drinking is seen as interrelated through various social networks in such a way that any (independent) change in individual consumption will have an equi-directional impact on the consumption of all others. Lemmens (2001) argues, however, that this is still

a disputed model. Earlier work by Tuck (1980) in the United Kingdom, found that the increase in total consumption from 1974 to 1979 was caused by an increase in the number of drinkers at moderate frequencies, but not in the number of (heavier) drinkers. Based on similar evidence, covering subsequent years, Duffy (1991) concluded that the changes in average consumption were due to changes in the frequency pattern of lower-frequency drinkers and thus not consistently along the entire consumption scale as would be predicted by the social interaction model. Other research has found similar findings (Lemmens 1995, Fillmore et al 1997). These examples highlight that although overall per capita alcohol consumption data is an important indicator of heavy drinking in a society, it cannot be relied on as a sole indicator.

Per capita alcohol consumption measures are a convenient way of collecting relevant data and can be useful proxy indicators of levels of drinking patterns in populations and in particular heavy drinking in the absence of individual population level survey data (Edwards et al 1994, WHO 2000). However, they do not capture the myriad ways in which individuals drink. To attain a better understanding of drinking among individuals and groups, the harms and benefits that may accompany their drinking, and interventions likely to minimize harm, it is necessary to understand patterns of drinking in more detail.

3.2 Alcohol consumption and population surveys

The richest source of information on drinking patterns is sample surveys of the general population, enquiring about individual drinking patterns. In North America, and in particular the US, the first nationwide survey covering detailed patterns of drinking within a sample frame was performed in 1946 (Room 1979). The measure of individual drinking patterns in the general population in Scotland is, however, a relatively new development. The methods of survey research were first applied in Scotland in a detailed study of drinking practices by Dight (1976). Dight's study of a nationally representative sample of approximately 2500 adults aged eighteen years and over in 1972, revealed a significant gender gap in both the volume and frequency of drinking: 74% of men were identified as 'regular' drinkers compared to 46% of women, whilst mean weekly consumption among men was 20.5 units, compared to 4.8 units among women. Dight also estimated that 30% of all alcohol drunk in a typical week in Scotland was consumed by only 3% of the total population (Dight 1976).

Dight's study was notable in two respects. Firstly, it highlighted the differences between European and North American traditions of asking about drinking behaviour in surveys. In European studies of the time, it was particularly common to list all drinking occasions in a specified period of time usually, as in the case of Dight's study, within the last week (Gmel and Rehm 2004). This approach had been criticised as resulting in considerable under-estimation and misclassification of amount of

alcohol drunk, particularly for less frequent drinkers, unless information was collected over several drinking occasions other than in the last week (Room 2000). The 'North American approach', on the other hand, asked for the respondent's summary of his or her customary drinking behaviour, the so called Quantity Frequency (QF) measure which dates back to the work of Straus and Bacon (1953) from which the measure takes its name (Rehm 1998, Room 2000, Gmel and Rehm 2004).

QF methods, of which there are many variants, inquire about "average" or "typical" consumption patterns, usually over a specific time period such as within the last year. These methods, also known as estimation formulas (Sobell and Sobell 2003), require respondents to report an average pattern of consumption (e.g., "How many days *on average* - in a specific time interval - did you drink beer, and when you drank beer, *on average* how many beers did you drink?"). Most QF methods repeat these questions for each major alcoholic beverage type (i.e., beer, wine and spirits) and then sum across beverage types (see Box 3.1 for example of QF in its most basic form). Drinking parameters (e.g., total amount consumed, mean number of drinks per day) are calculated based on the aggregate questions (e.g., "How many days *on average*- in a specified time interval - did you drink beer, and when you drank beer, *on average* how many beers did you drink?").

Box 3.1 Quantity Frequency questions

Frequency: Thinking about the last year, how often do you have an alcoholic drink?

Almost every day, five or six days a week, three or more days a week, once or twice a week, once or twice a month, once every couple of months, once or twice a year, less than once a year, never drunk or ex-drinker.

Dight's study of drinking practices was also particularly notable because it introduced the concept of the alcohol 'unit' which was Dight's construction to deal with the problem that the predominant Scottish drink, beer, was sold primarily in two different drink sizes, a half-pint and a pint. Dight chose the smaller size as the ``standard unit," although an ordinary male drinker in Scotland would think of `a drink' in terms of a pint which is equal to two standard units (Room 2000). This alcohol 'unit' (approximately equivalent to 8 grams of alcohol) was subsequently used to define government guidelines, in the mid-1980s, on safe and sensible drinking levels as described in Chapter 1. It would also eventually become the standard measure of alcohol drinking in national surveys, when from the late 1980s the measurement of alcohol consumption in the general population in Scotland became routine, with a number of nationally representative population surveys established and repeated over time. These surveys provide a range of information on drinking frequency and patterns among adults in Scotland over the last twenty years.

3.2.1 Drinking in Scotland 1988-2009, a comparison of three surveys

Between 1988 and 1995, three types of repeated national surveys were established with samples of the

Scottish adult population and which included questions on alcohol consumption; the General Lifestyle Survey (GLS), the Scottish Health Survey (SHeS) and the Health Education Population Survey (HEPS) which ran between 1996 and 2006. A description of each of the surveys is provided in Table 3.1.

Table 3.1 National Surveys in Scotland covering alcohol consumption

Survey	Description
Health Education Population Survey (HEPS) (survey years 1996-1999, 2001-2007)	Monitors health-related knowledge, attitudes, behaviours and motivations to change among the adult population in Scotland and had been carried out continuously since 1996, though survey was suspended in 1999 before restarting in 2000. Questions on drinking behaviour have been asked since 1996. HEPS has a sample size of approximately 1800 adults aged 16-74 years. Fieldwork was undertaken in two waves each year, usually March and September. The survey was discontinued from 2007 with elements from HEPS incorporated, as a module, into the Scottish Health Survey.
The General Lifestyle Survey (GLS) (survey years: 1988-1996, 2000-2008)	Formerly known as the General Household Survey (GHS), this is a multi-purpose continuous survey collecting information on a range of topics from people aged 16 years and above, living in private households in Great Britain. GLS started in 1971 and has been carried out continuously since then, except for breaks to review it in 1997/1998 and to re-develop it in 1999/2000. Questions about drinking alcohol have been included in the GLS since 1978. Prior to 1988, the questions were only asked of those aged 18 years and over. Since 1988 respondents aged 16 and 17 years have answered these questions using a self-completion questionnaire. GLS has included a Scottish sample since 1988 with an approximate sample size of 1500.
Scottish Health Survey (SHeS) (survey years 1995, 1998, 2003, 2008, 2009)	Provides a detailed picture of the health of the Scottish population in private households collecting in-depth information on a range of health and behavioural topics, socio-demographic information and physiological measurements taken by nurses. SHeS began running continuously in 2008 with a contract let for the four years from 2008 – 2011, following recommendations of a comprehensive review of the survey carried out by the then Scottish Executive (Corbett et al 2009). SHeS has the largest sample size of the three national surveys; approximately 8000 adults aged 16-64 years in 1995, and aged 16-74 years in 1998; and approximately 6500 -7000 adults aged 16 years and over in 2003. Surveys in 2008 and 2009 have slightly smaller sample sizes of approximately 4500 (Corbett et al 2010). Questions on drinking behaviour have been included since the first survey in 1995.

All three surveys use a quantity-frequency measure to elicit details of alcohol consumption, with SHeS and HEPS adopting the GLS alcohol module first used in 1988 with some slight refinements. An example of the approach used in SHeS is provided in Box 3.2. The main measure of drinking behaviour until 1998 was average weekly alcohol consumption expressed in terms of units per week. Following UK government recommendations in 1995 on safe daily drinking levels (Department of Health 1995), new questions about consumption on the heaviest day during the previous week were included on the GLS, HEPS and SHeS to monitor trends in measures of daily drinking.

Box 3.2 Quantity-Frequency questions in Scottish Health Survey

To estimate weekly consumption, informants aged 16 years and over, after preliminary questions on whether they drank alcohol at all, were asked how often during the past 12 months they had drunk each of six different types of alcoholic drink (normal/strong beer, lager, cider and shandy; sherry and martini, spirits and liqueurs, wine, alcoholic soft drinks ("alcopops").

From this question, the average number of days a week the informant had drunk each type of drink was estimated.

A follow-up question asked how much of each drink type they had usually drunk on each occasion. This data is converted into units of alcohol and multiplied by the amount they said they usually drank on any one day to provide a weekly estimate (Corbett et al 2009)

More recently, significant changes have taken place in the methods used to calculate levels of alcohol consumption in both the SHES and GLS. When drinking surveys were first carried out in the 1970s, the assumption that one unit was found in a half pint of beer, a glass of table wine, a small glass of fortified wine, and a single measure of spirits was reasonable. Since then, and particularly in recent years, the average strength by volume of some alcohol products (especially wine) has been increasing (Goddard 2007, Catto and Gibbs 2008). To take account of this, the Office for National Statistics undertook a review of the existing methodology for converting volumes into units in the GLS and the Health Survey for England. This work resulted in the publication of new unit conversion factors based on average strengths of alcohol in 2006 (Goddard 2007); for example under the original conversion factors one glass of wine = 1 unit and a half pint of strong beer = 1.5 units, compared to 2 units (for both) under the revised conversion factors (Appendix F outlines how the volumes of alcohol reported in the 2003 SHeS were originally converted into units and how the new conversion factors have changed this). These factors have been applied retrospectively to the estimates from the 2006 GLS and updated figures have been published. These factors have also been adopted for use in the Scottish Health Survey from 2008 onwards. The SHeS data from the 2003 survey, published in 2005, was also reanalysed using the new conversion factors (Bromley et al 2008). HEPS data is based on the original conversion factors.

The impact of the revised conversion factors has been to produce more accurate (and increased) estimates of daily and weekly alcohol units consumed in the Scottish population. On the other hand, it means that any assessment of trends over time in alcohol consumption data from SHeS and GLS is problematic. Nevertheless, the standard approach to measuring alcohol consumption (i.e. average weekly consumption, exceeding weekly and daily recommended safe drinking guidelines) across the three surveys has ensured consistency in the way survey analysis has been aggregated and summarised allowing for some comparison of trends in alcohol consumption by gender, age and deprivation over approximately a twenty year period, in Scotland.

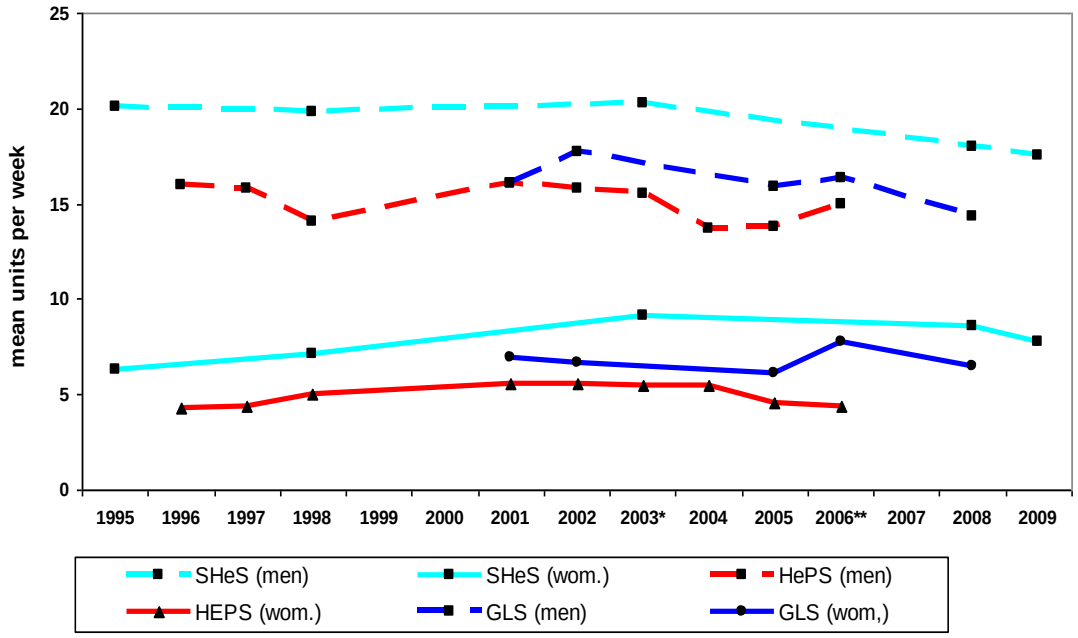
3.2.1.1 Trends in alcohol consumption in Scotland by gender

3.2.1.1.1 Average weekly consumption (units per week)

The mean unit consumption per week for men has declined over time (Figure 3.4). Over a ten year period, HEPS reported that mean weekly consumption in men fell from 16 units per week (u/w) in 1996 to 15 u/w in 2006. Between 2001 and 2008, GLS reported a decrease from 16.1 u/w to 14.3 u/w, and SHeS also reported a decrease from 20.1 u/w in 1995 to 17.5 u/w in 2009. Data from SHeS and GLS would suggest that the decline in average weekly consumption has been constant since the turn of the century, even taking into account the revised consumption estimates in 2003 (SHeS) and 2006 (GLS).

There was greater variability between surveys in trends among women's weekly mean consumption of alcohol (Figure 3.4). SHeS reported that mean weekly consumption in women increased from 6.3 u/w in 1995, to 7.8 u/w in 2009. Whether this is a real increase is difficult to say as survey estimates of alcohol consumption are increased from 2003 onwards, based on revised unit conversion factors. GLS reported a decrease in weekly consumption in women from 2001 to 2005 until they updated their estimates in 2006 with the new alcohol unit conversion factors. The decrease in weekly mean consumption resumed in the 2008 GLS. In HEPS, mean weekly consumption in women increased to a high in 2002 (5.6 u/w), from 4.3 in 1996, and then dropped back to 4.3 u/w in 2006.

Figure 3.4 Mean number of units consumed per week by gender; trends across three surveys (SHeS, GHS, HEPS), 1995-1998, 2001-2006, 2008-2009



*Revised conversion factors (RCU) used in SHeS data from 2003 and **GLS from 2006

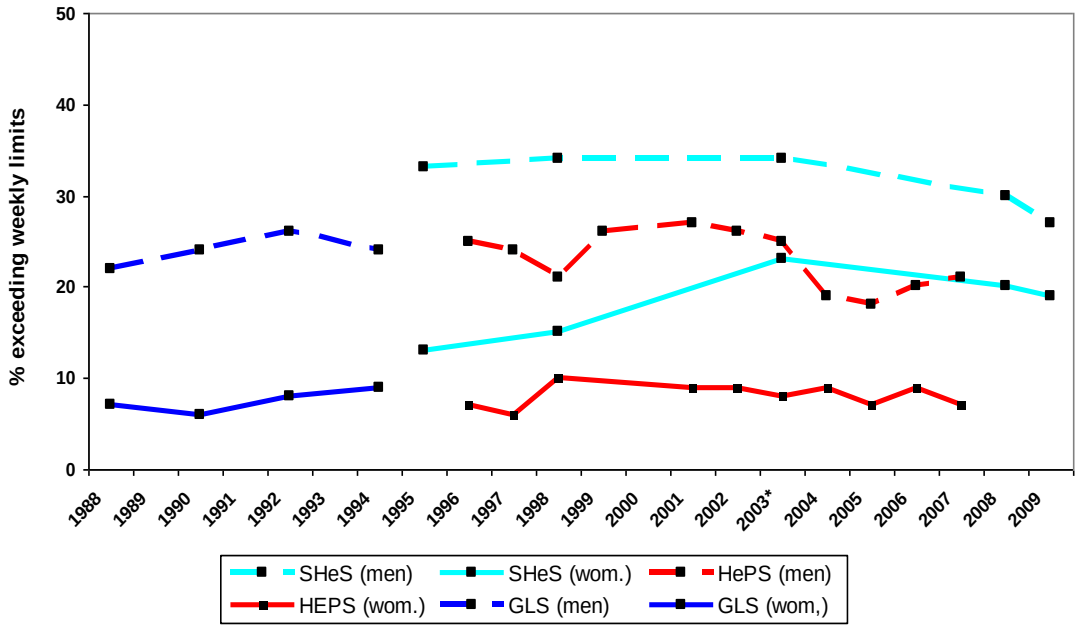
3.2.1.1. 2 Exceeding recommended weekly limits

Both SHeS and HEPS have consistently reported on the proportion of people exceeding recommended weekly limits in men (>21 u/w) and women (>14 u/w) whilst the GLS only used this measure between 1988 and 1994, switching to daily measures of alcohol consumption from 1998 onwards.

The percentage of men exceeding recommended weekly limits has been on the decrease since early 2000 (Figure 3.5). Even taking into account the updated consumption estimates in 2003, SHeS reported the percentage of men exceeding weekly limits falling from 34% in 1998 to 27% in 2009. The proportion of men exceeding weekly limits, reported by HEPS, peaked at 27% in 2001 falling to 21% by 2007.

For women, the proportion exceeding weekly limits reported by HEPS, has remained relatively constant from 2001 to 2007 at approximately 7-8% (Figure 3.5). SHeS reported an increase in women exceeding weekly limits from 1995-2003 (13% of women (aged 16-64yrs) in 1995 to 23% in 2003 (aged 16 and over), but has fallen to 19% in 2009. Between 1995 and 2009, the gap between women and men in the proportion exceeding recommended weekly drinking levels has narrowed considerably: based on SHES, in 1995 men were 2.5 times (33% and 13%) more likely than women to exceed recommended weekly safe limits, in 2009 27% of men and 19% of men reported exceeding recommended weekly limits.

Figure 3.5 Percentage exceeding weekly limits by gender; trends across three surveys (SHeS, GHS, HEPS), 1988-1998, 2001-2005, 2008-2009



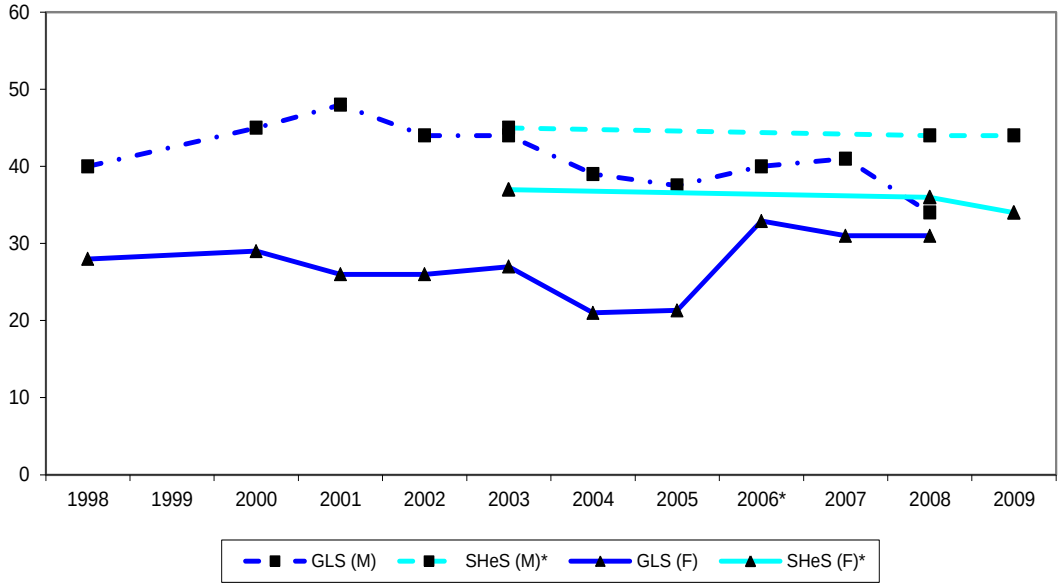
* RCU used in SHeS data from 2003 and **GLS from 2006

3.3.1.3 Exceeding recommended daily limits

Both SHeS and GLS report on the percentage of their survey population exceeding recommended safe daily drinking limits[28]. The proportion of men drinking >4 units per day (u/d) has remained relatively constant since 1998 in both surveys at approximately 40% of weekly drinkers (Figure 3.6). The GLS has however reported a small decrease from 2001 onwards and although this trend was reversed in 2006 following the introduction of revised conversion factors, in 2009 the lowest ever figure, for men exceeding daily limits (31%) was reported by the GLS. SHeS reported a small decrease in the proportion of women drinking >3 u/d from 37% in 2003 to 34% in 2009 (Figure 3.6). A similar downward trend was also reported by GLS from 1998 to 2005, though following introduction of revised unit conversion factors in 2006, the proportion of women exceeding daily limits has remained fairly constant (at approximately 30%).

[28]The 1998 and 2003 SHES defined daily drinking above recommended limits as ≥3 units for women and ≥4 for men. These thresholds have now been adjusted to use the following thresholds to enable comparability with surveys of alcohol consumption across Britain; of: drinking above 'safe' daily drinking limits - women: >3 units; men: >4 units.

Figure 3.6 Percentage exceeding daily limits, trends across two surveys, by gender (SHeS, GLS), 1998, 2000-2009



* RCU used in GLS from 2006

3.3.1.4 'Binge' drinking

Patterns of excessive drinking are also reported in each of the three surveys and are defined by various measures of what is considered unsafe daily drinking. This is commonly termed 'binge drinking' though the term 'risky single occasion drinking' is probably more accurate (Murgraff et al 1999, Gmel et al 2011). SHeS use a definition of 'binge drinking' as 'double the recommended daily safe drinking limits (>8 units for men and >6 units for women) on the respondents' heaviest drinking day in the past week**.** GLS ask how often respondents have drunk >8 and >6 units for men and women respectively, on at least one day in the past week. HEPS uses a measure based on amount drunk on a single drinking occasion in the past month, defined as drinking sixteen units for men and ten units for women.

Trends in each of the survey measures for men and women are presented in Figures 3.7 and 3.9 respectively. SHeS data have shown very little change, between 1998 and 2009, in the proportions of men and women who reported 'binge' drinking on their heaviest drinking day, with men twice as likely as women to drink double the recommended safe daily drinking limits. The GLS data shows a steady decline in the proportion of men reporting 'binge' drinking, from 30% in 2001 to 19% in 2008. In contrast, the proportion of women reporting binge drinking has increased from 12% in 2001 to 16% in 2008. The gender gap in excessive daily drinking reported by GLS in 1998 (30% of men and 12% of women drinking double recommended daily limits) had all but disappeared in 2009 (19% of men and 16% of women). In HEPS, the proportion of men 'binge' has shown very little change over time; from 18% in 1996 to 17% in 2007. In contrast, the proportion of women binge drinking has doubled

from 4% in 1996 to 8% in 2007.

Figure 3.7 ‘Excessive’ drinking in men, trends across three surveys 1996 to 2009

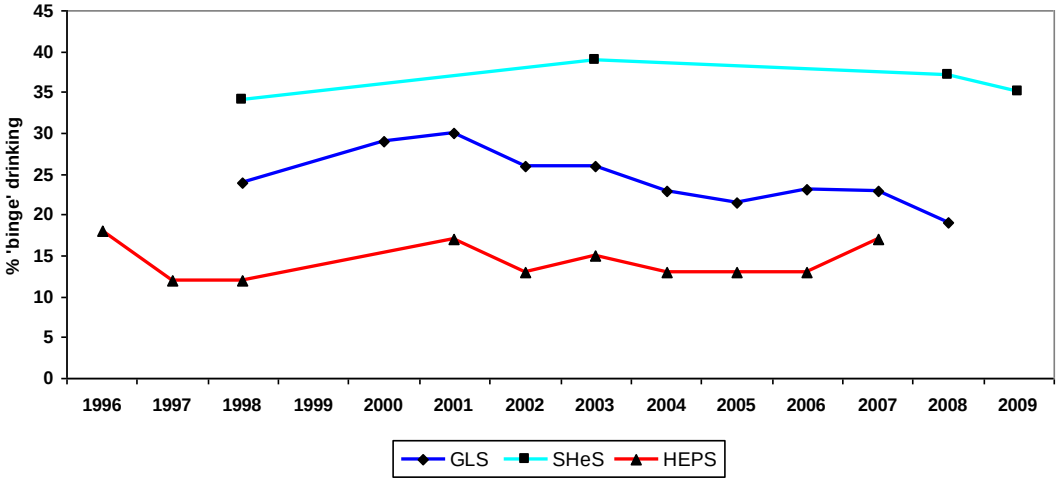
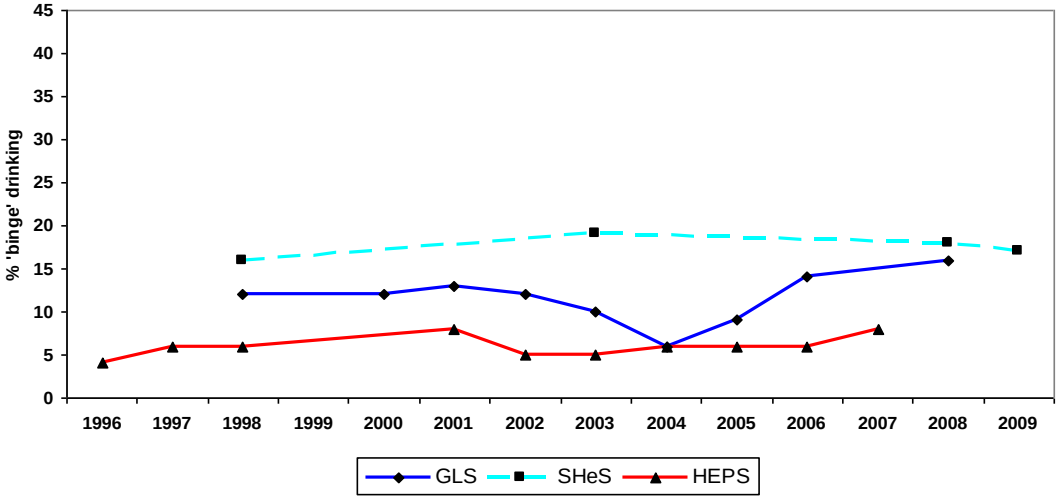


Figure 3.8 ‘Excessive drinking’ in women, trends across three surveys 1996 to 2009



* RCU used in SHeS data from 2003 and **GLS from 2006

Direct comparisons between the surveys are, however, problematic because of the differences in ‘binge’ drinking measures used each survey. In addition, SHeS and GLS data from 2006 onwards are based on the new alcohol unit conversion factors and, therefore, not directly comparable with previous surveys. The impact of the new conversion factors may, however, conceal a continuing downward trend in SHeS and GLS reports in men reporting ‘binge drinking’ that had been apparent prior to the changes in methodology.

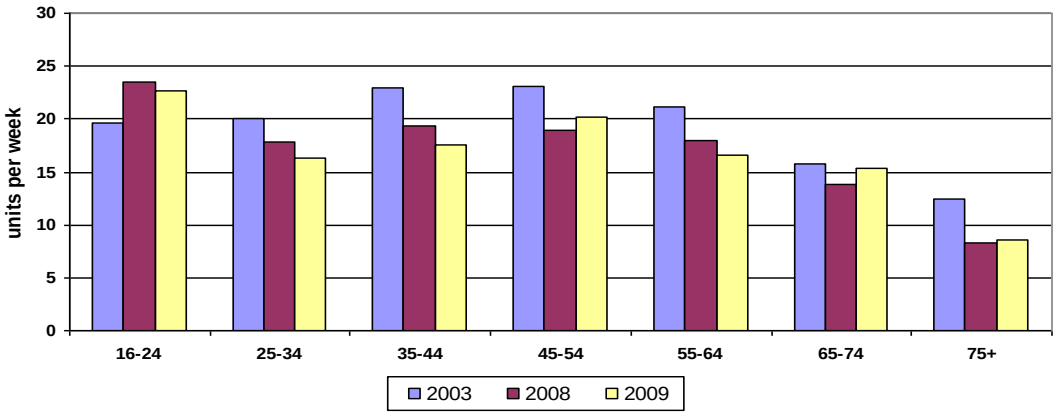
3.2.1.2 Alcohol consumption in Scotland by age-group

This section uses data from SHeS (Corbett et al 2010), to describe average weekly consumption and binge drinking[29] reports in six age groups (16-24, 25-34, 35-44, 45-54, 55-64, 65-74, >75 years), by gender, across three surveys (2003, n=8027; 2008, n=6375; 2009 n=7498).

Average weekly consumption by age group

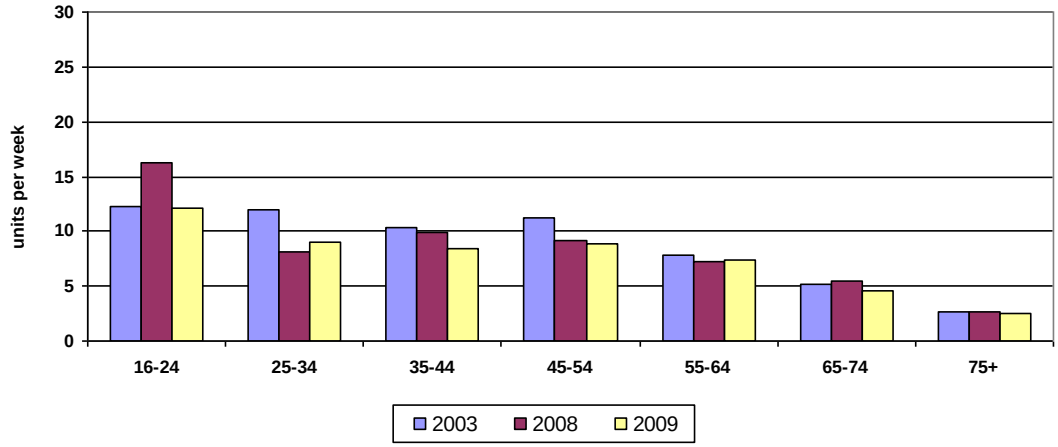
Average weekly consumption has decreased in men, aged 25-44 and 55-64 years, in each of three SHeS surveys (Figure 3.9). As a result, in 2009, young men aged 16-24 years had the highest average weekly consumption levels (22.7 u/w) of all age-groups and were the only age-group to exceed the recommended weekly safe drinking limits, for men, of >21 units. Average weekly consumption in women by age-group broadly follows a similar pattern to that observed for men (Figure 3.10). Young women aged 16-24yrs have the highest average weekly alcohol consumption levels (12.1 u/w) though, unlike men, still below the recommended safe weekly drinking levels for women (>14 units).

Figure 3.9 Mean number of units consumed per week in men by age group (SHeS, 2003, 2008, 2009)



[29] alcohol consumption data has been calculated using the new alcohol unit conversion factors (Corbett et al 2010)

Figure 3.10 Mean number of units consumed per week in women by age group (SHeS, 2003, 2008, 2009)



Excessive daily drinking, by age group

In 2009, approximately one in three men aged between 16-44 years, drank >8 units on their heaviest drinking day (Figure 3.11) and one in four women aged between 16-34 years drank >6 units on their heaviest drinking day (Figure 3.12). The proportion of men aged 16-34 years reporting excessive daily drinking has fallen in each of three SHES surveys. Trends are less consistent among women, however, women aged 16-64 years are less likely to report excessive daily drinking in 2009 than they were in 2003.

Figure 3.11 Drinking double the daily recommended daily limits on the heaviest drinking day, men, by age group (SHeS, 2003, 2008, 2009)

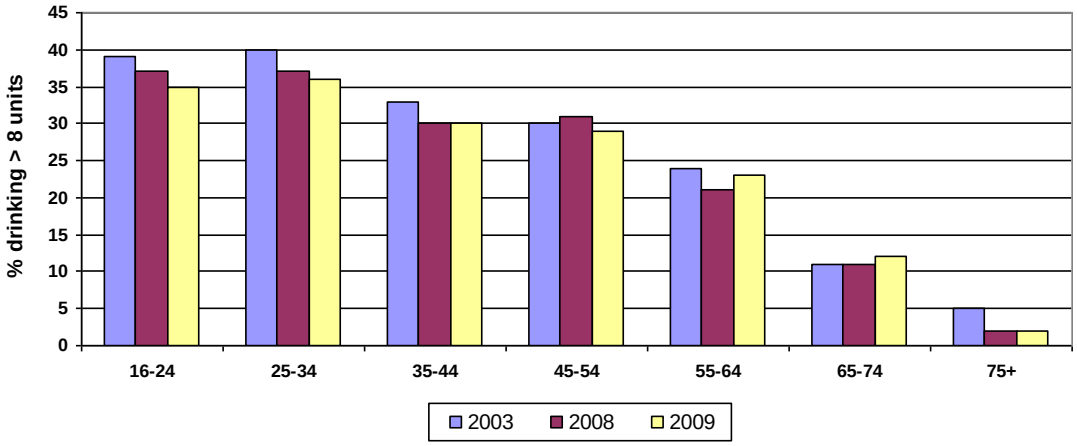
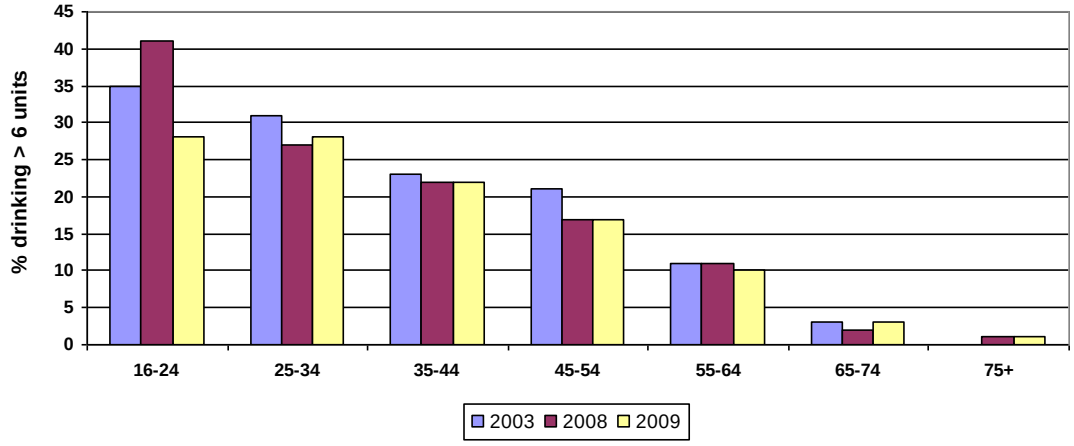


Figure 3.12 Drinking double the daily recommended daily limits on the heaviest drinking day, women by age group (SHeS, 2003, 2008, 2009)



Overall, men and women aged between 16-24 years tend to drink more on average per week than other age groups and men and women aged 16-34 years are more likely to report excessive daily drinking than those >34years. Trend data from SHeS suggests a decrease in weekly and excessive drinking, in both men and women, in nearly all age groups with the exception of average weekly intake in 16-24 year old males and among women aged 25-54 years. Interpreting trends in SHeS age-group consumption levels may, however, be unreliable due to small sample sizes in each age group (e.g. approximately 500 men and 500 women aged 16-24 years, 650 men aged 45-54 years, 300 men and women aged >75 years)[30] and therefore represent chance findings.

3.2.1.3 Alcohol consumption and deprivation

Alcohol consumption and association with socio-economic deprivation is reported by SHeS using the Scottish Index of Multiple Deprivation[31] (SIMD) quintiles which enables comparisons to be drawn between the most and least deprived 20% of areas in Scotland (and the intermediate three quintiles). Data from the 2009 SHeS are used below to describe the variation in weekly and daily alcohol consumption by area deprivation (Corbett et al 2010).

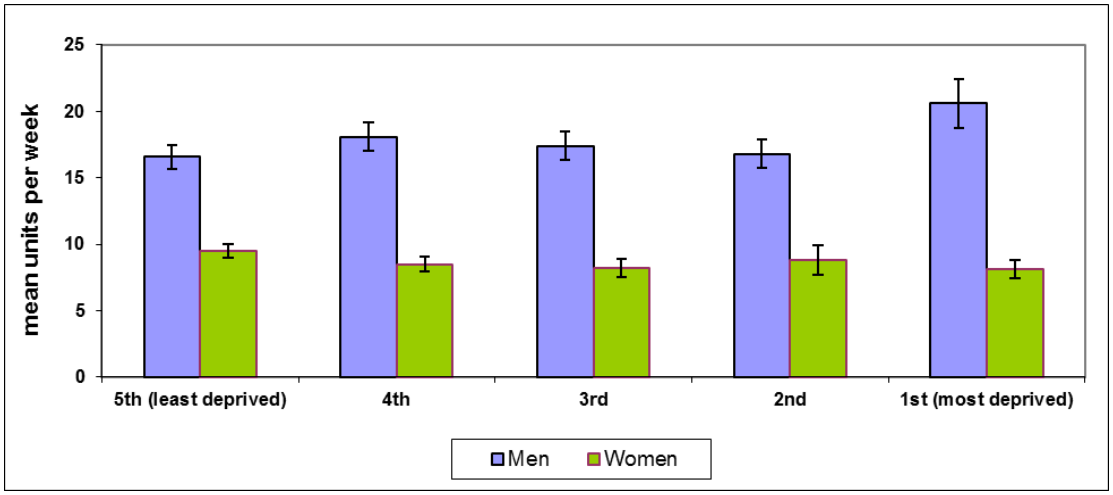
The relationship between drinking behaviour and SIMD varies depending on the measure of alcohol consumption and by gender. For men, mean weekly consumption was significantly higher in the most deprived quintile (20.6 units per week) compared to the least deprived quintile (16.6 units per week)

[30]These are base weighted averages (Corbett el 2010). See Appendix G for weighted and unweighted sample bases.

[31]SIMD is the Scottish Government's official measure of area based multiple deprivation. It is based on 37 indicators across 7 individual domains of current income, employment, housing, health, education, skills and training and geographic access to services and telecommunications. See Chapter 5 for a more detailed description.

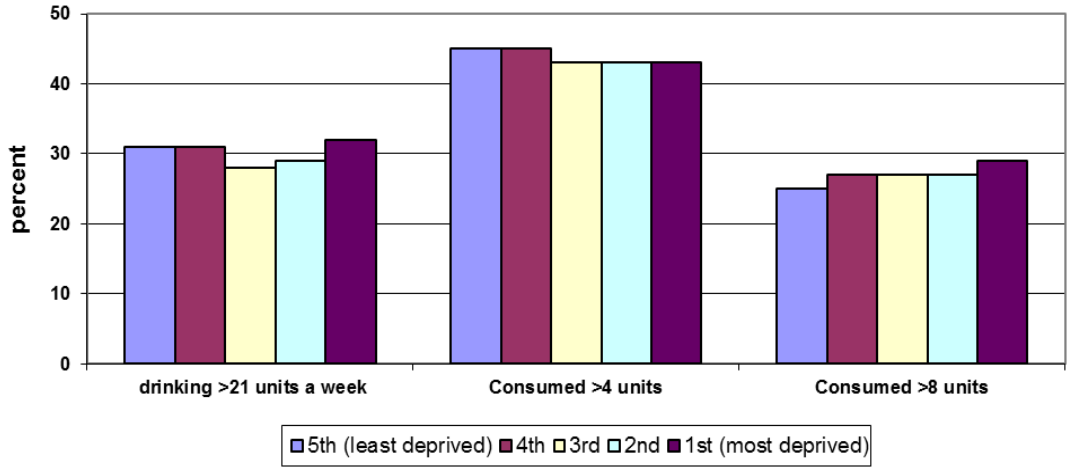
though there was no consistent trend of increased risk with increasing levels of deprivation (Figure 3.13). Conversely, mean consumption reported by women in the least deprived quintile was slightly higher (9.5 units per week) than that reported in other quintiles (Figure 3.13).

Figure 3.13 Mean weekly consumption by gender and SIMD quintile (SHeS 2009)



In men, the proportions drinking over the recommended safe weekly drinking limits (>21 units) and recommended daily drinking limits (>4 units) were broadly similar across the different deprivation quintiles (Figure 3.14). The proportion of men reporting drinking >8 units per day on the heaviest drinking day, however, was higher in the most deprived quintile (1st) compared to the least deprived quintile (5th), (29% and 25% respectively).

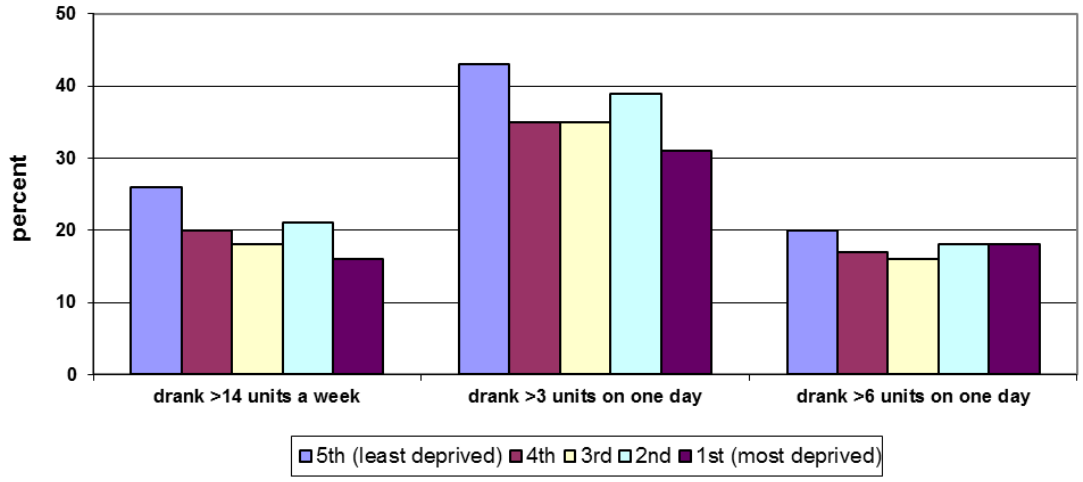
Figure 3.14 Exceeding weekly and daily limits and 'binge' drinking in men, by SIMD quintile (SHeS 2009)



Women living in the least deprived quintile were more likely to report drinking over both the safe weekly limits (>14 units) and safe daily limits (>3 units) than women living in the most deprived quintile (weekly 26% and 16% respectively, daily 43% and 31% respectively), (Figure 3.15). The

proportion of women from the least deprived quintile reporting drinking >6 u/d, on the heaviest drinking day, was also slightly higher than that reported in other quintiles (20% vs. range 16-18%).

Figure 3.15 Exceeding weekly and daily limits and binge drinking in women by SIMD quintile (SHeS 2009)



Overall, data from the 2009 SHeS suggest that men in more deprived quintiles drink more, on average, per week, and are more likely to be 'binge drinkers', than those living in the least deprived areas. There were no differences between SIMD quintiles in men reporting exceeding both weekly and daily safe drinking limits. In contrast, women from least deprived quintiles were more far likely than women living in the remaining quintiles, to exceed both weekly and daily safe recommended drinking levels. Although differences here were of a greater magnitude (>10%), than those for men, sample size and confounding from age, geography or factors related to the composition of the female sample in SHeS will account for a large part if not all of the observed differences. There was no obvious evidence of linear relationship between area deprivation and weekly and 'binge drinking' measures of alcohol consumption though no formal test for trend was undertaken.

3.2.2 Limitations of alcohol consumption survey data

The validity of self-reported alcohol consumption from surveys, especially in terms of underreporting, is a longstanding methodological concern of alcohol researchers (Midanik 1982, Dawson 1998, Room 1990; 2000). There are several lines of reasoning that have been put forward to account for underreporting, discussed below, including individual response patterns, selective non-response error and measurement error (Room 1977, Alanko 1984, Groves 1989, Gmel and Rehm 2004).

Measurement error can arise from inaccurate recording by interviewers, inaccurate reporting by respondents and weaknesses in the questionnaire wording, or errors due to mode of data collection and mode of data administration (Poikolainen 1985, Groves 1989). One aspect of measurement error

concerns the possible bias introduced by the type of questionnaire used, to elicit details on alcohol consumption. The beverage specific quantity frequency (QF) measure is a common feature of population surveys on alcohol drinking in Scotland and it has been consistently found that greater detail included in this type of approach yields higher volumes of drinking (Dawson 1998, Knibbe and Bloomfield 2001). However, QF measures are also widely criticised for providing lower estimates of drinking when compared to other measures based on recent drinking occasions and, in particular, the graduated frequency (GF) approach[32] which seem to yield comparable results as well as consistently higher estimates of the prevalence of high risk drinking and harm (Room 1990, Midanik 1988, Midanik and Room 1992, Rehm et al 1999). Theoretically, the GF should result in more valid estimates because special drinking situations are covered, yet its superiority over the QF approach in practical research is far from being conclusive (Dawson 2003, Gmel and Rehm 2004, Graham et al 2004, Greenfield and Kerr 2008) and has been argued by some to overestimate actual alcohol consumption (Poikolainen et al 2002, Gmel et al 2006). In contrast to the QF approach, the GF approach provides a standard set of drinking pattern measures that is, the quantities of drinks for which frequencies are reported are the same for all respondents. This standardization can be achieved only if respondents are required to report their consumption in terms of standard drinks rather than actual drink sizes. This requirement may introduce a source of error, however, because past research has shown that not all respondents attempt to convert their actual drinks to standard drinks and that some are incapable of doing so because they cannot accurately estimate their actual drink sizes (Kaskutas and Graves 2000). These findings suggest that the standardization of data across respondents, which is part of the appeal of the GF approach, may be more apparent than real (Dawson 2003). The difference in consumption estimates that may arise between the GF and QF approach are only thought to explain the gap between survey and per capita alcohol consumption data to a minor extent (Gmel and Rehm 2004).

Selective non-response is another source of survey error which can occur either as sample selection bias or as self-selection bias. Sample selection bias is systematic error due to a non-random sample of a population, causing some members of the population to be less likely to be included in the sample than others. National population surveys of alcohol drinking in Scotland (SHeS, GLF, HEPS) are, however, based on a stratified, clustered random probability sample of individuals living in private households across the whole of mainland Scotland (plus the larger inhabited islands which are included in the SHeS sample). Weighting has been applied in each survey to take account of disproportionate sampling within regions, differing probabilities of selection within households of different sizes and within multi-occupied addresses, and differential response (Malam et al 2004, Gray et al 2009, ONS 2011). Selective non-response error is, therefore, unlikely to explain the consistent

[32] the GF measure is a series of questions on the frequency of consuming specific numbers of drinks which ranges from the most ever consumed in the last year to 1–2 drinks per occasion.

differences in estimates of alcohol consumption reported by each survey described in section 3.2.1.Sample selection effects in these surveys are still possible since people who have no fixed abode or who are living in an institution are not included in the sampling frame. On balance, these people are suspected of containing a higher proportion of heavy drinkers than individuals living in households (McAuliffe et al 1998, Goddard 2001). Due to the skewed distribution of alcohol consumption, even small subgroups with high consumption that are not included in the survey, may be a significant omission from population-based estimates. In survey samples, it is often the case that the highest drinker category can account for the majority of alcohol drunk (Gmel and Rehm 2004).

Surveys will also suffer from self-selection bias, where certain groups e.g. abstainers, heavy drinkers, though included in sampling frame, are reluctant to participate or respond truthfully to questions on their drinking (Lahaut et al 2001, Gmel and Rehm 2004). Several studies have reported significant differences in the health status, health related behaviour, socio-economic background and mortality of survey respondents and non-respondents; Aromaa et al (2003) reported that non-participation seemed to be selective: in the younger age-groups with addictive behaviours or problematic life situations, in the middle-aged persons with higher disease risk and in the elderly with chronic diseases and/or disabilities. Several studies have reported that survey non-respondents have poorer health (Knudsen et al 2010) and higher mortality rates than survey respondents (Jousilahti et al 2005). There is some indication that abstention (i.e. teetotallers) is also more likely than heavy drinking to be related to non-response. Lahaut et al (2002) found that non-drinkers were overrepresented among non-respondents, whereas only weak evidence was found for overrepresentation of frequent heavy drinkers among non-respondents. Other studies have also found that non-respondents had had lower mean consumption and a lower proportion of high consumers, than respondents (Caspar 1992, Romelsjö et al 1995, Hill et al 1997). Gmel and Rehm (2004), however, argue that non-response effects are generally small and not likely to explain the differences between per capita and survey estimates of drinking: non-response correction would usually increase mean consumption estimates for the respondents by around 3%-6% only (Makela 1971, McAuliffe et al 1998, Gmel 2000).

One other source of survey error is individual response patterns which may be involuntary, such as memory deficits or involuntary such as denial and concealment of alcohol consumption (Gmel and Rehm 2004). It has been argued that people tend to underestimate the amount they drink in response to existing social values around alcohol drinking. (Goddard 2001). There is some evidence of differential reporting of diet by socioeconomic status (Hebert et al 2002). Bobak (2005) argues that it is conceivable that similar bias occurs with alcohol and that it also relates to characteristics other than social status, possibly including alcohol-related health outcomes. In QF measures of alcohol consumption, there also seems to be a tendency of respondents to interpret usual or customary drinking as the modal value although researchers actually interpret these as means (Duffy and Alanko 1992, Kühlhorn and Leifman 1993). Therefore, the modal quantity would generally underestimate the

'true' mean quantity because the individual's quantity distribution (i.e. the distribution of quantities over separate drinking occasions) is usually highly right skewed.

Recall of drink sizes and amounts consumed are seen to represent a major contributor to individual's underestimating their alcohol consumption (Dawson 1998). Standard drinks or standard serving sizes in surveys are usually based on sizes as served in restaurants and bars and these may be considerable underestimation of what is poured into glasses in people's homes. Kaskutas and Grove (2000) in a study of 321 heavy-drinking pregnant women found that women consumed drink sizes that were much larger (up to four times that of a standard drink) and similarly they underestimated amount poured. In a Dutch study, the use of standard drinks for both home and outside home consumption resulted in an underestimation of total volume of drinking of 7.3% (11.9% for women and 5.8% for men) compared with the use of self-reported servings for at home drinking (Lemmens 1994). McAskill et al (2008), in a study of Scottish drinkers, found that, on average, home based vodka measures were twice normal pub measures and that for all drinks, a poured drink ranged from one to four units. Population surveys have also been criticised for underestimating the typical size of home-based measures of spirits and wine (Goddard 2007, Catto and Gibbs 2008). Gill and Donaghy (2004) investigated size of home based measures using a 175ml glass (surveys have traditionally used 125ml glass measure), but many participants reported that this was much smaller than the glass that they would use at home, suggesting that 160ml represents a conservative estimate of the size of a typical home-poured glass of wine. Until recently, national population surveys in Scotland (and the UK) have also undercounted the number of units in a typical serving of beer/lager/cider and wine by failing to take into account the increased strength of beverage alcohol in the UK (Catto and Gibbs 2008); half of the most popular brands of lager now contain at least 3 units per pint. To date, Scotland's surveys have used a conversion factor of 2 units for normal strength beers. The strength of the most popular brands of wine ranges from 11.5% to 14.5% ABV (alcohol by volume), but surveys have counted one glass of wine as 1 unit, which assumes an ABV of only 8%. Assuming that the average glass of wine, consumed either at home or in a licensed setting, is 175ml in size, a typical serving will contain between 2 and 2.5 units, more than double that estimated in surveys to date (Catto and Gibbs 2008).

When issues of validity of survey results were raised in the mid-1970s the response was to view the proportion of alcohol sold (or released for sale, i.e. per capita consumption) which could be accounted for in a survey as the 'gold standard for the validity of drinking measures. Volume of drinking, expressed as units of ethanol per member of the drinking-age population, derived from population survey, was seen as the most direct equivalent of the alcohol sales figures (Pernanen 1974, Rehm 1998, Room 2000). Following this, a number of American studies observed that coverage of national alcohol consumption in national surveys was quite low with only a third (35%) to a half (50%) generally accounted for by respondent's drinking in the past 12 months (Pernanen 1974, Kasukatas 2000, WHO 2002). Goddard (2001) estimated that surveys in United Kingdom only accounted for 55-

60% of actual alcohol consumed compared with UK sales data, whilst Catto and Gibbs (2008) recently estimated survey underestimation of alcohol intake in Scotland may be as great as 50%. From 2003 and 2006, SHeS and GLF respectively, have used updated unit conversion factors for beers, lagers, ciders and wine and included in their survey questions on wine consumption in terms of small (125ml), plus new measures of medium (175ml) or large glasses (250ml), to more accurately reflect the amount people drink. Estimates based on the new alcohol conversion factors have resulted in significant increases across most measures of alcohol consumption; for example, in the 2003 SHeS, mean consumption among men and women, aged 16 years and over, using original conversion factors, was 17.2 and 6.5 units p/w respectively; the figures using the revised conversions factors were 20.1 units p/w for men and 9.1 units p/w for women (Bromley et al 2008). These revisions reduced the estimates of SHeS survey under-reporting, compared to per capita alcohol consumption, from about around 50% reported by Catto and Gibbs (2008) to approximately 35%. According to Rehm (1998), this is as reasonable a coverage that one can expect from a population survey: coverage rates shouldn't expect to be higher than 70% since based on the approximately log normal distribution of alcohol consumption a small minority of the population are expected to drink a large proportion of alcohol.

One final aspect to consider in assessing the accuracy of population survey estimates concerns the actual summarizing and aggregating measures of alcohol consumption used in surveys. In one form or another, researchers have tended toward a measure of overall volume of drinking, that is, of the cumulative total amount of alcohol consumed per year or other unit of time. Though, as Room (1979) observes, the reasoning has often been left implicit, this dimension was perhaps seen as fairly representing the importance of alcohol in the respondent's life and as probably the most directly related to the risk of long-term physiological complications such as cirrhosis. An overall volume measure also has the virtue for analytical purposes of being an interval scale easily used in regression and other statistical analysis (Room 1979, Greenfield and Kerr 2003). Volume measures are commonly used in epidemiological studies especially those with cancer as an outcome. Yet volume of drinking remains essentially a crude summary measure of drinking behaviour, ignoring the fact that there might be different categories of drinkers within the population, with normal distribution and with quite complex drinking patterns and of amounts drunk, within each group(Tuck 1980, Midanik and Room 1992, Single and Leino 1998, Gmel and Rehm 2004).

3.3 Conclusion

This chapter has presented an analysis of trends and patterns of alcohol consumption in Scotland based on estimates from national population surveys (i.e. self-reported alcohol consumption) and statistics on alcohol 'sales' (i.e. per capita alcohol consumption estimates).

Of the three surveys, SHeS, consistently report higher estimates of mean consumption per week and in the proportion of men and women exceeding weekly and daily limits, than those reported by GLF or HEPS. Alcohol consumption estimates from GLF and HEPS, (both with sample sizes of approximately 1500 adults aged 16 years and over), are similar to each other across drinking measures. SHeS, simply because of its size (approximately four times larger than that of GLF and HEPS) offers greater precision than the GLF and HEPS. Differences in alcohol consumption estimates between surveys may be explained by differences in the age, gender and geographical sample sources of each of the surveys.

Despite some variation in the estimate ranges of various drinking measures, alcohol consumption survey trends in Scotland are broadly in agreement and suggest a decrease in men exceeding weekly recommended limits, in excessive daily drinking and in their mean consumption per week albeit from very high levels in the first place. For women, the opposite is true, with weekly and daily consumption either remaining constant or slightly increasing, which may be indicative of a convergence in both the volume drunk and drinking patterns between men and women in Scotland over the last twenty years. Similar patterns have been observed in England and Wales (BMA 2008). Levels of drinking vary greatly by age with younger drinkers (16-34 years) more likely to exceed daily limits and 'binge' drink and middle age drinkers (35-54 years) more likely to drink more per week than other age groups. The strong socio-economic patterning in alcohol-related mortality and morbidity in Scotland has been well documented (Leyland 2007, SHAAP 2009, ISD 2010b). The evidence for an association between alcohol consumption and socio-economic deprivation is, however, inconsistent and varies by both gender and the measure of drinking behaviour and there was no obvious evidence of linear relationship between area deprivation and weekly and 'binge drinking' measures of alcohol consumption.

Taken together, recent per capita alcohol consumption data and population survey data would seem to suggest that levels of drinking in the Scottish population may be falling or, at least, stabilising although it is too early to conclude that this is a long term trend. Nevertheless, approximately one in four of adults in Scotland still exceed the recommended safe weekly drinking guidelines and over one in three of adult weekly drinkers exceed the recommended safe daily drinking limits (Corbett et al 2010). It is also very likely, as discussed in Section 3.2.2, that consumption data from population surveys will underestimate the true levels of drinking in the population by approximately 30%. Furthermore, levels of population drinking in Scotland, based on per capita alcohol consumption data, compare unfavourably to many other countries (Robinson et al 2010, WHO 2010) and are

considerably higher than consumption levels in the countries supplying the majority of epidemiological studies reporting on the association between alcohol consumption and cancer (described in Chapter 2). At the same time, Scotland's experience of trends in cancer incidence, particularly those linked with alcohol consumption, e.g. oral, oesophageal, breast and colorectal cancer, also compare unfavourably with many other countries in the European Union (Botha et al 2003, La Vecchia et al 2003). The potential contribution of alcohol consumption levels, past and present, to these cancer trends in Scotland cannot be underestimated; cancers of the upper aero-digestive tract (oral, pharyngeal, laryngeal and oesophageal cancer) rank among the top ten most common sites in Scottish men and women, and lung, colorectal and breast cancer are ranked as the top three most common cancer sites in Scotland. Other common cancers include prostate, kidney and ovarian cancer (ISD 2010a). Surveillance of trends in incidence rates for alcohol-related cancers is, therefore, of interest to determine if they are correlated with levels of the drinking in the Scottish population. In the next chapter trends in incidence rates for those cancers commonly linked to alcohol consumption are summarised and the contribution of alcohol consumption and other prevalent risk factors in Scotland, to these trends, is discussed.

Chapter 4 Trends in alcohol related cancers in Scotland

This chapter presents data, from the Scottish Cancer Registry, on trends in cancers commonly linked with alcohol consumption.

The Scottish Cancer Registry (SCR) is responsible for the collection of information on all new cases of primary malignant neoplasms, carcinoma in situ, neoplasms of uncertain behaviour and benign brain and spinal cord tumours arising in residents of Scotland. Data quality is monitored using routine indicators, computer validation and ad hoc studies of data accuracy and completeness of ascertainment (see Chapter 5.1.3 for further details of the SCR). SCR data is published on the ISD website and available to download at http://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/. Cancer sites are classified according to the International Classification of Diseases (ICD) 9th version from 1985 and from 1996 the 10th version, (see Chapter 7.1.1, Table 7.2 for a list of relevant ICD codes).

Using published data (1985–2008) from the SCR, European age-standardised incidence rates (EASRs) per 100 000 person years at risk (pys)[33], are presented for the following cancers; cancers of the UADT (oral, pharyngeal, laryngeal and oesophageal cancer), gastrointestinal cancers (liver, pancreatic gastric colon and rectal cancer), urological cancers (prostate, bladder, and kidney cancer) and lung, breast and ovarian cancer. Consistency in the temporal trends in incidence rates between men and women and, variation by deprivation are also examined. The chapter concludes with an assessment of the contribution of alcohol consumption and other prevalent risk factors in Scotland, to these trends.

4.1 Trends in cancers of the upper aero digestive tract

European age-standardised incidence rates (EASRs) for cancers of the upper aero digestive tract in Scotland between 1985 and 2008 are presented in Figures 4.1 (men) and 4.2 (women).

[33] Person time at risk is the time in years between entry into an analysis and exit from an analysis. This is the time during which a subject is at risk of having an event (whether second cancer, death, etc.) as defined by the analysis. Total person time at risk for a given subcategory is calculated by adding the person time at risk counted in that subcategory for each subject in the analysis (Breslow and Day 1987). Further details of the methodology are provided in Appendix H.

Figure 4.1 EASRs for cancers of the UADT in men, 1985-2008 (Source ISD 2010c)

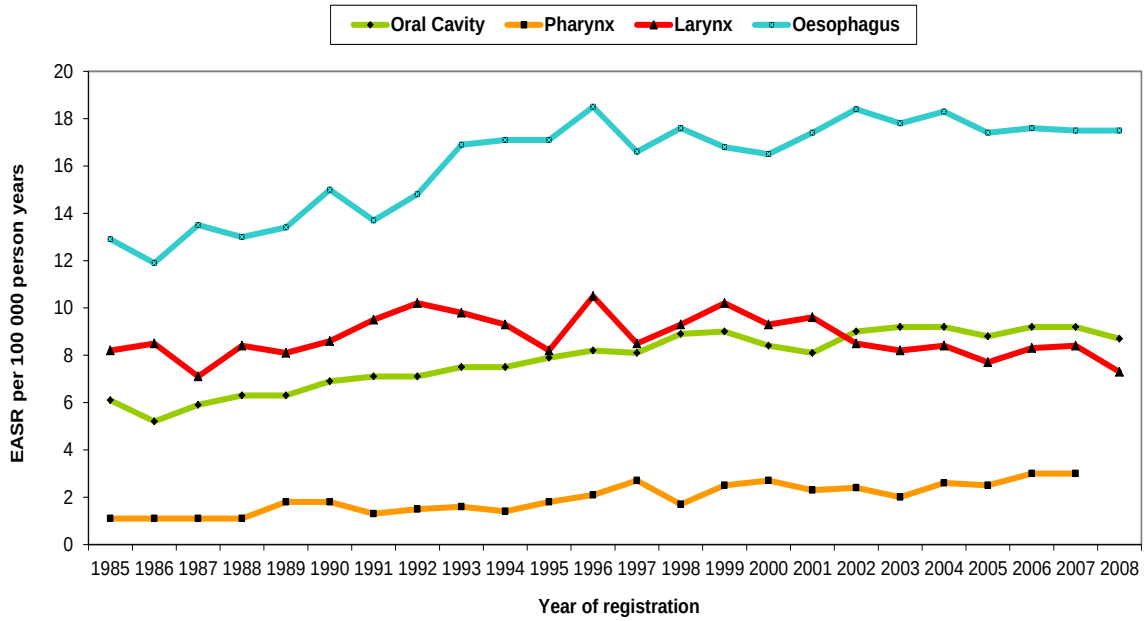
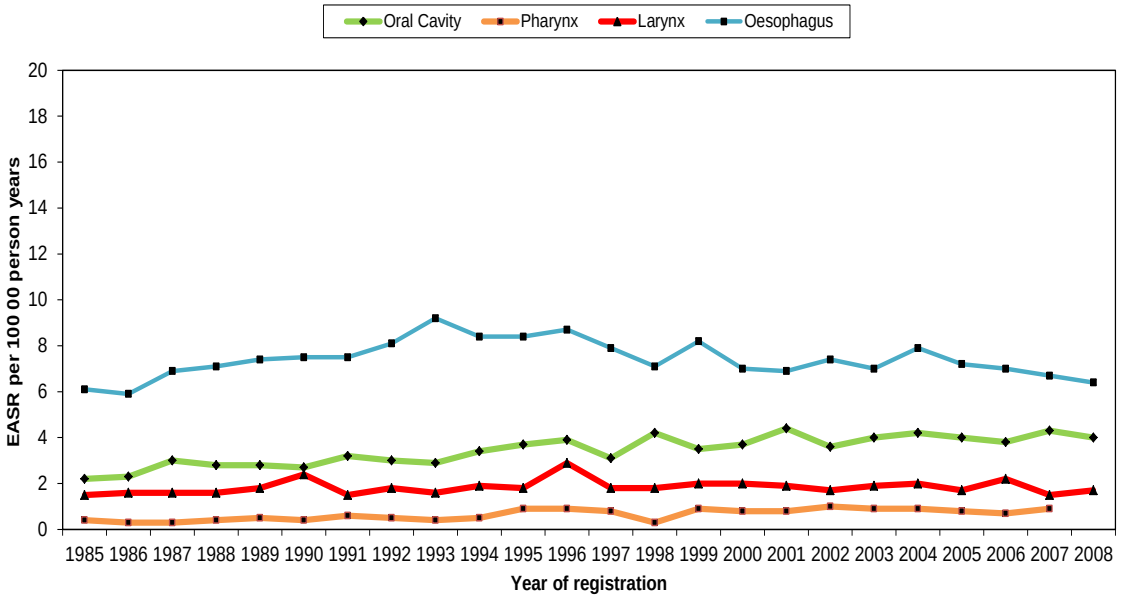


Figure 4.2 EASRs for cancers of the UADT in women, 1985-2008 (Source ISD 2010c)



EASRs for oral cancers in men increased, between 1985 and 2008, from 6.1 to 8.7 per 100,000 pys and almost doubled in women (2.2 to 4.0 per 100 pys). Although cancers of the pharynx are rare, there has been an approximate threefold increase in incidence of this cancer in men (1.1 per 100 000 pys in 1985 to 3.0 in 2007) and a two-fold increase in women (from 0.4 to 0.9 per 100 000 pys).

Laryngeal cancer EASRs reached a high in men in the mid-1990s at approximately 10 per 100 000 pys, but have fallen subsequently over time to 7.3 per 100 000 pys in 2008. EASRs for laryngeal

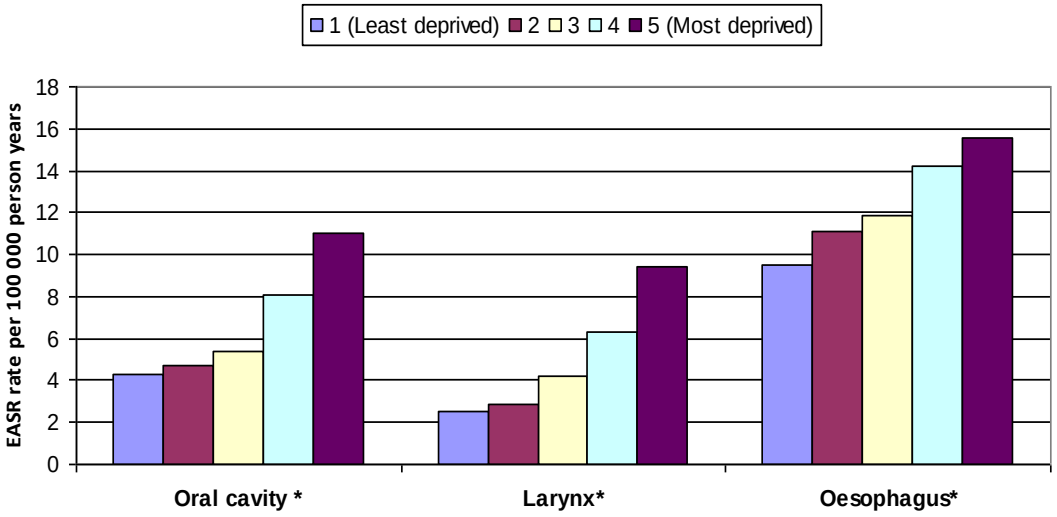
cancer in women have remained constant, between 1985 and 2008, at approximately 1.5 per 100 000 pys.

Between 1985 and 2008, the EASR for oesophageal cancer has increased in men (from 12.9 to 17.5 per 100 000 pys), but has not changed in women (from 6.1 to 6.4 per 100 00 pys). Much of the increase in the incidence of oesophageal cancer in men occurred between 1985 and 1996 (18.5 per 100 000 pys), but the EASR since then has remained around this level. The EASR for oesophageal cancer in women also increased from 1985 to 1993 (6.1 to 9.1 per 100 000 pys), but since then the EASR has returned to levels close to those reported in the 1980s. The gender ratio for UADT cancers in Scotland has not changed since 1985 (See Appendix H, Table H1).

The risk of developing UADT cancer increases with age. In Scotland, the majority of oral and pharyngeal cancer cases occur in people aged 50 or over and for laryngeal and oesophageal cancers, in people aged 60 years and over (Cancer Research UK 2010). The incidence of oral and pharyngeal cancer continues to rise across the UK in all age groups with significant increases observed in people aged less than 45 years (Conway et al 2006, Conway et al 2007).

Figure 4.3 highlights that cancers of the UADT are most common in areas of high deprivation (Figure 4.3). This reflects the strong gradient in smoking prevalence across deprivation quintiles in Scotland, where the most deprived communities have smoking prevalence rates similar to those seen nationally in the 1970s (McKinney et al 1995, Taulbut et al 2008). EASRs for cancers of the oral cavity and larynx are over three times and four times, respectively, higher in the 20% most deprived areas, compared to the 20% least deprived areas of Scotland. There was a similar pattern for cancers of the oesophagus, but not as marked a difference as that found in cancers of the oral cavity and larynx. There was a significant increase in incidence rate of cancers of the UADT with increasing severity (*p value for trend* <0.001) of deprivation (ISD Scotland 2010c).

Figure 4.3 EASRs[1] for cancers of the UADT, by SIMD 2006 deprivation quintile (Source ISD 2010c)



** p test for trend <0.001. [1] Rates are calculated using the populations in 2006*

4.1.1 Discussion

In summary, oral and pharyngeal cancer rates have steadily increased in men and women over the last 30 years. Over the same time period, laryngeal cancer rates have fallen in men and remained fairly constant on women. Smoking, a major risk factor for these cancers, is on the decline in the Scotland; the proportion of adults who smoke has reduced by about half (from 47% in 1972 to 24% in 2008) since the early 1970s (Taulbut, et al 2008, Robinson and Bugler 2010). In a recent pooled analysis, results demonstrated that the larynx was the organ within the head and neck that was most susceptible to the effects of cigarette smoking (Hashibe et al 2007). Trends in laryngeal cancer in Scotland are, therefore, most likely to be closely correlated with the trends in smoking prevalence in men and women in Scotland. Numerous studies have described the increase, over the last thirty years, in the incidence of oral and pharyngeal cancer in Scotland, largely attributing these trends to increasing levels of drinking in the Scottish population at a time when overall smoking prevalence was declining (MacFarlane et al 1992, Llewellyn and Mitchell 1994, MacFarlane et al 1996, Leon et al 2003, La Vecchia et al 2004, Conway et al 2006). Similar patterns in incidence rates in Scotland have been observed for cancers of the oesophagus, especially in men (MacFarlane and Boyle 1994, Swerdlow et al 1998, Corley and Buffler 2001, Botterweck et al 2001). The relationship between UADT cancer risk and socio-economic factors is also well established both in Scotland (McKinney et al 1995, MacFarlane et al 1996, Edwards and Jones 1999, Conway et al 2007) and across western industrialised countries (IARC 1997) and as the incidence of oral cancer has increased in Scotland, so has the gap in oral cancer incidence between affluent and deprived socio-economic groups (Conway et al 2007).

It is interesting to compare the trends in oesophageal cancer with those for oral and pharyngeal cancers, for which alcohol and tobacco are major aetiological factors. The very large increase in

incidence of oral and pharyngeal cancers in young men in recent years is not matched by a similar scale of increase in cancer of the oesophagus. The secular trends in oesophageal cancer are also very different from those for lung cancer, suggesting that smoking is not the dominant reason for the trends. However, trends in the incidence of oesophageal cancer are difficult to interpret due to variations in trends in the two main histological types of oesophageal cancer; squamous cell carcinoma (SCC) and oesophageal adenocarcinoma. Until the 1970s, SCC accounted for the vast majority of oesophageal cancer diagnosed in Scotland. Whilst incidence rate of SCC of the oesophagus has increased since the 1970s, there has been a more striking increase in incidence rates of oesophageal adenocarcinoma (Botterweck et al 2000, Vizcaino et al 2002). Brewster et al (2000) reported that among Scottish males the estimated percentage changes in incidence rates of oesophageal adenocarcinoma and SCC of the oesophagus, between 1977 and 1996, were +139.5% (*p-value* <0.0001) and +42.7% (*p-value* <0.001) respectively. Corresponding estimates for females were +124.6% (*p-value* <0.0001) and +57.3% (*p-value* =0.0001). In the early 1990s, oesophageal adenocarcinoma became the dominant histological type of oesophageal cancer in men in Scotland and incidence rates have continued to increase in men and women since then. Incidence rates of SCC of the oesophagus have remained relatively stable over the same time period (Park and Brewster 2002, Bosetti et al 2008). The evidence presented in Chapter 2.1.2 would suggest, however, that alcohol consumption is an unlikely risk factor for the rise he incidence of oesophageal adenocarcinoma. A more likely explanation lies in the high levels of obesity in the Scottish population, with obesity being positively associated with an increased risk of oesophageal adenocarcinoma, but not SCC of the oesophagus (Renehan et al 2008, Steffen et al 2009).

4.2 Trends in alcohol-related gastrointestinal cancers

European age-standardised rates (EASRs) for alcohol-related gastrointestinal (liver, pancreas, gastric and colorectal) cancers in Scotland between 1985 and 2008 are presented in Figures 4.4 (men) and 4.5 (women).

EASRs for liver cancer in Scotland have approximately doubled between 1985 and 2008 from 3.8 to 7.3 per 100,000 pys in men and from (1.5 to 2.8 per 100 000 pys) in women. In contrast, EASRS for gastric cancer have almost halved in the same time period, in both men (33.1 to 16 per 100 000 pys) and women (14.8 to 6.4 per 100 000 pys). Pancreatic EASRs in men and women have remained relatively constant over the last 30 years. EASRs for colon and rectal cancer have increased in men (from 33.4 to 41.5 per 100 000 pys and 19.5 to 24.6 per 100 000 pys) though EASR rates for colon and rectal cancer in men have been fairly stable since the mid-1990s. For women, there has been little change in the EASR rate for colon cancer (28.8 to 29.8 per 100 000 pys) and rectal cancer (11.1 to

12.8 per 100 000 pys) between 1985 and 2008. The gender ratio for these alcohol related gastrointestinal cancers in Scotland has not changed since 1985 (See Appendix H, Table H2).

Figure 4.4 EASRs for gastrointestinal cancers in men, 1985-2008. (Source ISD 2010c)

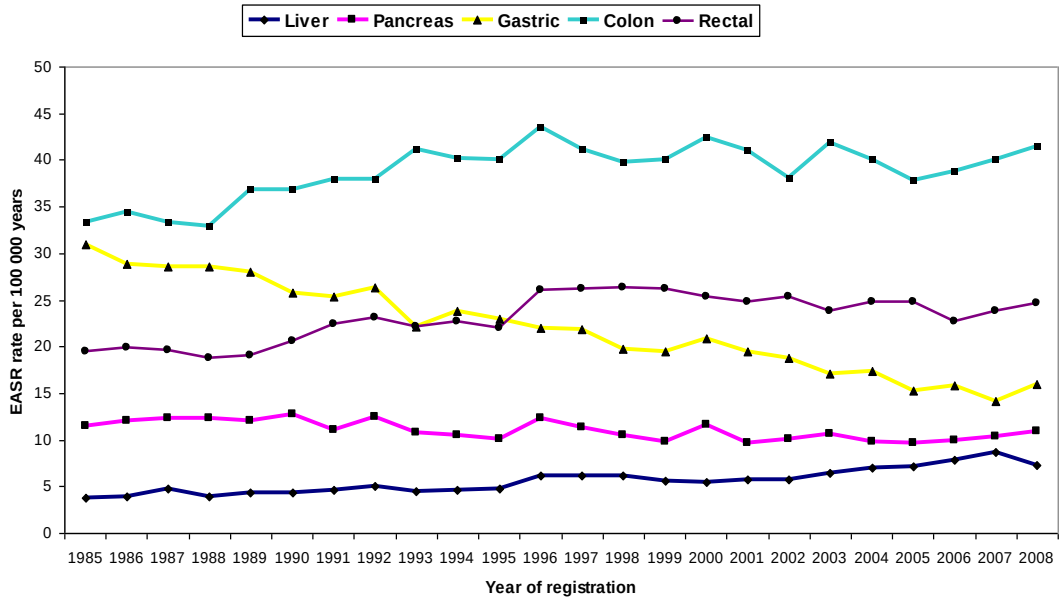
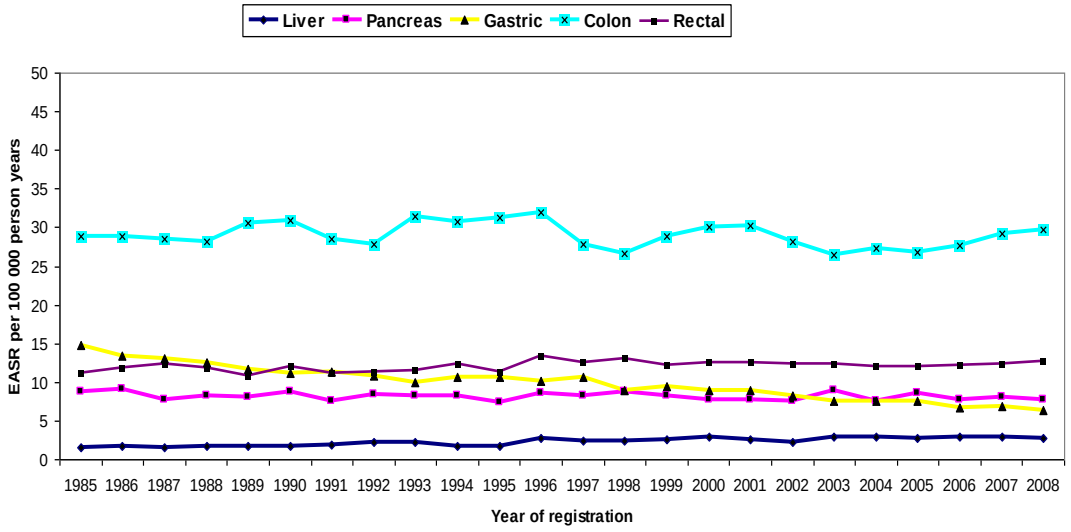


Figure 4.5 EASRs for gastrointestinal cancers in women, 1985-2008. (Source ISD 2010c)

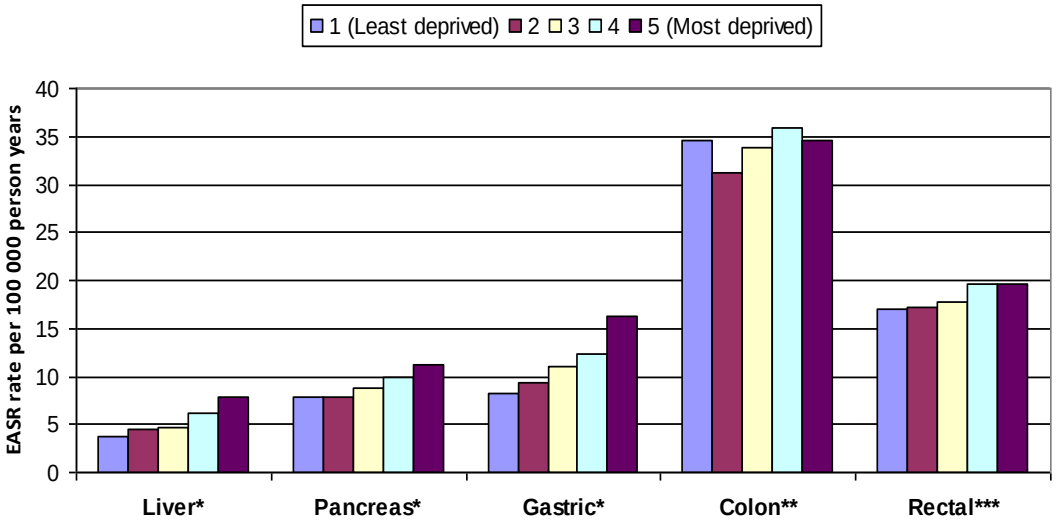


Incidence rates for gastrointestinal cancers increase steeply with age and the highest rates occur in the oldest age groups (Cancer Research UK 2010, ISD Scotland 2010a). Around three-quarters (75%) of liver and pancreatic cancer cases occur in people aged 65 years or over. Gastric (stomach) cancer occurs mainly in older people with less than 8% of cases diagnosed before the age of 55 years and the incidence rates increase steeply from age 60 years. The occurrence of colon and rectal cancer is also strongly related to age, with 84% of cases arising in people who are 60 years or older. Until 50 years

of age, men and women have similar incidence rates for colon and rectal cancer, but in later life incidence is higher among men than women.

Incidence rates for most gastrointestinal cancers are strongly related to social class and measures of deprivation, with higher rates in socially and economically deprived groups (Figure 4.6). Incidence rates for cancer of the liver, pancreas and gastric cancer significantly increase (*p value for trend* <0.0001) with increasing levels of deprivation. EASRs for rectal cancer also increase across each deprivation quintile though less strongly (*p value for trend* =0.001) than that noted for gastric, liver and pancreatic cancer. There was no association between measures of deprivation and colon cancer (*p value for trend* =0.3571).

Figure 4.6 EASRs[1] for gastrointestinal cancers, by SIMD 2006 deprivation quintile (Source ISD 2010c)



** Test for trend p <0.0001; ** Test for trend p=0.3571; *** Test for trend p=0.001.[1] Rates are calculated using the populations in 2006*

4.2.1 Discussion

Significantly higher incidence rates of colorectal cancer have been reported in Scotland, compared to many other European countries (Janout and Kollarova 2001, Karim-Kosa et al 2008). Swerdlow et al (1998) observed that the reasons for the changes in incidence in Scotland are unclear with a large range of factors having been suggested as potentially affecting colorectal cancer risk - aspects of diet (including saturated fats, and dietary fibre), alcohol consumption, patterns of cholecystectomy, sex hormones and non-steroidal anti-inflammatory drugs. It is probable that dietary factors play a large role and changes in diet are at least partly responsible for the trend (Swerdlow et al 1998 Karim-Kosa et al 2008).

Most cases of liver cancer occur in patients with cirrhosis of the liver (El-Serag 2007). In addition to excessive alcohol consumption, chronic viral hepatitis and non-alcoholic fatty liver disease (which is

associated with obesity) are other significant aetiological factors for cirrhosis of the liver (Bhala et al 2009). Scotland has one of the fastest growing mortality rates of chronic liver disease (which includes cirrhosis mortality) in the world at a time when rates in most of Western Europe are falling (Whyte 2006).

In contrast to many other types of cancer, gastric cancer has a falling incidence in Scotland and in Europe (Karim-Kosa et al 2008), but is still one of the more common cancers reported, in men and women, in Scotland. There are established links between the development of gastric cancer and deprivation (Brewster et al 2000, Quinn 2005), particularly deprivation in childhood. The majority of gastric cancers in Scotland are adenocarcinoma (as opposed to lymphomas; Thompson 2001) and smoking and alcohol do not appear to be important predisposing factors for gastric cancer (IARC 1988, WCRF/AICR 2007). The decrease in gastric cancer may also relate to better social and sanitary conditions in early life, and changes over time in the prevalence of infection with Helicobacter pylori (Swerdlow et al 1998).

Pancreatic cancer trends in Scotland match those of several other countries in that there has been a slow decline in the incidence rates for pancreatic cancer in both men and women (Garden 2001, Karim-Kosa et al 2008). Smoking is the most important known risk factor for pancreatic cancer, with an attributable risk of between 20-40% for men and 10-20% for women (Fryzek et al 1997, Working Group on Diet and Cancer 1998).

4.3 Trends in bladder, kidney and prostate cancer

European age-standardised rates (EASRs) for selected urological cancers (prostate [men only], bladder and kidney) in Scotland between 1985 and 2008 are presented in Figures 4.7 (men) and 4.8 (women).

EASRs for prostate cancer in men have almost more than doubled since 1985 (from 46.0 in 1985 to 84.3 per 100 000 pys in 2008). Incidence rates of bladder cancer in men and women, remained fairly constant at approximately 35 per 100 000 pys and 10 per 100 000 pys, respectively, from 1985 to 1997, thereafter incidence rates have fallen significantly in both men and women: EASRs for bladder cancer in men and women in 2008 were 18.8 and 5.7 per 100 000 pys, respectively. Between 1985 and 2008 the EASRs for kidney cancer have risen gradually in both men (from 9.9 to 15 per 100 000 pys) and women (from 5.1 to 8.7 per 100 000 pys) from 1985 to 2008. Men are three times more likely to develop cancer of the bladder and twice as likely to develop kidney cancer as women. The gender ratio for incidence of bladder and kidney cancers in Scotland has not changed since 1985 (Appendix H, Table H3).

Figure 4.7 EASRs for alcohol related urological cancers in men, 1985-2008 (Source ISD 2010c)

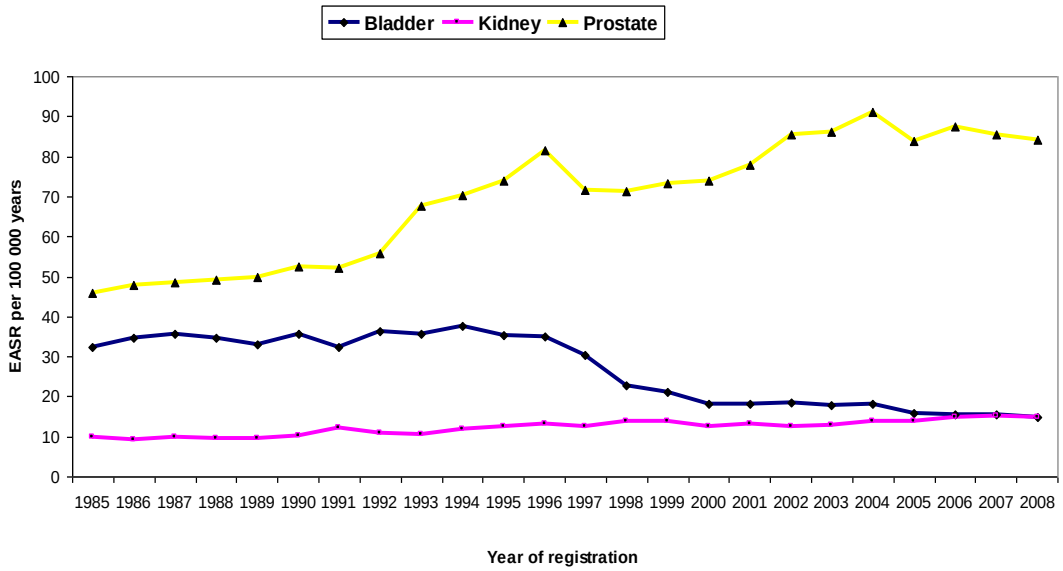
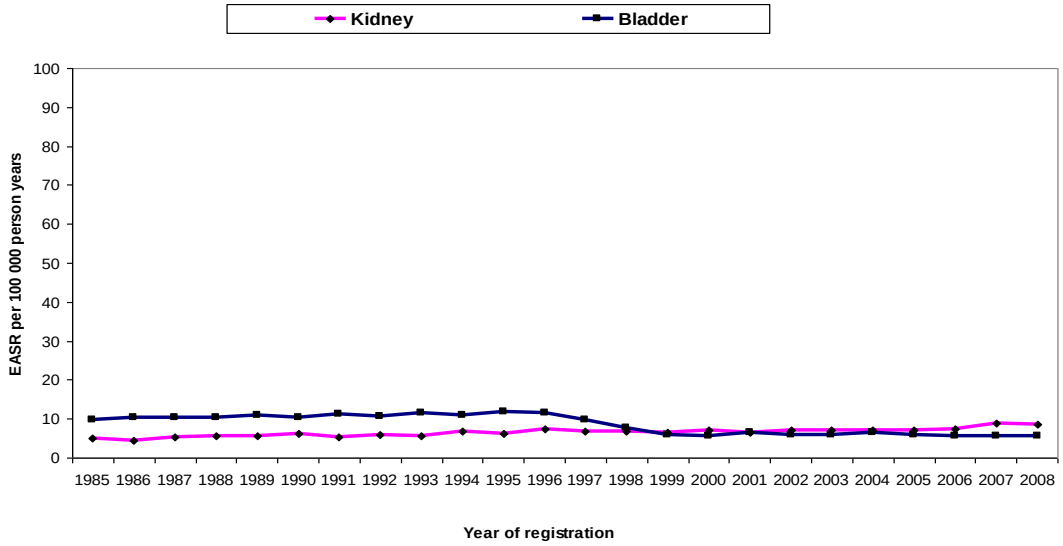


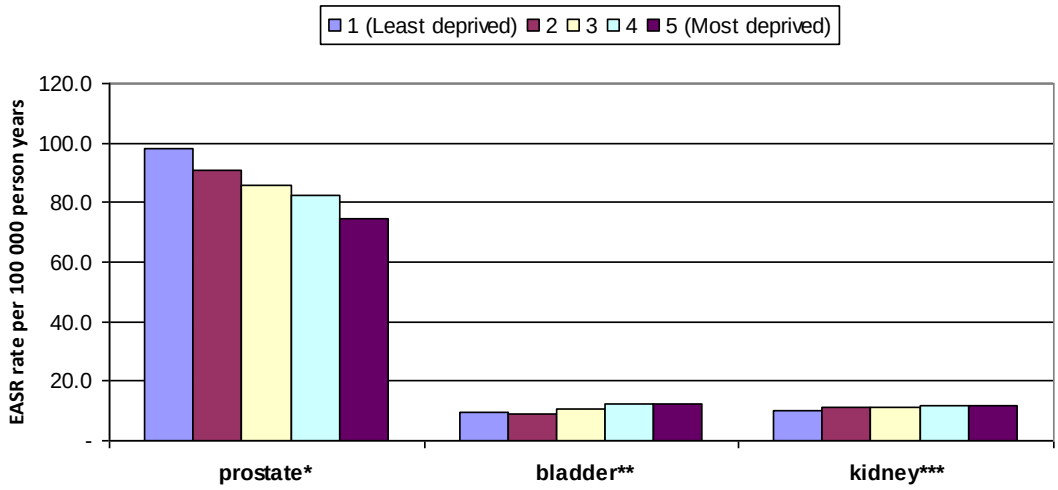
Figure 4.8 EASRs for alcohol related urological cancers in women, 1985-2008 (Source ISD 2010c)



The incidence of bladder, kidney and prostate cancer increases steeply with age (ISD Scotland 2010c). There are very few cases of these cancers, in Scotland in early adulthood, but from age 40 for cancers of the kidney and from 50 years of age for cancers of the prostate and bladder, the rates begin to rise steeply with age to reach a peak in the oldest age-groups.

Incidence rates for bladder cancer significantly increase (*p value for trend* <0.0001) with increasing levels of deprivation (Figure 4.9). Conversely, incidence rates for prostate cancer significantly increase (*p value for trend* <0.0001) with decreasing levels of deprivation. There was a weak association between measures of deprivation and kidney cancer (*p value for trend* =0.027).

Figure 4.9 EASRs[1] for cancers of the prostate, kidney and bladder, by SIMD 2006 deprivation quintile (Source ISD 2010c)



** Test for trend p <0.0001, ** Test for trend p <0.0001, *** Test for trend p =0.0027. [1] Rates are calculated using the populations in 2006*

4.3.1 Discussion

Incidence rates for prostate cancer have been increasing for many years in Scotland. Although there is some evidence of a genuine increase in risk in prostate cancer, much of the observed increase in incidence has probably been due to increased detection of small, non-lethal cancers following transurethral resection for benign prostatic hyperplasia, and more recently through the introduction and increasing use of the prostate-specific antigen (PSA) test for screening (Brewster et al 2000a). The incidence of prostate cancer is higher among men from areas of less socioeconomic deprivation, but it is not clear whether this is due to genuine differences in risk or simply differences in detection through use of the PSA test (Brewster et al 2000a).

Even though kidney cancer is relatively rare, there have been reports of increasing incidence and mortality across Europe (Karim-Kosa et al 2008). Some, but not all, of this increase is believed to be due to the wider application of diagnostic imaging techniques resulting in more kidney tumours being found incidentally (ISD Scotland 2010c).

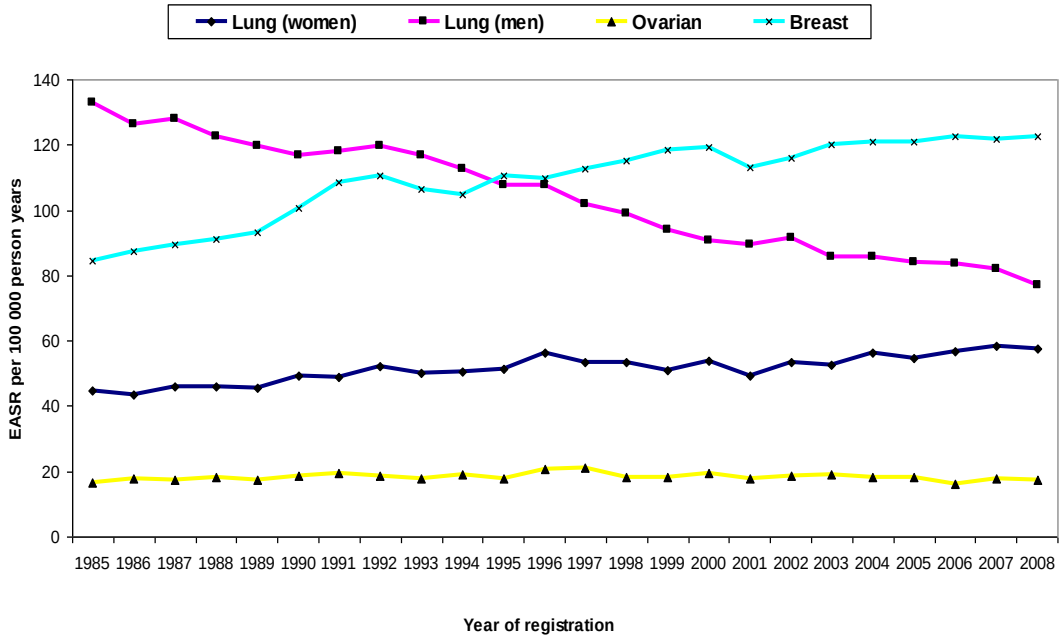
The decline in bladder cancer incidence since 1998 is an artefact due to a change in coding practice across cancer registries in the UK. Around a quarter of bladder tumors are no longer coded as invasive bladder cancers. This decrease is large enough to have an impact on the incidence figures for all cancers combined (ISD Scotland 2010a).

4.4 Trends in lung, breast and ovarian cancer

European age-standardised rates (EASRs) for lung, breast (women only) and ovarian cancers (women only) in Scotland, between 1985 and 2008, are presented in Figure 4.10.

EASRs for lung cancer have declined from 1985 to 2008 in men (133 and 77.2 per 100 000 pys), respectively. In women, however, incidence rates rose quite markedly between 1985 (44.8 per 100 000 pys) and 1996 (56.2 per 100 000 pys), thereafter continuing to increase up to 2008 (57.5 per 100 000 pys). EASRs for breast cancer in women have increased from 84.6 per 100 000 pys in 1985 to 122.8 per 100 000 pys in 2008. There has been very little change in the EASRs for ovarian cancer between 1985 (16.5 per 100 000 pys) and 2008 (17.2 per 100 000 pys).

Figure 4.10 EASRs for cancers of the breast, ovary and lung, 1985-2008 (Source ISD 2010c)

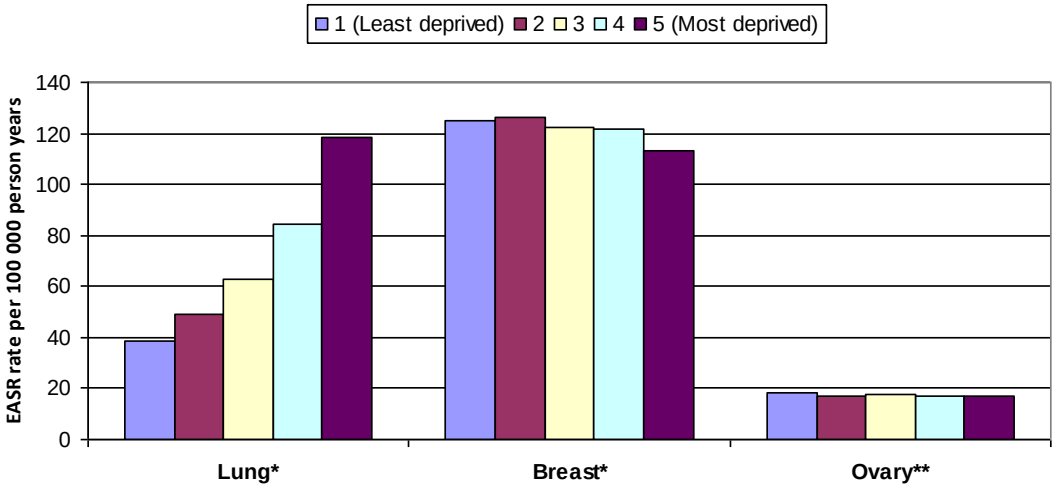


Lung cancer is uncommon below the age of 40 years, but thereafter, incidence increases quite steeply with age peaking in people aged 75-84 years. Most cases (86%) occur in people over the age of 60 years (Cancer Research UK 2010, ISD Scotland 2010a). Ovarian and breast cancer is predominantly a disease of older, post-menopausal women with over 80% of cases being diagnosed in women over 50 years (ISD Scotland 2010a). There is a steep increase in incidence of both breast and ovarian cancer after the usual age of the menopause. The highest incidence rates are for women aged 65 years and over.

For lung cancer, incidence rates in the most deprived areas are approximately three times as high (118.2 per 100 000 pys) as those in the least deprived areas (38.7 per 100 000 pys) with incidence rates rising with increasing levels of deprivation (*p value for trend* <0.0001) (Figure 4.11). In contrast, women from less deprived areas have a higher incidence of breast cancer than women from more

deprived areas (125.2 and 113.4 per 100 000 pys, respectively), with a clear trend of decreasing rates from least to most deprived groups (*p value for trend* <0.0001). EASRs for ovarian cancer are also the highest in the least deprived SIMD quintile, but they are not significantly different from EASRs in other quintiles and there was no evidence of a linear association (*p value for trend* =0.027).

Figure 4.11 EASRs[1] for cancers of the lung, breast and ovary, by SIMD 2006 deprivation quintile (Source ISD 2010c)



** Test for trend p <0.0001; ** Test for trend p 0.0207. [1] Rates are calculated using the populations in 2006*

4.4.1 Discussion

In Scotland lung cancer is the second most frequently diagnosed cancer in men and women. The incidence of lung cancer has been falling in men since the late 1970's but has been increasing in women for several decades to reach a more recent plateau. Tobacco use, predominantly cigarette smoking, is the main cause of lung cancer (IARC, 1986), accounting for at least 90% of cases in high incidence populations. Variations in risk of lung cancer between males and females, between countries, and over time, are due to historical smoking patterns (Peto et al 2000, Alberg et al 2007, Jemal et al 2008). The prevalence of smoking in Scotland has declined in both men and women since surveys began in 1975 (Taulbut et al 2008). However, there is a latency period between exposure and outcome, and although incidence rates have declined in men, incidence rates are expected to continue to increase in women at least until the middle of the next decade (Stockton et al 2004).

Cancer of the ovary is the fifth most frequent cancer experienced by women in Scotland and incidence and mortality rates in Scotland, and across Europe, have remained fairly stable in recent years (Karim-Kosa et al 2008, ISD Scotland 2010c). The epidemiology of cancer of the ovary is complicated by the existence of several main histological types, and the aetiology of these may vary. Despite the identification of numerous risk factors (including those of hormonal or genetic origin), the aetiology of ovarian cancer remains unclear (Elmasry and Gayther 2006). Trends in ovarian cancer incidence

(other than to the extent they are artefacts of diagnosis or registration) are likely to reflect mainly changes in key risk factors including parity, age at menarche and in recent cohorts, oral contraceptive use (Swerdlow et al 1998).

Breast cancer is the most common female cancer in Scotland, in common with many Western countries, with the incidence rate continuing to rise (Swerdlow 1998, Ferlay et al 2007). Over the last decade, the incidence rate has increased by 8%. This is partly due to increased detection by the Scottish Breast Screening Programme, which has seen a rise in attendance over the same time period, and an extension in the age range invited for screening to include women up to the age of 70 years, phased in over the 3-year period beginning 1st April 2003 (Ferlay et al 2007, Brown 2010, ISD 2010c). However, increases in the incidence of breast cancer might also be anticipated with higher prevalence of known risk factors among the female population, such as increases in the mother's age at the birth of her first child. The association between deprivation and socio-economic status and risk of breast cancer is well established, with women in the least deprived areas and higher socio-economic groupings being at higher risk (Bray et al 2004, Brown et al 2007, Shack et al 2008). Breast cancer incidence rates in Scottish women are rising in parallel across all socio-economic categories and the incidence gap between deprived and affluent still remains. Trends in late age at first pregnancy, prevalence of obesity and screening uptake do not fully explain the observed trends (Brown et al 2007).

4.5. Summary

Overall, there is considerable variation in many alcohol related cancer trends and it is difficult to assess the impact of trends in the levels of alcohol drinking on cancer trends, independently of the impact of trends in tobacco use. The one exception to this, possibly, is the rise in the incidence of oral and pharyngeal cancer. Interpreting trends in alcohol related cancers is also complicated by confounding with trends with other cancer risk factors. Lag times for impacts of changes in alcohol use on cancer rates are uncertain, further complicating any assessment of the impact of increases in alcohol consumption and prevalence of heavy or excessive drinking (Polednak 2005). Yet the incidence of many of the cancers associated with alcohol consumption is increasing in Scotland and is expected to continue to do so well into the next decade (Stockton 2004). To further clarify the association between alcohol consumption and cancer risk in the Scottish population, the following chapters present an analysis and discussion of two Scottish population cohort studies investigating the association between alcohol intake and cancer risk.

Chapter 5 Alcohol consumption and risk of cancer in two Scottish prospective cohort studies

In the previous chapter it was shown that those cancers with the strongest association with alcohol consumption have incidence rates which have either been increasing (colorectal, breast and liver cancer), or have remained constant (cancers of the oral cavity, pharynx larynx and squamous cell carcinoma of the oesophagus) over the last 10 years (ISD 2010a). Smoking, a major risk factor for many of these cancers, is on the decline in the Scotland; the percentage of adults who smoke has reduced by about half since the early 1970s (Taulbut et al 2008). One explanation for the increasing incidence of some cancers may be their association with changing levels of alcohol consumption in Scotland (as presented in Chapter 3), although other changes in other lifestyle risk factors such as diet and nutrition, physical activity levles and obesity may also be relevant. Despite an extensive body of research on the relationship between alcohol consumption and cancer (described in Chapter 2), there have been few studies that have explored the association between alcohol consumption and cancer risk in Scotland (or in the United Kingdom (UK)).

Two papers from a UK wide case control study, investigating the association between alcohol consumption and oesophageal adenocarcinoma (Cheng et al 2000) and squamous cell carcinoma of the oesophagus (Sharp et al 2001) in women, included a small number of cases (n=73) and controls (n=73) from five NHS health board areas in Scotland. Other UK-wide studies published between 1999 and 2009 have not disaggregated their study population by region of the UK. These have included a study by Allen et al (2009) on moderate alcohol intake and incidence of twenty-one cancers, in a cohort of 1,280,296 middle-aged women recruited from breast cancer screening clinics in the United Kingdom, and a nested case control study within the UK General Practitioners Research Database reporting on alcohol consumption and risk of oesophageal, and gastric cancer among men and women (Lindblad et al 2005).

In order to address the limited research base in the UK, this study took advantage of a recent ability to link data on national lifestyle behaviours and hospitalization, cancer registration and mortality data across Scotland to investigate the association between alcohol consumption and the risk of the fourteen cancers included in the systematic review. Two approaches using different definitions of alcohol drinkers are employed to quantify this risk relationship. Firstly a population based cohort study, based on a linkage between a representative general population sample and hospital, cancer registry and death records in Scotland describes risk of cancer by amount of alcohol consumed per week and by drinking frequency. There are, however, some inherent weaknesses of general population surveys which lead to an under-representation of excessive and/or problem drinkers in the survey population (Goddard 2001). Survey samples of people living in private households by definition exclude those living in institutions and people who have no fixed address – groups which

probably contain a higher than average proportion of excessive drinkers and/or problem drinkers (Goddard 2001). Excessive and/or problem drinkers may also be more likely than others to be difficult to contact (Pernanen 1974, Chick 1982) e.g. young single people are generally under-represented in survey samples and their alcohol consumption is substantially higher than average (Goddard 2001), or if reached, more likely to refuse to participate in a survey than light and moderate drinkers (Wild et al 2001). Another consideration common to most epidemiological studies is the likelihood that surveys contain a small number of heavy drinkers. In order to adequately investigate how heavy or excessive levels of alcohol intake affect cancer risk, and in line with previous record linkage studies of 'alcoholics' (Adami et al 1992, Kuper et al 2000) a second cohort study describes the risk of cancer in the Scottish population that has been admitted to hospital with an alcohol related diagnosis.

Analyses and results from these two studies are presented in Chapters 6 and 7. The remainder of this chapter describes the data sources used in these analyses.

5.1 Data Sources

5.1.1 The Scottish Morbidity Record (SMR01)

The Scottish Morbidity Record (SMR01) is an episode-based database, held by the Information and Services Division (ISD)[34], of NHS National Services Scotland relating to all inpatients and day cases discharged from non-psychiatric, non-obstetric wards in Scottish hospitals (acute hospital admissions). General acute admissions are categorised as follows (ISD 2010d);

- Inpatients - are patients who occupy a staffed bed in a hospital and: either remain overnight whatever the original intention at admission, or are expected to remain overnight, but are discharged earlier. Discharges include transfers-out and deaths.
- Day cases - are patients' who make a planned attendance to a specialty for clinical care, see a doctor or dentist or nurse and require the use of a bed or trolley in lieu of a bed. A day case patient is not expected to, and does not, remain overnight.

The Scottish Morbidity Record (SMR) is a routine hospital activity monitoring scheme dating back to 1961. Initially, data collected related to all inpatient discharges (except obstetric and psychiatric patients) from NHS Hospitals using a paper form called SMR01 (National Services Scotland 2012). SMR01 records have, however, been computerised since 1968 (ScotPHO 2010). A record is formed when a patient is discharged from hospital, changes consultant or is transferred to another hospital or hospital department. Data from patient case records are used to code up to six, one principal and five

[34] ISD is Scotland's national organisation for health information, statistics and IT services. ISD is part of NHS National Services Scotland a 'special NHS Board, which provides advice and services to the rest of NHSScotland.

secondary, diagnoses at the time of discharge according to the World Health Organization Classification of Diseases ("discharge" includes both live discharges and deaths). Discharge diagnoses use the International Classification of Diseases (ICD) Ninth Revision for discharges from 1981 to 1995, and Tenth Revision for discharges since 1996, with data to 2007 used for this analysis. Approximately 1 million records are created annually. The episode based database includes information on demographic factors (e.g. age, gender, postcode of residence, ethnicity), diagnoses, clinical procedures and means of discharge.

The SMR01 has been subjected to a number of reviews relating to its quality and ability to link hospital episodes (Kendrick and Clarke, 1993, Harley and Jones 1996). ISD monitors the accuracy levels of SMR01 coding by undertaking routine quality assurance assessments. The most recent assessment involving 5430 SMR01 records (1.75% sample of 3 months' data) across 38 NHS acute hospitals for inpatient and day case discharges during time period 2004 to 2006, reported an overall accuracy for Main Condition coding of 88% and 93% for Main Operation coding (ISD 2007). SMR01 accuracy rates have remained fairly static at these levels over the last fifteen years (ISD 2007).

5.1.2 The Scottish Morbidity Record (SMR04)

The Scottish Morbidity Record (SMR04) records information on all inpatient admissions and discharges from NHS mental health (psychiatric) hospitals in Scotland. Data are collected on all patients at the time of admission to hospital and at the time of discharge from hospital. Admissions are classified into three main types (ISD 2010e):

- First admissions - Patients who have not previously received psychiatric inpatient care
- Re-admissions - Patients who are re-admitted following a break from psychiatric inpatient care
- Transfers - Direct transfer from another psychiatric hospital or from one consultant to another within the same hospital

Current national data (2009/2010) completeness for psychiatric hospital activity is estimated to be 97% (ISD 2010f).

5.1.3 The Scottish Cancer Registry

The Scottish Cancer Registry (SCR) has been collecting information on cancer diagnoses since 1958. The registry is responsible for the collection of information on all new cases of primary malignant neoplasms, carcinoma in situ, neoplasms of uncertain behaviour and (since 1 January 2000) benign brain and spinal cord tumours arising in residents of Scotland. Cancer information is stored on SOCRATES (Scottish Open Cancer Registration And Tumour Enumeration System) which receives notification of cancer from hospital systems, including discharges (SMR01 records), radiotherapy, oncology, haematology and pathology records, prospective audit datasets, deaths from the National

Records of Scotland (NRS, formerly the General Register Office for Scotland) and paper records from private hospitals. There are approximately 800,000 source records processed annually by the SOCRATES system using a complex set of rules and linkage routines to create provisional records. Data quality is monitored using routine indicators, computer validation and ad hoc studies of data accuracy and completeness of cancer ascertainment. Overall, the quality of recent cancer registration data in Scotland appears to be high with in-house studies, compared with clinical trial databases, reporting discrepancies occurring in approximately 2-3% of cases ; Brewster et al 1994, Counsell et al 1997, Brewster et al 2002, Brewster and Stockton 2008). This compares favourably to that reported by other cancer registries; estimated ascertainment by the Trent Cancer Registry in England of cancers diagnosed in 1997 was only 88% (Stotter et al 2000). Information on cancer incidence data in Scotland was available for these analyses to the end of 2007.

5.1.4 Scottish Death Registrations

Statutory registration of death began in Scotland in 1855, when civil registration replaced the old system of registration by parishes of the Established Church (Church of Scotland). All deaths in Scotland are now reported to the NRS which produces a database containing identifying information and the underlying and contributing causes of death. Mortality data is routinely provided to ISD for data linkage and this study uses this linked data rather than data provided directly from NRS.

5.1.5 Record Linkage

The ISD linked database contains information on Scotland's SMR01 records for acute specialty day case and inpatient discharges from hospital since January 1981, cancer registrations (SOCRATES) for patients diagnosed since January 1980, NRS death registrations from January 1980, and mental health (SMR04) admissions from January 1981. Using patient identifying information, these records are routinely linked, resulting in a linked database of all such patient records covering the period 1981 to the present day. This database only contains records from Scottish sources e.g. hospital admissions to Scottish hospitals, deaths registered in Scotland. Record linkage is done by probability matching[35] using the following information (Kendrick and Clarke 1993, Kendrick 2004):

- Surname (and its phonetic code to overcome differences in spelling)
- First initial (also full forename and second initial when available)
- Gender
- Year, month and day of birth
- Postcode
- Date of death, if available

[35] A computer matching algorithm calculates a score for each pair of records that are compared; the odds that they belong to the same person. The overall score is the sum of scores derived from the comparison of each item of identifying information, weighted according to the rarity of the information (e.g. the initial Z has a high weight). Similar negative weightings are applied to levels of disagreement between items (Kendrick and Clarke 1993).

- Patient identifiers: Hospital Case Reference Number, Community Health Index/ Unique Patient Identifier and NHS Number, where available

It is estimated that for each of the core items of identifying information used to link the records (surname, initial, year, month and day of birth), there may be a discrepancy rate of up to 3% in pairs of records belonging to the same person. Thus exact matching using these items could miss up to 15 % of true links (Kendrick 1997). To allow for the imperfections of the data, the system uses methods of probability matching which have been developed and refined in Canada, England and Scotland (Baldwin et al (eds.) 1968, Heasman 1968, Newcomb 1988). Murray et al (2000) estimated that the method of probability matching is estimated to be 13-14% more accurate than 'exact matching'. From an independent check of the quality of linkages carried out by the Scottish record linkage team there was a false positive (incorrect links) rate of 3.7% and a false negative (missed links) rate of 1.9% between two incidence databases (3077 subjects). In that analysis, the rates were higher for non-post coded data (4.2% false positive and 2.4% false negative). The independent analysis was based on 'clinical' events and would be lower if transfers and additional treatments were included (ScotPHO 2010).

5.1.6 Carstairs Index of Deprivation

To control for the effects of deprivation, this study utilises the area based Carstairs index of deprivation available on the ISD linked database and on the Scottish Health Survey. The Carstairs index was originally developed in the 1980s using 1981 census data (Carstairs and Morris 1989). It is composed of four indicators at postcode sector level that were judged to represent material disadvantage in the population; *overcrowding* (the proportion of all persons living in private households with a density of more than one person per room), *male unemployment* (the proportion of economically active males seeking or waiting to start work), *households without a car* (the proportion of all persons in private households which do not own a car), and *low social class* (the proportion of all persons in private households with an economically active head with head of household in the Registrar General's social class IV or V) The index has also been calculated based on 1991 and 2001 census data (McLoone 1994, McLoone 2004). The scores are not a measure of the extent of individual material wellbeing or relative disadvantage, but are rather a summary measure applied to populations contained within small geographic localities (McLoone 2004).

The Scottish Index of Multiple Deprivation (SIMD) published by the Scottish Government (2011a), also identifies small area concentrations of multiple deprivation across all of Scotland. The SIMD is calculated using data such as current income, employment, health, education, skills and training, telecommunications, and housing at the level of data zones. 'Data zones' are intended to be effective in identifying small areas with particular social characteristics, and are therefore more internally homogeneous than postcode sectors (Macintyre et al 2005). The first SIMD published in 2004

covered the years 2001 to 2002, 2003, and updates in 2006 and 2009 covered the years 2004 to 2006 and 2007 to 2009 respectively (Scottish Government 2011b).

The Carstairs index was chosen for use in this study because it covered a greater period of the observation time of the two prospective cohort studies (1987 to 2007) described in Chapter 6 and Chapter 7 respectively. The Carstairs index published in 1981 and updated using the 1991 and 2001 census (McLoone 1994, McLoone 2004), covers at least fourteen years of this study's observation time. The SIMD available from 2001 onwards, although it has also been assessed as suitable for analysis from 1997 onwards (ISD 2004), covers between six to ten years of observation time.

5.1.7 Scottish Health Survey

The Scottish Health Survey (SHeS) is a cross sectional survey that draws a nationally representative sample of the general population living in Scottish private households. SHeS was established to provide detailed information on a range of behavioural, biological, psychological and social characteristics. The survey is based on a stratified, clustered random sample of individuals living in private households across the whole of mainland Scotland plus the larger inhabited islands, with one in three postcode sectors (average population of 5000) in Scotland selected at each wave (Gray et al 2010). Previous Scottish Health Surveys were undertaken in 1995, 1998, and 2003 (Dong & Erins 1997, Shaw et al 2000, Bromley et al 2005). The continuous Scottish Health Survey began in January 2008 and is running continuously from 2008-2011. An annual report is published for each year of the survey (Corbett et al 2009; 2010). The survey will continue for a further four years from 2012-2015.

Over time, the range of ages included in the surveys has widened. The survey in 1995 only included adults up to the age of 65 years; in 1998, children over 2 years of age and adults up to the age of 75 years were sampled, and, in 2003, 2008 and 2009, the full age range was surveyed. Weighting has been applied to take account of disproportionate sampling within health regions, differing probabilities of selection within households of different sizes and within multi-occupied addresses, and differential response (Gray et al 2010). SHeS interview response has varied from 81% in 1995 and 76% in 1998 to 60% in 2003, 61% in 2008 and 64% in 2009.

Survey data are gathered in two stages: a face-to-face interview, followed by a nurse visit for the collection of biological material. In each survey, interviews are carried out using Computer Assisted Personal Interviewing (CAPI). Each survey consists of information on somatic and psychological health with dedicated modules on specific conditions and risk factors, such as asthma, dental health, physical activity, eating habits, smoking and drinking.8 Additionally, anthropometric and, for a subsample, biological measurements such as blood pressure and blood and saliva specimens have been taken (Table 5.1).

Table 5.1 Baseline SHeS variables included in data linkage to Scottish linked dataset (Gray et al 2010)

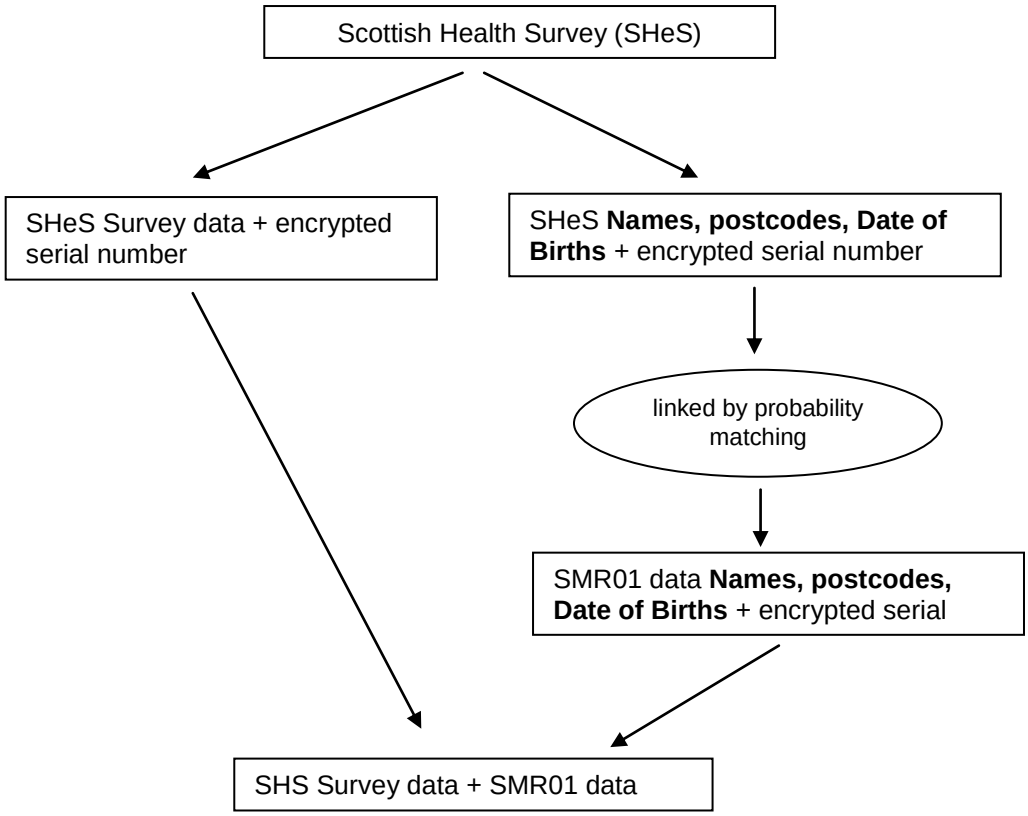
Health measures	**Health-related behaviours**	**Biological measurements**
CVD	Alcohol consumption	Anthropometry[c]
Diabetes	Cigarette smoking	Respiratory function
Respiratory health	Dietary characteristics	Blood pressure
Accidents	Physical activity	Blood analytes[d]
Food poisoning	Use of prescribed drugs and supplements[b]	Urine measurements[e]
Self-assessed general health	Immunizations[a]	Biochemical measurement of smoking
Longstanding illness	Infant feeding[a]	Electrocardiogram[a]
Acute sickness	Exposure to environmental tobacco smoke	**Household characteristics**
Psychiatric morbidity	**Individual socio-demographic characteristics**	Composition
Health-related quality of life[a]	Economic activity status	Relationships of householders[a]
Dental health	Parental social class[a]	Tenure
Use of health services	Occupational social class	Car ownership
Use of dental services	Education	Receipt of state benefits
	Ethnicity	Income[a]
	Religion[a]	Economic status/occupation of household reference person[a]
		Area deprivation

[a]2003 only; [b]prescribed drugs, contraceptive pills, vitamin supplements and nicotine replacement therapy; [c]height (length, demispan), weight, waist, hip and mid-upper arm circumference (1998 and 2003); [d]total cholesterol, high-density lipid cholesterol, C-reactive protein (1998 and 2003), g-glutamyl transferase (1995 only), fibrinogen, glycated haemoglobin, blood lead (1995 only) (for adults) and ferritin, total and house dust mite-specific immunoglobulin E (1998 and 2003) and haemoglobin (for children 11–15 years); [e]sodium, potassium and creatinine (for 2003 adults).

5.1.8 Scottish Health Survey and Record Linkage

A prospective element of the surveys is provided by linkage to data on hospitalisations (Scottish Morbidity Records), cancer registrations and deaths in Scotland. As part of the Scottish health survey interview, participants are asked for their consent to their name, address and date of birth being sent to the ISD for confidential linkage to their health records. Approximately 92% of respondents in each survey consented to their records being linked to NHS administrative data (Gray et al 2010). For those who gave such permission, their health survey information was linked to the SMR data by standard probability matching (see section 5.1.5) based on name, postcode and date of birth (Figure 5.1). This included adults aged 16-64 from the 1995 survey, adults aged 16-74 in 1998 and all ages in 2003. Since 2004, they have been followed up with regular mortality and hospital discharge data linkage from 1981 to December 2008, and cancer registrations (also from 1981) to December 2007; on-going linkage is planned for the surveys being conducted from 2008 to 2011. Retrospective data from 1981, until conduct of survey interview, provides information on hospital diagnoses of any pre-existing morbidity.

Figure 5.1 SHeS-SMR Linked Datasets (Craig 2008)



For each of the three surveys, data on consenting respondents are available in two distinct formats: the 'minimum' datasets and the 'full' datasets (Gray et al 2010). The minimum datasets contain a set of summary variables derived from the linked SMR data (e.g. causes of death, incidence of acute myocardial infarction, stroke and cancer along with the complete health survey record. The full datasets contain fields from individual, anonymised patient SMR records. The minimum datasets are freely available to the wider research community by request from the Medical Record Linkage Team at ISD Scotland.

The SHeS data have been linked to the Community Health Index (CHI), a population register, which is used in Scotland for health care purposes (the CHI number uniquely identifies a person on the index), to determine whether respondents have been registered with a Scottish General Practice at the end of the SMR follow-up period. This allows identification of a small number (approximately 5%) of emigrants for whom follow-up morbidity records in the linked datasets may be incomplete (Lawder et al 2007, Gray et al 2010).

The linkage of pooled data from these three large surveys with follow-up for hospitalisations and mortality has generated a large prospective cohort study that facilitates the examination of the role of a range of social, psychological, lifestyle and biological factors in the development of a range of

important chronic diseases. The linkage for the most recent (2003) survey only took place in 2007 and there has only been one paper related to alcohol; based on a linkage of the 1995, 1998 and 2003 SHeS data, McDonald et al (2009) reported that moderate and higher levels of usual alcohol consumption and binge drinking were highly significant risk factors for an alcohol-related hospitalisation.

In the following chapters, analysis and results from two prospective cohort studies, based on the ISD/SHeS linked database, are presented. Chapter 6 describes the risk of cancer associated with alcohol consumption in a representative sample of the Scottish population and in Chapter 7 the risk of cancer in a cohort of people admitted to hospital in Scotland with an alcohol related condition is described

Chapter 6 Self-reported alcohol consumption and subsequent cancer risk in a sample of the Scottish population (1995-2007)

6.1 Methods

An analysis of the linked SHeS/hospital admission/cancer registry/death record database (as described in Chapter 5), was performed.

6.1.1 Study population

The study population included adults aged 16 years and over participating in three Scottish Health Surveys in 1995, 1998 and 2003, who consented to their survey records being linked to health care records (*n* =7,365, 8,305, 7,710, for the three respective survey years)[36]. Overall, 91-93% of adult survey participants in 1995-2003 consented to their records being linked (Gray et al 2010). The initial study population therefore consisted of 23,380 adults (10,401 men and 12,979 women) aged 16 years and over at the interview date for each of three surveys, (March 1995 to March 1996, April 1998 to March 1999 and June 2003 to December 2004) with follow up until 31 December 2007.

For the present analysis, 191 (0.8%), records with missing data for gender and/or age, and 280 (1.5%) records with incomplete information on drinking frequency and estimated weekly alcohol consumption were excluded. By linkage to the Scottish Cancer Registry, all those with a previous cancer diagnosis other than non-melanoma skin cancer (n =978) were identified and excluded from the cohort. Thus, the final study cohort comprised 21,931 men and women, aged 16 years and over, who had no history of cancer, had consented to linkage and had linked data available, at the start of follow-up.

6.1.2 Exposure measurement

Alcohol consumption

The quantity-frequency (Q-F) measure has been used by the Scottish Health Survey, since the series began in 1995, to elicit information on levels of alcohol consumption. Respondents aged 16 and over, after preliminary questions on whether they drank alcohol at all, are asked how often (i.e. Almost every day/Every day; Five or six days a week; Three or four days a week; Once or twice a week; Once or twice a month; Once every couple of months; Once or twice; Not at all in the last 12 months), they had drunk six different types of alcoholic drink (beer, spirits, wine, fortified wine and shandy and

[36] For further details of the record linkage, see Chapter 5.1.5

'alcopops[37]) during the past twelve months. From this question, the average number of days a week the informant had drunk each type of drink was estimated. A follow-up question asks how much of each drink type the respondent usually drank on any one day (Corbett et al 2010). The amount given to the latter question are converted into units of alcohol, with a unit equal to half a pint of normal strength beer/lager/cider/alcoholic soft drink, a single measure of spirits, one glass of wine, or one small glass of fortified wine. A half pint of strong beer/lager/cider is equal to 1.5 units[38]. The number of units are multiplied by the frequency to give an estimate of weekly consumption of each type of drink. The frequency multipliers used are listed in Table 6.1. The separate consumption figures for each type of drink are rounded to two decimal places and then added together to give an overall weekly (unit) consumption figure. Unit measures were then converted into gram equivalencies assuming 1 unit is equivalent to 8 grams of ethanol (Goddard et al 2007, Corbett et al 2010). The conversion to a gram measure was undertaken to be consistent with results published in the international literature which are predominantly presented in gram measures (WCRF/AICR 2007).

Table 6.1 Drinking frequency multiplying factor

Drinking frequency	**Multiplier**
Almost every day	7
5 or 6 days a week	5.5
3 or 4 days a week	3.5
Once or twice a week	1.5
Once or twice a month	0.375 (1.5 ÷ 4)
Once every couple of months	0.115 (6 ÷ 52)
Once or twice a year	0.029 (1.5 ÷ 52)

Source; Bromley et al (2005)

The association between alcohol consumption and cancer was evaluated through categorical indicators for tertiles of alcohol intake (grams per week), among the study population who drank. Categories included; >0-24, >24-104, >104 grams per week, and non-drinkers. Gender-specific tertiles were then created from the study population to allow for the risk of prostate cancer (men only) and breast cancer (women only) to be modelled and for further analysis by gender, where numbers allowed. Categories for men included; >0-60, >60-168 and >168 grams per week and categories for women included; 0-16, >16-60, and >60 grams per week. Non-drinkers were defined as those

[37] The module of drinking questions in 1998 differed in a number of ways from the 1995 Health Survey questions. One change was the distinction made in 1998 between normal (alcoholic strength less than 6%) and strong (6% or more) beer, lager and cider. The separate question on shandy asked in 1995 was dropped, and shandy was included with normal strength beer. A question on alcoholic soft drinks (or 'alcopops') was also included in 1998 (Bromley et al 2005).

[2] In 2008, the Scottish Government published updated alcohol consumption estimates, from the 2003 SHeS (Bromley et al 2008), using new updated unit conversion factors published by the Office for National Statistics (Goddard 2007) which take in to account the changing strength of alcohol. The impact of these changes is discussed in Chapter 3, and the unit factors (old and new) are provided in Appendix F. At time of linkage of surveys for this study, the 2003 revised consumption estimates were not available.

drinking less than once a year which means that the category of non-drinkers included both total abstainers and subjects with a very low alcohol intake, as well as former drinkers.

The frequency question of the QF measure in SHeS asks respondents to report their usual frequency of alcohol intake in nine possible response categories (Table 6.2). For pattern of drinking in relation to drinking frequency during the last year, the following categories of decreasing frequency were applied (Room 1977, Tolstrup et al 2006, Paradis et al 2009): (1) almost daily drinkers: current drinkers who reported consuming alcoholic beverages on five to seven days in the week; (2) weekly nondaily drinkers: current drinkers who reported drinking between one and four days per week; (3) monthly or less drinkers: current drinkers who reported drinking once or twice a month or every couple of months; (4) non-drinkers: those reporting not drinking in the last 12 months including abstainers and former drinkers or those reporting drinking on less than one occasion in the past year (Table 6.2).

Table 6.2 Drinking frequency dimensions in order of decreasing frequency

Frequency question: response categories	Aggregated groupings
Almost every day	almost daily drinkers
Five or six days a week	
Three or four days a week	weekly non-daily drinkers
Once or twice a week	
Once or twice a month	monthly or less drinkers
Once every couple of months,	
Once or twice a year,	
Less than once a year	non-drinkers
Not drunk alcohol in the past 12 months	

Other variables

All three surveys included a physical activity module to collect information on the frequency, usual duration and usual intensity of physical activity over the four-week period immediately prior to interview. The SHeS 2003 physical activity module is directly comparable to the SHeS 1998, but the 1995 module collected different information on types and frequency of physical activity (Bromley et al 2005) therefore it was not possible to create an aggregate variable for the whole cohort. Information on usual intake of a wide range of foods, including protein, starch, fat and fibre has been collected in each SHeS by a modified version of the Dietary Instrument of Nutrition Education (DINE) questionnaire developed by the Imperial Cancer Research Fund's General Practice Research Group (Roe et al 1994). The DINE module use in 1995 is directly comparable with the module used in the 2003 SHeS. However, a revised DINE module was used in 1998 which meant it was not possible to create an aggregate variable for the whole cohort. Information on smoking, weight, and deprivation was, however, available across all three surveys.

Smoking

Smoking prevalence is measured in two ways in SHeS. Informants are asked directly whether they "smoke cigarettes, pipes or cigars nowadays", and cotinine levels in saliva are measured for those providing a saliva sample at the nurse interview.

The measurement of cotinine levels in SHeS series provides an objective cross-check on self-reports of smoking behaviour, which are known not always to be accurate. Cotinine is a metabolite of nicotine. It is one of several biological markers that are indicators of smoking (others include carbon monoxide and thiocyanate), and is generally considered the most useful. It can be measured in, among other things, saliva or serum. A saliva cotinine level of 15 ng/ml and over is taken as defining that the informant currently smokes (those who use other nicotine products are excluded). Cotinine has a half-life in the body of between 16 and 20 hours, which means that the level of 15 ng/ml in saliva will detect regular smoking (even if the person has not smoked that day), but will not detect occasional smoking if the last occasion was more than a day ago. A level of 15 ng/ml is also sufficiently high to avoid misclassifying people who are exposed to others' smoke as current smokers. Non-smokers who are exposed to heavy passive smoking would not be mis-classified as smokers using 15 ng/ml and over as the definition of a smoker (Corbett et al 210).

SHeS use the following classifications of smoking status (Corbett et al 2010):

- *Current smoking status:* current smokers (within the last year), ex-regular smokers, ex-occasional smokers, never smoked at all.
- *Number of cigarettes smoked by current smokers:* 'Light' (under 10 cigarettes per day), "moderate" (10 to fewer than 20 cigarettes per day), and "heavy" (20 or more cigarettes per day),

Weight

Height and weight measurements were collected by the nurse at physical examination. Informants who were pregnant, chair bound, or unsteady on their feet were not weighed. Body Mass Index (BMI; weight (kg) divided by height squared (m^2)) was calculated for all those informants for whom a valid height and weight measurement was recorded and categorised in SHeS into four groups; <20 kg/m^2 (underweight), >20–25 kg/m^2 ("desirable" weight), >25–30 (overweight), >30kg/m^2 (obese).

Deprivation

The deprivation measure was based on the Carstairs index (as described in Chapter 5.1.5), which combines four census indicators (overcrowding, unemployment, social class, and car ownership), judged to represent material disadvantage in the population (Carstairs and Morris 1991). Carstairs deprivation scores (coded as quintiles) were available for each linked record; deprivation score was determined from postcode sector of residence and was based on 2001 census variables (McLoone

1994). The highest number quintile (i.e. quintile 5) corresponds to the 20% most deprived localities in Scotland.

6.1.3 Identification of alcohol-related cancer cases and follow-up of the cohort

Survey respondents (n=21,931) who developed an alcohol related cancer during follow up, were identified through record linkage between survey dataset and the Scottish Cancer Registry. All cancers reviewed in chapter 2 were included and were defined according to the 9th (1981 to 1995) and 10th (from 1996) revision of the International Classification of Diseases (WHO 1979; 1992). Table 6.3 lists the cancers defined as 'alcohol related' and their respective ICD-9 and ICD-10 codes. Data on vital status were available up to 31 December 2007. The observation period for each survey respondent was from entry into the study until time of death, date of diagnosis of alcohol related cancer or 31 December 2007, whichever came first.

Table 6.3 Alcohol related cancers– ICD-9 and ICD-10 classifications

NEOPLASM	ICD-9	ICD-10
Lip, Oral cavity (incl. tongue)	140,141, 143-145	C00, C01-C06
Pharynx/tonsil	146	C09 & C10
Hypopharynx	148	C13
Oesophagus	150	C15
Larynx	161	C32
Colorectal	153, 154.0-154.1	C18-C20
Liver	155	C22
Pancreas	157	C25
Lung	162,	C33-C34
Breast	174, 233.0	C50, D05
Ovarian	183.0, 236.2	C56
Prostate	185	C61
Bladder	188	C67
Kidney	189.0-189.1	C64 C65

Source: Percy 1995

During follow-up, 853 alcohol related cancers in total were observed. Of the fourteen cancer sites under investigation, more than 50 cases were observed in four cancer sites: breast, lung, colorectal and prostate (Table 6.4). Of the breast cancer cases, three were identified in men. These cases were excluded from analysis, restricting observation to breast cancer cases occurring in women only (n=200). Cancers of the oral cavity (including lip) oropharynx, hypopharynx, larynx and oesophagus were grouped, in line with established practice, as upper aero-digestive tract (UADT) cancers for further analysis (Dobrossy 2005, Lagiou et al 2009). The low number of cases identified for cancer of the bladder (n=46), ovary (n=31), stomach (n=30), kidney (n=27) and liver (n=9) restricted any further meaningful analysis. No further analyses were conducted with these outcomes to determine the risk associated with levels of alcohol intake and drinking frequency. Cancers of the UADT, breast (women only in both the numerator and denominator), lung, colorectum and prostate were further investigated for an association with alcohol consumption.

6.1.4 Statistical analysis

From the minimum linked SHeS dataset supplied by the ISD Medical Record Linkage team (as described in Chapter 5.1.8), person-years were accumulated up to death, cancer diagnosis or the end of 2007, whichever occurred first. Cox proportional hazards models were used to analyze the association between alcohol intake and cancer incidence for both sexes combined and for gender specific strata. Hazard ratios (HRs), including 95% confidence intervals (CIs), were calculated for weekly alcohol consumption and drinking frequency, and risk of breast, colorectal, lung, prostate and UADT cancers. These models take account of survival time until the event as well as whether or not a participant has the event, and are also able to adjust for other variables which may be confounders (Andersen et al 1993).

In a first series of models, age-adjusted HRs were estimated for cancers of the colorectum, lung and upper aero-digestive tract with weekly alcohol consumption entered into the model in four categories (1.non-drinkers, 2.>0-24, 3.>24-104 and 4.>104 grams per week). For cancers of the breast (women) and prostate (men), gender-specific intake categories were used in the model; 1.non-drinkers, 2.0-60, 3.>60-168, and 4.>168 grams per week for men and non-drinkers, 1.non-drinkers, 2.>0-16, 3,>16-60, and 4.>60 grams per week for women. HRs were estimated using the second category as the reference category since this was category with the largest number of cases. For each cancer, other potential confounders i.e. gender, smoking status (five levels) body mass index (three levels) and deprivation (quintiles) were then entered into the models singly and only those that were statistically independent risk factors, and that changed the estimates in the model by 5% were included in the final model for that cancer. All of the afore-mentioned variables were found to be confounders for some but not all cancers using these criteria and these are reported with the results. In the final model, multivariate adjusted HRs were produced for each cancer. A second series of models was constructed, including the same covariates as above, but using drinking frequency instead of total intake. Drinking frequency was entered into the model in four categories (almost daily, weekly not daily, monthly or less and non-drinkers) with weekly not daily drinkers, as the reference group because this represented the group containing the largest number of people.

For the trend tests, median values for each exposure category of a categorized variable were included in the model (Rothman and Greenland 1998). Variables were also analyzed in continuous form when the results from the categorized analyses were compatible with the assumption that the effects are linear. The interaction between sex and alcohol intake for selected cancers was investigated by entering the factor and its interaction term in the model using the STATA ‘logit’ command (Mitchell and Chen 2005). All analyses were repeated after excluding the first two years of follow up in order to eliminate or reduce the possible impact of selection bias due to the presence of an alcohol related cancer at the baseline assessments. Scaled Schoenfeld residuals were used to check the validity of the proportional hazards assumption of the models (Schoenfeld 1982). *P* values less than 0·05 were

regarded as statistically significant. According to these tests, the proportional hazards assumption was not violated in the models. Intercooled Stata version 11 (STATA statistical software, release 11; Stata Corporation, College Station, TX) was used for all analyses.

6.2 Results

During a total of 199,037 person years of follow-up, 853 (3.9%) alcohol related cancers occurred (Table 6.4). Mean follow up was 9.1 years for the whole study population. The three most common cancers observed among the cohort in men (lung, prostate colorectal) and in women (breast, lung, colorectal) are the also the three most common cancers in Scottish men and women respectively (see page 287 for further detail (ISD 2010a), and which suggests that the study includes a representative sample of the whole population.

Lung, breast colorectal and prostate cancers formed over two-thirds (71.5%) of the alcohol-related cancers identified during follow-up (Table 6.4). Mean follow up varied by cancer type, ranging from 4.8 years for cancer of oral cavity (including lip) and stomach to 6.8 years for cancers of the oropharynx, 6.9 years for ovarian cancer and 7.2 years for cancer of the kidney. Oral (mean 52.5 years, SD 11.3), breast (53.0 years, SD 12.6) and ovarian (54.0 years, SD 13.4) cancer cases identified during follow-up tended to be younger on entry into cohort compared to cases of cancer of the liver (mean 64.8 years, SD 7.0), pancreas (63.0 years, SD 8.9), lung (62.7 years, SD 9.7) and prostate (62.5 years, SD 9.3).

Table 6.4 Alcohol related cancers in observed in study population, 1995-2007

Cancer	**Cases M*/F***	**Cases Total**	**Mean age at cohort entry (SD)**	**Mean follow up (yrs) to cancer diagnosis**
Oral cavity (incl. lip)	*7/7*	*14*	*52.5 (11.3)*	*4.8*
Oropharynx	*5/2*	*7*	*59.7 (10.0)*	*6.8*
Larynx	*9/4*	*13*	*56.1 (11.8)*	*5.5*
Oesophagus	*28/13*	*41*	*60.1 (9.7)*	*6.1*
Upper Aero-Digestive Tract[1]	**49/26**	**75**	**58.1 (10.6)**	**5.8**
Gastric	15/15	30	61.9 (11.7)	4.8
Liver	3/6	9	64.8 (7.0)	5.9
Pancreas	10/15	25	63.0 (8.9)	5.6
Colorectal	68/66	134	59.2 (10.7)	5.5
Breast	3/200	200[2]	53.0 (12.6)	5.7
Prostate	76/0	76	62.5 (9.3)	5.7
Ovarian	0/31	31	54.0 (13.4)	6.9
Lung	107/90	197	62.7 (9.7)	5.7
Bladder	33/13	46	58.0 (11.8)	6.2
Kidney	18/9	27	58.1 (10.7)	7.2

[1] UADT consists of cancers of the lip, oral cavity, oropharynx, larynx and oesophagus.* m= male, f= female [2] excluding male breast cancer cases

In this cohort, over half of the study population were women (55.6%). The mean age at entry to the cohort was 44.7 (SD 15.9) years (Table 6.5). Median alcohol consumption in the study population was 48 grams per week (equivalent to 6 units per week) though median levels of consumption among men and women varied considerably (98 grams and 24.3 grams, respectively). Approximately half (48.7%) of the study population drank on a weekly, but not daily basis (i.e. 4-7 days per week). Men were more than twice as likely as women (31.2% versus 13.6% respectively) to exceed gender specific weekly drinking guidelines[39]. Over a third (39.6%) of the cohort were current smokers of whom 13.3% reported smoking >20 cigarettes per day.

Table 6.5 Characteristics of study population by survey year

	1995	**1998**	**2003**	**Total**
Survey participants	7204	7846	6881	21931
Women (n)	*3953*	*4392*	*3850*	*12195*
Men (n)	*3251*	*3454*	*3031*	*9736*
Total person years of follow up	90,110	76,238	32,689	199,037
Mean age at entry into cohort (SD) years	40.1(13.2)	44.8(15.7)	49.3(17.4)	44.7(15.9)
Amount drunk				
grams per week (median)	49.0	48.0	44.9	48.0
males median grams per week	111.5	104.41	84	98
females median grams per week	24.9	24.5	24.0	24.3
% above weekly limits- males	33.7	32.2	27.5	31.2
% above weekly limits- females	13.0	13.6	14.3	13.6
Drinking frequency				
% almost daily drinkers	10.1	12.7	15.7	12.8
% weekly not daily drinkers	52.3	48.6	45.1	48.7
% monthly or less drinkers	29.5	28.5	28.8	28.9
% non-drinkers	8.2	10.2	10.4	9.6
Weight (Body Mass Index)				
% overweight (BMI≥25 kg/m^2)	35.0	37.6	39.8	37.4
% obese (BMI≥30 kg/m^2)	17.3	21.9	25.5	21.4
Deprivation				
% living in most deprived Carstairs quintile	22.5	19.5	17.2	19.8
% living in least deprived Carstairs quintile	18.0	17.8	18.9	18.2
Smoking				
% never smoked	33.4	41.4	44.2	34.3
% former smoker	26.8	23.7	28.0	26,1
% current smoker	39.8	34.9	27.8	39.6
% of which heavy smoker,≥20 p/day	33.4	41.4	44.2	13.3
Alcohol related cancers				
number of cancers observed	306	375	172	853
mean age at cohort entry	52. 5	60.2	66.9	

[39] >21 units per week for men and >14 units per week for women

Across the three surveys, the mean age increased in each respective year e.g. those participating in the 2003 survey were over a decade older, on average, than those entering in 1995 due to the changing eligibility criteria (Table 6.5). Over a fifth (22.5%) of the study population in the 1995 survey were living in the twenty per cent most deprived areas of Scotland, in contrast to 17.2% of those participating in the 2003 survey. The proportion of 'almost daily' and 'non-drinkers' significantly ($p<0.001$) increased across the three surveys. Although the proportion of those classified as current smokers reduced from 39.8% in 1995 to 27.8% in 2003 ($p<0.001$), the proportion of current smokers who were classified as heavy smokers (i.e. ≥20 cigarettes per day) increased from 33.4% in 1995 to 44.2% ($p<0.001$). The proportion of people classified as obese (BMI ≥30 kg/m2), also increased significantly ($p<0.001$) from 17.3% in 1995 to 25.5% in 2003.

'Daily' drinkers were more likely to be men, and women were more likely to be monthly (or less) drinkers or non-drinkers (Table 6.6). Daily drinkers had a median mean weekly alcohol intake (183 grams per week) more than double that of weekly (not daily) drinkers (84 grams per week). Monthly (or less) drinkers drank on average 6 grams per week. Levels of weekly drinking were twice as high in men, than those in women, irrespective of drinking frequency status (with the obvious exception of non-drinkers). Drinking frequency did not vary by current smoking status, however, non-drinkers and monthly drinkers were more likely than 'daily' drinkers to be non-smokers. Approximately a quarter of non-drinkers (26%) and monthly drinkers (22%) were living in the most deprived Carstairs quintiles, compared to 14% of daily drinkers and 19% of weekly drinkers. Conversely 27% of daily drinkers were more likely to be living in the least deprived Carstairs quintiles, compared to 14% of monthly and 13% of non-drinkers.

Table 6.6 Characteristics of study population by drinking frequency

	Drinking frequency			
Study characteristics	**'daily' drinkers**	**weekly drinkers**	**monthly or less drinkers**	**never drinkers**
Number	2804	10680	6341	2106
Men (%)	62.2	50.2	30.7	32.5
Mean age at entry	50.6 (14.8)	42.4 (14.6)	44.01 (16.5)	50.9 (17.8)
Amount drunk				
grams per week (median)	183.0	84.0	6.0	0
males median grams per week	248.0	124.6	8.3	0
females median grams per week	121.0	60.0	4.6	0
% above weekly limits- males	70.3	33.8	0.2	n/a
% above weekly limits- females	59.6	19.3	0.1	n/a
Weight (BMI)				
% overweight (including obese) (BMI≥25)	61.2	57.6	59.5	57.7
Smoking				
% current smoker	32.7	35.1	34.4	31.6
% never smoked	32.7	39.1	41.7	45.2
% *heavy smoker, 20 plus per day*	15.5	12.8	12.9	13.3
Deprivation				
% living in most deprived Carstairs quintile	14	19	22	26
% living in least deprived Carstairs quintile	27	19	14	13
Alcohol related cancers				
Number of cancers observed	153	343	265	92

6.2.1 Hazard ratios for selected alcohol related cancers by weekly intake.

The hazard ratios for categories for alcohol intake and risk of cancer of the upper aero-digestive tract (UADT) are presented in Table 6.7. A threefold increased risk of UADT cancer was observed in age-adjusted HRs (3.71, 95% CI 1.92-7.15), for survey respondents drinking >104 grams a week of alcohol, compared to those drinking between >0-24 grams per week. This statistically significant increased risk of UADT cancer remained, but was considerably reduced after further adjustment for gender, amount smoked, deprivation quintiles and BMI category (HR 2.54, 95% CI 1.25-5.14) (Table 6.7), Both non-drinkers and those drinking between 24 grams and 104 grams per week had a non-statistically, significant increased risk (24% and 62% respectively) of cancer of the UADT in both age and multivariate adjusted models compared to those drinking 0-24 grams per day. The test for linear trend in risk of UADT by increasing levels of alcohol consumption was statistically significant (*p value for trend*=0.005). Due to small number of UADT cases identified in the cohort, it was not possible to analyse the effects of gender.

Table 6.7 Hazard ratios for cancer of the UADT by weekly alcohol intake

Tertiles of alcohol intake grams per week	Cases	HR[1]	95% CI	p-value	HR[2]	95% CI	p-value	Test for trend
non-drinkers	7	1.30	0.51-3.32	0.58	1.24	0.49-3.17	*0.65*	
>0-24	12	1.00*			1.00*			
>24-104	20	1.72	0.84-3.52	0.14	1.62	0.78-3.33	*0.19*	
>104	36	3.71	1.92-7.15	<0.001	2.54	1.25-5.14	*0.01*	p=0.005

[1] adjusted for age [2]models adjusted for age, gender, smoking, deprivation (quintiles) and BMI. *referent group

There was no statistically significant association between colorectal cancer and alcohol consumption at any level of alcohol consumption in either the age or multivariate models (Table 6.8). A small, but not statistically significant, increased risk of colorectal cancer (HR1.18, 95% CI 0.75-1.79, *p value for trend* =0.47) was reported among survey respondents drinking >104 grams per week, compared to those drinking 0-24 grams per week.

Table 6.8 Hazard ratios for colorectal cancer by weekly alcohol intake

Tertiles of alcohol intake grams per week	Cases	HR[1]	95% CI	p-value	HR[2]	95% CI	p-value	Test for trend
non-drinkers	17	0.88	0.50-1.55	0.66	0.92	0.53-1.62	0.78	
>0-24	43	1.00*			1.00*			
>24-104	34	0.82	0.52-1.29	0.40	0.82	0.52-1.29	0.38	
>104	40	1.16	0.75-1.79	0.51	1.18	0.78-1.85	0.47	p=0.283

[1] adjusted for age [2] adjusted for age smoking and BMI. *referent group

Hazard ratios for weekly alcohol intake (gender specific categories) and risk of colorectal cancer, adjusted for age smoking and BMI, and stratified by gender are presented in Table 6.9. Men drinking more than 60 grams per week, compared to men drinking >0-60 grams per week, were not at an increased risk of colorectal cancer. Male non-drinkers had a non-statistically significant reduced risk of colorectal cancer (HR 0.53, 95% CI 0.18-1.52, *p value for trend* =0.26) though this estimate was based on only four cases. In women, there was a positive, non-significant, association between drinking ≥60 grams per week, compared to those drinking >0-16 grams per week and risk of colorectal cancer (HR 1.30 95% CI0.69-2.45, *p value for trend* =0.41*)*. A formal test of interaction between alcohol intake and gender in relation to colorectal cancer risk was not statistically significant ($P_{interaction}$ =0.19).

Table 6.9 Hazard ratios for colorectal cancer by weekly alcohol intake and gender

Men					Women				
Tertiles of alcohol intake grams per week	**Cases**	**HR[1]**	**95% CI**	**p-value**	**Tertiles of alcohol intake grams per week**	**Cases**	**HR[1]**	**95% CI**	**p-value**
non-drinkers	4	0.55	0.19-1.56	0.26	non-drinkers	13	1.25	0.63-2.48	0.52
>0-60	26	1.00*			>0-16	23	1.00*		
>60-168	16	0.67	0.36-1.25	0.21	>16-60	12	0.73	0.36-1.48	0.38
>168	22	1.02	0.57-1.81	0.95	>60	18	1.30	0.69-2.45	0.41

[1] model adjusted for age smoking and BMI. *referent group

In age adjusted HRs, survey respondents drinking >104 grams per week, had a statistically non-significant, increased risk of lung cancer (HR 1.33 95% CI 0.94-1.90, *p value for trend* =0.11) (Table 6.10). After further adjustment for amount smoked, weight and by deprivation quintile, alcohol intake at this level was not associated with an increased risk of lung cancer (HR 1.05, 95% CI 0.73-1.50, *p value for trend* =0.81).

Table 6.10 Hazard ratios for lung cancer by weekly alcohol intake

Tertiles of alcohol intake grams per week	**Cases**	**HR[1]**	**95% CI**	**p-value**	**HR[2]**	**95% CI**	**p-value**	**Test for trend**
non-drinkers	26	0.84	0.53-1.32	0.44	0.79	0.50-1.25	0.32	
>0-24	67	1.00*			1.00*			
>24-104	56	0.80	0.55-1.18	0.26	0.77	0.53-1.13	0.19	
>104	49	1.33	0.94-1.90	0.11	1.05	0.73-1.50	0.81	p=0.178

[1] adjusted for age, [2] adjusted for age, smoking deprivation and BMI. *referent group

Hazard ratios for weekly alcohol intake and risk of lung cancer were further stratified by gender (Table 6.11). There was no association between lung cancer at any alcohol intake category in both men, compared to those drinking 0-≤24 grams per week, and women, compared to those drinking >0-16 grams per week. A formal test of interaction between alcohol intake and gender in relation to lung cancer risk was not statistically significant ($P_{interaction}$ =0.19).

Table 6.11 Hazard ratios for lung cancer by weekly alcohol intake and gender

Men					Women				
Tertiles of alcohol intake grams per week	**Cases**	**HR[1]**	**95% CI**	**p-value**	**Tertiles of alcohol intake grams per week**	**Cases**	**HR[1]**	**95% CI**	**p-value**
non-drinkers	10	0.93	0.45-1.88	0.83	non-drinkers	16	0.85	0.47-1.55	0.60
>0-60	33	1.00*			>0-16	34	1.00*		
>60-168	32	0.99	0.61-1.61	0.97	>16-60	23	1.02	0.60-1.74	0.93
>168	32	1.07	0.65-1.75	0.79	>60	17	0.95	0.52-1.72	0.86

[1] model adjusted for age, smoking, deprivation, and BMI. *referent group

Alcohol intake, up to and including >60 grams per week was not associated with an increased risk of breast cancer among women in either age adjusted or multivariate models (Table 6.12). However, non-drinkers, compared to very low level drinkers (>0-16 grams per week), had a borderline, statistically significant, protection against breast cancer (multivariate HR 0.58, 95% CI 0.35-0.96, *p value for trend* =0.41).

Table 6.12 Hazard ratios for breast cancer in women, by weekly alcohol intake

Tertiles of alcohol intake Grams per week	**Cases**	**HR[1]**	**95% CI**	**p-value**	**HR[2]**	**95% CI**	**P value**	**Test for trend**
non-drinkers	19	0.57	0.34-0.94	0.03	0.58	0.35-0.96	0.04	
>0-16	77	1.00*			1.00*			
>16-60	56	0.96	0.68-1.35	0.81	0.94	0.66-1.33	0.73	
>60	48	0.84	0.58-1.21	0.35	0.81	0.56-1.17	0.26	p=0.363

[1] adjusted for age [2] adjusted for age and BMI. *referent group

Although, men drinking >60 grams per week had an increased hazard (15-16% higher) of prostate cancer compared to more moderate drinkers (≥0 to ≤60grams per week) there were no statistically significant relationships with any category of intake (Table 6.13).

Table 6.13 Hazard ratios for prostate cancer by weekly alcohol intake

Tertiles of alcohol intake Grams per week	**Cases**	**HR[1]**	**95% CI**	**p-value**	**HR[2]**	**95% CI**	**p-value**	**Test for trend**
non-drinkers	7	1.01	0.43-2.36	0.98	1.05	0.45-2.44	0.92	
>0-60	23	1.00*			1.00*			
>60-168	24	1.14	0.64-2.03	0.65	1.15	0.65-2.03	0.64	
>168	22	1.17	0.65-2.11	0.59	1.16	0.65-2.10	0.61	p=0.613

[1] adjusted for age [2] adjusted for age and BMI. *referent group

6.2.3 Hazard ratios for selected alcohol related cancers by drinking frequency

'Daily' drinking, compared to weekly (not daily) drinking, was associated with a statistically significant increased risk of UADT cancers (multivariate HR 1.96, 95% CI 1.15-3.34) (Table 6.14). An inverse association between those reporting drinking monthly (or less), compared to weekly (not daily drinkers) and risk of UADT cancer was observed. Non-drinkers also had a, small, reduced risk of UADT cancer, but the HR was not statistically significant.

'Daily' drinking, compared to weekly (not daily) drinking, was also associated with a, small statistically significant elevated increased risk of colorectal cancer (multivariate HR 1.68, 95% CI 1.06-2.67, *p* value=0.03). Neither 'monthly' nor non-drinkers were at increased risk of colorectal cancer, compared to weekly (not daily) drinkers (Table 6.14).

Daily and monthly drinkers had, respectively, a 37% and 53%, increased risk of prostate cancer, compared to weekly (not daily) drinkers, but neither point estimate was statistically significant. There was no evidence of an association between drinking frequency and risk of lung cancer (Table 6.14).

Non-drinkers (including ex-drinkers) were approximately 40% less likely than weekly not daily drinkers to develop breast cancer. Monthly drinkers had a small, but not statistically significant, increased risk of breast cancer (HR1.19, 95% CI 0.87-1.63, *p* value =0.26). Daily drinking was not associated with an increased risk of breast cancer (Table 6.14).

Table 6.14 Crude and adjusted hazard ratios (HR) of selected alcohol related cancers according to drinking frequency

Frequency	Cases	Crude HR	95% CI	p-value	Adjusted HR	95% CI	p-value
Upper Aero-Digestive Tract[1]							
non drinkers	7	1.16	0.51-2.62	*0.72*	0.69	0.30-1.57	*0.37*
monthly or less	10	0.51	0.25-1.04	*0.06*	0.46	0.23-0.93	*0.03*
weekly not daily	34	1.00*****			1.00*****		
almost daily	24	3.07	1.82-5.19	*<0.05*	1.96	1.15-3.34	*0.01*
Colorectal[2]							
non drinkers	17	2.02	1.16-3.51	*0.01*	1.21	0.69-2.12	*0.52*
monthly or less	40	1.48	0.97-2.25	*0.07*	1.30	0.85-1.99	*0.22*
weekly not daily	47	1.00*****			1.00*****		
almost daily	30	2.73	1.73-4.32	*<0.05*	1.68	1.06-2.67	*0.03*
Breast[3]							
non drinkers	19	0.84	0.50-1.41	*0.51*	0.62	0.36-1.06	*0.08*
monthly or less	82	1.23	0.91-1.67	*0.18*	1.19	0.87-1.63	*0.26*
weekly not daily	83	1.00*****			1.00*****		
almost daily	19	1.34	0.81-2.20	*0.25*	0.96	0.58-1.59	*0.88*
Lung[1]							
non drinkers	24	1.66	1.05-2.62	*0.03*	0.80	0.51-1.27	*0.35*
monthly or less	57	1.21	0.87-1.70	*0.26*	1.02	0.73-1.44	*0.89*
weekly not daily	82	1.00*****			1.00******		
almost daily	34	1.83	1.22-2.72	*<0.05*	0.96	0.64-1.45	*0.86*
Prostate[3]							
non drinkers	6	1.74	0.73-4.19	*0.21*	1.02	0.42-2.46	*0.96*
monthly or less	18	1.70	0.95-3.04	*0.07*	1.53	0.86-2.74	*0.15*
weekly not daily	31	1.00*****			1.00*****		
almost daily	21	2.36	1.35-4.11	*<0.05*	1.37	0.78-2.40	*0.27*

[1] adjusted for age, gender, smoking, deprivation, BMI, [2] adjusted for age, BMI and smoking, [3] adjusted for age, BMI. ***** Reference group

6.3 Discussion

In the literature review, only two case control studies were identified that reported the risk of (oesophageal) cancer from alcohol consumption in a Scottish population (Cheng et al 2001, Sharp et al 2001). This study, therefore, represents the first published retrospective cohort study of self-reported alcohol intake and subsequent cancer in Scotland. Findings from the present study support an

overall association between alcohol consumption and risk of UADT cancer for those drinking at the highest alcohol exposure category compared to those drinking low amounts of alcohol. Drinking 'daily' was also associated with an increased risk of UADT cancer compared to weekly drinkers. No statistically significant association was observed between alcohol consumption and drinking frequency, and risk of prostate, lung, and (in women) breast cancer.

6.3.1 Alcohol and cancers of the upper-aero digestive tract

In the present study, there was more than a two-fold increased risk of UADT cancer in those drinking >104 grams per week (approximately 13 units per week) and among 'daily' drinkers, with a dose response effect apparent. These estimates are consistent with other studies that have reported the effects of moderate drinking on risk of UADT cancer (Kasum et al 2002, Weikert et al 2009). The data add to consistent epidemiological evidence from around the world that clearly document that alcohol consumption increases the risk of UADT cancer (IARC 1988, WCRF/AICR 2007).

As a result of the small number of UADT cancer cases (n=75) identified in the present study, it was not possible to explore the association between alcohol consumption and risk of UADT cancer by individual site. Head and neck (which include the oral cavity and pharynx) and oesophageal cancers are, respectively, the fourth and fifth most frequently occurring among men in Scotland, though in women they are far less common (ISD Scotland 2010a). The majority of the present study's population were women (55.6%) which could potentially reduce the study's power to detect UADT cancers. Another contributory factor to the small number of observed UADT cancers is the relatively young age, compared to other similar studies, of the overall study population (mean age at cohort entry 44.7 years) combined with an average follow up of less than ten years.

Cancers of the UADT as an aggregate grouping may have limited value as such a grouping assumes a constant risk across cancer sub-sites. Although the effect sizes by UADT sub-site reported in the epidemiological literature, can vary considerably (see Chapter 2), this could be a result of many factors e.g. study size, study length, levels of drinking in study population. There has, however, been little formal testing of whether the associations of alcohol intake with UADT sub-site significantly differ and what evidence does exist is far from conclusive. In a meta-analysis of fourteen studies, published between 1966 and 2001, Zeka et al (2003) found that alcohol consumption appeared to have a much stronger effect on the oropharynx than on any of the other upper aero-digestive sites. Weikert et al (2009), based on a large European prospective cohort study, reported no significant differences between cancers of the oesophagus and the oral cavity or pharynx and between laryngeal and oral cavity/pharyngeal cancer. The multivariable adjusted relative risk per 10 grams per day (g/d) increase in baseline alcohol intake was higher for oesophageal compared to laryngeal cancer (($P_{interaction}$ =0.003).

Although the present study controlled for the effects of smoking it is not possible to rule out the effects of residual confounding from smoking. Furthermore, risk of UADT cancer is further aggravated by diets deficient in fruits and vegetables (WCRF/AICR 2007) and it was not possible to control for the effect of diet in the present study. The effect of this may be to reduce the effect size reported in the study, if heavy drinkers were to eat less fruit and vegetables.

6.3.2 Alcohol and colorectal cancer

In the present study, alcohol consumption was not associated with a statistically significant increased risk of colorectal cancer in men and women. This finding is consistent with results from the published literature, discussed in Chapter 2.5, which suggests that a, statistically significant, increased risk of colorectal cancer is only found in those drinking ≥30 g/d, and a pooled analysis of eight cohort studies which observed that the increased risk of colorectal cancer was restricted to those drinking >210 grams per week (g/w); pooled multivariate relative risks were 1.16 (95% CI 0.99-1.36) for persons who drank >210-<295 g/w and 1.41 (95% CI 1.16-1.72) for those who drank ≥295 g/w, compared to non-drinkers (Cho et al 2004). The highest alcohol exposure category in the present study was >104 g/w therefore an increased risk of colorectal cancer in the present population cannot be ruled out as too few of the study population drank >210 g/w to allow an analysis of the risk of colorectal cancer at this level of drinking.

'Daily' drinkers in the present study, compared to 'weekly' drinkers, did, however, have a statistically significant increased risk of colorectal cancer after adjustment for age, gender, body weight and smoking. No other studies have reported on drinking frequency and risk of colorectal cancer. The positive association between daily drinkers and increased risk of colorectal cancer can be attributed to daily drinkers drinking considerably more than the overall study population (median weekly intake of 183 and 48 grams respectively). Daily drinkers in the present study population are also twice as likely as weekly (not daily) drinkers, to exceed the recommended weekly safe limits in the UK (of 21 units for men and 14 units for women) suggesting that this group are more likely than the overall study population to be drinking at levels (i.e. >30 grams per day) which are similar to the drinking levels consistently linked in the international literature with an increased risk of colorectal cancer (WCRF/AICR 2007). Due to the small number of colorectal cancer cases (n=30) who were 'daily' drinkers in the present study, it was not possible to investigate further, the relationship between 'daily' drinking and risk of colorectal cancer by different alcohol intake levels.

The positive associations between 'daily' drinking and increased risk of colorectal cancer may, however, be explained by the lack of complete control for potential confounders of the alcohol-colorectal cancer association. Several other risk factors for colorectal cancer have been identified through epidemiological studies (WCRF/AICR 2007); diet and micronutrients, including high intake

of fat, meat, protein, low intake of fibre, low intake of folate and calcium, low physical activity, large body size, and smoking. There is a possibility of confounding from lack of adjustment for dietary factors in this study as this information was not available and may explain the increased risk observed among daily drinkers especially if daily drinkers had a poor diet with low intake of fibre and folate. Overall, the results from the present study are consistent with those reported in the international literature which provides no strong evidence of an association between low to moderate levels of alcohol consumption and an increased risk of colorectal cancer.

6.3.3 Alcohol and breast cancer

In the present study, non-drinkers, compared to women drinking between >0-≤16 grams per week, had a weak statistically significant inverse association with breast cancer. Women drinking 16-60 g/w, did not have an increased risk of breast cancer, compared to light drinkers. Levels of reported alcohol consumption in the present study cohort were low among women. One reason for this is that the present record linkage between the Scottish Health Survey was based on old alcohol unit conversion factors which do not take into account the increasing strength of beverage alcohol in the UK (see Chapter 3, Section 3.2.2). Catto and Gibbs (2008) for example have shown that, for example, a typical serving of one glass of wine will contain between 2 and 2.5 units, more than double that estimated in surveys to date. In the present study, the highest alcohol intake category of >60 g/w is equivalent to approximately 8 UK alcohol units, which is considerably lower than current recommended weekly UK drinking guidelines for women. Very few studies, cohort or case control, have observed a statistically significant association with cancer at the intake levels reported in this study's cohort. In a UK prospective cohort study, women drinking between 3-6 drinks per week, similar to the highest alcohol exposure category in the present study, had a small, but statistically significant, increased risk of breast cancer (RR 1.08, 95% FCI[40] 1.05-1.10) compared to women drinking ≤2 drinks per week (Allen et al 2009). Results of the present study and those by Allen et al (2009), however, are not directly comparable because in the present study one unit was equivalent to eight grams of alcohol and in the Allen et al study, one unit was equivalent to ten grams of alcohol. Across the majority of studies on the alcohol and the alcohol breast cancer association described in Chapter 2.4, however, an increased risk of breast cancer, either significant or non-significant, was often only associated with alcohol consumption of approximately 15 grams a day or more, which is more than twice the levels of the highest alcohol intake category in the present study. In this regard, the findings of the present study reflect existing evidence (WCRF/AICR 2007) of no association between very low levels of alcohol consumption and breast cancer.

[40] floating confidence interval (FCI)

No significant association was observed between drinking frequency and breast cancer risk. This finding is consistent with some studies that have reported on the association between drinking frequency and risk of breast cancer (Lenz et al 2002, Tjonneland et al 2003, Lin et al 2005). It is highly likely, however, that that the drinking frequencies used in the present study are not sufficiently precise to detect an association with breast cancer. Horn- Ross et al (2004) demonstrated this by combining frequency with amount drunk and found that breast cancer risk was significantly increased among 'daily' heavy drinkers (i.e., women consuming a weekly average of >20 grams per day of alcohol, but not in those drinking <20 grams per day. It was not possible to investigate this aspect due to the small number of breast cancers cases observed, and the low levels of alcohol intake overall, among women in the study cohort.

It was not possible to investigate whether risk varied by menopausal status because of the small number of female drinkers. Reports are inconsistent on the alcohol-related risk of breast cancer before and after the menopause. While not statistically different in some past studies, the effects of alcohol consumption were more consistent and somewhat greater in post-menopausal women than in pre-menopausal women in more recent studies (Smith-Warner et al 1998, Ellison et al 2001, Hanajima et al 2001). If menopausal status of women modifies the relationship between alcohol and breast cancer, the young age of female cohort members (44.8 SD16.0 years) in this study and follow up period of approximately ten years would make it more difficult to detect an association between alcohol and breast cancer.

Although the present study controlled for the effects of deprivation with the Carstairs Index, there is a still a risk of residual confounding from socio-economic status. Studies have shown women with higher levels of education are more at risk of breast cancer than those with lower levels of education (Heck and Pamuk 1997, Lichtenstein 2000). The Carstairs index, however, does not include an area measure of educational status Thus, even when models are adjusted for deprivation a residual effect might remain. The present study was also not able to control for the effects of diet and nutrition as this information was not available across all three Scottish Health Surveys. There has been a lot of research into the effects of dietary factors on breast cancer risk, but findings are generally inconsistent and inconclusive. Although a meta-analysis of 45 studies (Boyd et al 2003) reported that higher total fat intake increased breast cancer risk by 13%, the recent WRCF/AICR review (2007) concluded that there is limited evidence suggesting that high total dietary fat is a cause of breast cancer. Poor diet, however, may play some part by contributing to increased body weight which is considered a convincing risk factor for breast cancer. In the present study, body weight was controlled for in the models.

Overall, results from the present study are consistent with existing evidence of no association between breast cancer and low levels (approximately <1 drink per day) of alcohol consumption. Further studies

with longer follow-up are required to explore the effects of moderate and heavy drinking and risk of breast cancer in a Scottish general population.

6.3.4 Alcohol and lung cancer

In the present study, lung cancer was not associated with drinking frequency or weekly alcohol intake. Further stratification by gender did not show an increased risk of lung cancer in men drinking >168 g/w (equivalent to approximately more than 21 units per week) or in women drinking >60 g/w (approximately 7-8 units per week). These findings are consistent with those reported the international literature and discussed in Chapter 2.11. A recent pooled analysis of seven prospective cohort studies did provide some weak evidence of a positive association between alcohol consumption and lung cancer risk, but only in those drinking ≥30 g/d, compared to non-drinkers (Freudenheim et al 2005). It was not possible to replicate this finding due to the small number of the present study's population drinking >30 g/d. The role of alcohol consumption in lung cancer aetiology may been suggested in some studies (as described in Chapter 2.11), but this possible relationship has been often regarded with scepticism, with any indication of an association being attributed to confounding by cigarette smoking (Bofetta et al 2005).

6.3.5 Alcohol and prostate cancer

The present study found no statistically significant association between drinking frequency or weekly alcohol intake and an increased risk of prostate cancer. Epidemiological evidence suggests that prostate carcinogenesis may span decades and to fully explore the relationship between alcohol prostate cancer, it is necessary to look at the association with prostate cancer over longer period of time (Issacs 1994). The average length of the follow-up in the present study combined with the young age of the study population may, therefore, have limited the study's ability to detect a true association between alcohol intake and risk of prostate cancer.

Furthermore, since the aetiology of prostate cancer is poorly understood, adjusting for confounding factors in studies on of alcohol consumption and prostate cancer is problematic. Age was the only established risk factor controlled for in the present study. Previous studies have shown that although family history of prostate cancer is related to disease in the study population, it is not a confounder of an alcohol-prostate cancer association (Albersten and Gronbaek 2002, Schoonen et al 2005). Screening history has also been suggested as a possible confounder of the alcohol and prostate cancer association (Weiss 2003, Schoonen et al 2005). Although, there is currently no national screening programme for prostate cancer in Scotland, much of the increase in incidence of prostate cancer in

Scotland (described in Chapter 4) can be attributed to the use of prostate specific antigen (PSA)[41] testing. Since information on PSA testing status was not available for the present study's population, it was not possible to investigate the effect screening history on the alcohol and prostate cancer association.

The lack of association between measures of alcohol exposure and prostate cancer risk reported in the present study is supported by the literature review described in Chapter 2.16 and consistent with the findings of a comprehensive review of studies conducted between 1971 and 1996 (Breslow and Weed 1998) and a meta-analysis (Dennis and Hayes 2001), which found no association between alcohol consumption and an increased risk of prostate cancer although an association with heavy alcohol consumption still cannot be ruled out.

6.3.6 Advantages of present study

The advantages of the present study include the fact that it was based on a large sample size randomly sampled from the Scottish general population and, results may, therefore, be readily transferable to that population. Loss to follow-up, as a result of incomplete linkage records due to emigration, was approximately 5%. The impact of this, on the results in the present study, was not included in the modelling strategies used in the analysis. Previous studies, however, examining the relationship between alcohol and health outcomes from the SHeS and SMR linked dataset, have reported no significant differences between models including and excluding incomplete records due to emigration (Lawder et al 2007, MacDonald et al 2009). This suggests that whether emigrants are included or excluded from the modelling will have minimal impact on the results. The elimination of subjects with a history of cancer at baseline, meant that previous cancers were not allowed to influence the association between alcohol and cancer. Bias resulting from undetected presence of sub-clinical disease at baseline is also unlikely, because an analysis excluding all cases with less than one year of follow-up did not change the results significantly; hazard ratios were not significantly different from those reported for complete follow-up. There was close to complete ascertainment of cases (cases having been ascertained through the Scottish Cancer Registry). The three most common cancers observed among the cohort in men (lung 28%, prostate 19.9%, colorectal 17.8%) and in women (breast 42.5%, lung 19.1%, colorectal 14.1%) are the also the three most common cancers in Scottish men (prostate 19.1%, lung 18.7%, colorectal 14.8%) and women (breast 28.2%, lung 15.5%, colorectal 14.1%) (ISD 2010a), and which suggests that the study includes a representative sample of the whole population.

[41] The PSA test is a blood test that measures the level of PSA (prostate specific antigen) in blood. PSA is made by the prostate gland, and some of it will leak into the bloodstream depending on the age and the health of the prostate. A raised PSA level may indicate presence of prostate cancer.

A further advantage of the present study, is that because the information on alcohol consumption was collected at baseline, the possibility of bias due to differential recall is virtually non-existent. The present study has a modest length of follow-up period (mean 9.1yrs) which is shorter than follow-up in most other prospective cohort studies reporting on association between alcohol consumption and risk of alcohol related cancers. Therefore the information on alcohol intake given by participants at baseline is more likely to apply to their behaviour during follow-up than studies with longer follow-up. Studies of the stability of drinking over time have found aspects of both stability and change. Kerr et al (2002) observed high correlations between measurements for adult sample 5 years apart or less (from baseline measurement of drinking), but low for longer follow-up. Baseline measures of drinking groups were especially unreliable for younger samples and heavier drinkers (mean weekly consumption among men and women in the sample was 12 and 6 units respectively, almost half the recommended sensible weekly drinking guidelines in the UK).

The present study also reported on the association between cancer and drinking frequency. The effect of drinking frequency on the risk of alcohol related cancers has generally not been addressed partly because questions on drinking patterns have not been commonly included in epidemiological surveys (Arria and Gossop 1998). Only seven of the papers chosen for inclusion in the systematic review (chapter 2) reported drinking frequency in relation to risk of cancer. The present study was able to derive frequency groups that approximated to daily, weekly (not daily), monthly drinkers and non-drinkers (comprising of former and never drinkers), based on the quantity/ frequency measure used in the Scottish Health Survey. Overall, results for drinking frequency were broadly similar to those reported for weekly alcohol intake. These results, however, need to be treated with some caution. Simply using broad frequency categories, as in the present study, will hide the significant variation in amount consumed within these groups; some 'daily drinkers' may drink as much or as little as weekly 'not daily' drinkers. Aetiologically, the most interesting and valid comparison in relation to cancer risk would have involved taking into account both frequency and quantity, but estimation of risk using this approach was not possible due to the small number of cases in each group. Previous studies have highlighted that it is more often the amount of alcohol consumed as opposed to the number of days on which it was consumed that was important in determining risk (Tjonneland et al 2003, Horn-Ross et al 2004).

6.3.7 Limitations of present study

The present study also had limitations. The relatively low incidence of many of the cancers under investigation, the long latency periods for many of the cancers, the size of the study's cohort and the modest length of follow-up (mean 9.1yrs), may reduce the power of the study particularly its power to examine associations in sub-groups.

Random or non-differential misclassification of alcohol consumption is likely for several reasons. Firstly it is estimated that self reported alcohol use in the Scottish health survey accounts for only 50-60% of alcohol sales, suggesting that under-reporting of actual consumption is a significant issue in this cohort. The changing strength of alcohol of many drinks in recent years,[42] in particular wine and beer, and change in serving sizes in licensed premises (especially glasses of wine) contributes to survey under-estimation of levels of alcohol consumption (Catto and Gibb 2008). Secondly, it is also widely recognised that individuals who are very heavy drinkers are unlikely to participate in surveys (Goddard 2007). Thirdly, quantity/frequency measures used to elicit details of alcohol consumption in general population surveys (including the Scottish Health Survey) are also widely criticised for providing lower estimates of drinking when compared to other measures based on recent drinking occasions and the graduated frequency approach[43] which seem to yield comparable results to one another, as well as consistently higher estimates of the prevalence of high risk drinking and harm (Midanik 1988, Room 1991, Midanik and Room 1992, Rehm et al 1999). Furthermore, in quantity/frequency measures of alcohol consumption, there also seems to be a tendency for survey respondents to interpret usual or customary drinking as modal value i.e. capturing the typical amount of alcohol consumed in a given period of time, although researchers actually interpret these as means (Duffy and Alanko 1992, Kühlhorn and Leifman 1993). Therefore the modal quantity would generally underestimate the 'true' mean quantity because the individual's quantity distribution (i.e. the distribution of quantities over separate drinking occasions) is usually highly right-skewed. This type of misclassification could have resulted in an underestimation of the true effects of alcohol consumption on cancer risk if heavier drinkers underreported to a greater extent than light or moderate drinkers.

Alcohol intake in the present study population was limited to a rather narrow range i.e. within weekly limits with small numbers drinking at high levels of alcohol consumption and based on baseline consumption only. The lack of a sufficient number of heavy drinkers in the sample limited the power of the study's analyses to detect an association between alcohol consumption and the cancers under investigation in the present study. Furthermore abstainers and ex-drinkers were not separated in the study, but were included in the reference category. Ex-drinkers many differ in cancer risk from abstainers; therefore the estimated risk for each of the cancers may be biased in either direction.

A further limitation is possible false positive results resulting from multiple comparisons. The more statistical tests one conducts, the greater the likelihood that a "statistically significant" result will emerge purely by chance (Scheffe 1953, Miller 1983). If we test two independent true null

[42] To take into account changing strengths and serving sizes of alcohol drinks, new alcohol unit conversion factors for use in population surveys were published by ONS in 2007. These were used to recalculate drinking levels from the 2003 Scottish Health Survey and published in 2009 (see Appendix F).

[43] the graduated frequency measure is a series of questions on the frequency of consuming specific numbers of drinks which ranges from the most ever consumed in the last year to 1–2 drinks per occasion

hypotheses, when statistical significance is set at the $P < 0.05$ level, the probability that neither test will be significant is 0.95x0.95=0.90. If we test 20 such hypotheses the probability that none will be significant is 0.9520=0.36. This gives a probability of 1–0.36=0.64 of getting at least one significant result - we are more likely to get one than not. The expected number of spurious significant results is 20x0.05=1 (Bland and Altman 1995). Numerous methods (e.g. the Bonferroni correction, the Holm's test) have been proposed for dealing with this problem, but no one solution will be acceptable for all situations (Schaffer 1995).

Comparison of the results of this cohort study with the international literature is problematic due to differences in the measurement of alcohol intake. A standard unit of alcohol is defined in Scotland as containing 8g (10ml) of pure alcohol. In contrast, the international literature uses a typical alcohol content of between 10g and 15g of ethanol for a 'standard drink'; In a review of 27 studies, the standard drink used on average, in the epidemiological literature, provided 12 grams of alcohol (Turner 1990). This in turn complicates the transferability of many of the results of the observational studies included in the present review, to Scotland.

6.4 Summary

The study was the first of its type to investigate an association between alcohol consumption and risk of cancer in a sample of the Scottish population. In summary, the present study provides some evidence of a statistically significant relationship between alcohol drinking frequency, and weekly intake and cancers of the upper aero digestive tract. A small increased risk (though non-significant) of colorectal cancer for daily drinkers was observed, but no relationship was detected for amount consumed for this cancer. There was no statistically significant association observed between drinking frequency or amount consumed and risk of breast, lung and prostate cancer. Further studies with a larger sample and a longer-follow-up are required to further explore associations between alcohol and related cancers particularly the effect of heavy drinking and variation by gender, ideally with repeated measures of alcohol intake and complete recording of confounding factors.

Chapter 7 Cancer risk in a Scottish alcohol related hospital cohort

In this chapter, the risk of cancer in a population admitted to hospitals in Scotland with an alcohol related diagnosis is investigated using linked data from national hospital/ cancer/death records dataset, described in Chapter 5.

7.1 Methods

The design was a cohort study based on a record linkage between the Scottish Morbidity Record and the Scottish Cancer Registry, and analysis of first-occurring alcohol related cancer among a cohort of patients admitted to hospital with an alcohol related condition during 1981–2007 (see chapter 5 for description of Scottish Morbidity Record and the Scottish Cancer Registry, and the record linkage process).

7.1.1 Study Exposure/Study Population and Outcome

All records from the SMR01 episode database with an alcohol related hospital diagnosis, in any diagnostic position in the hospital discharge record, among patients aged 15 or over, and hospitalised between 1 January 1981 and 31 December 2007 were considered. An alcohol related hospital diagnosis was defined using the WHO International Classification of Diseases (ICD)-9 codes 291, 303 and 305a (WHO 1979) and ICD-10 codes F10.0 to F10.9 (WH0 1992) (Table 7.1)[44]. This list of codes is similar to that used in record linkage studies of alcohol related cancers in people with previous history of alcohol related hospital discharge (Adami et al 1992, Boffetta et al 2001, Ye et al 2003). In these studies, cohorts were based on WHO ICD versions seven to nine and labelled as alcoholism or 'alcoholic' cohorts reflecting ICD terminology of the time. For previous record linkage cohort studies, their emphasis was on those drinkers identified by the ICD 'alcoholic' categorisation which included only people with chronic alcohol related conditions. Subsequent revisions to the ICD (9th and 10th) have provided more detailed guidance on coding of alcohol problems and include not only those dependent on alcohol, but also those admitted for drunkenness or acute intoxication (see Table 7.1). Since a hospital admission for drunkenness does not necessarily imply alcohol dependence or 'alcoholism', the study cohort defined using the above codes will be referred to as an alcohol related hospital admission cohort.

[44] The International Statistical Classification of Diseases and Related Health Problems (ICD) is a comprehensive classification of causes of morbidity and mortality, and is published by the World Health Organisation. The previous 9th revision (ICD-9) was published in 1975 and came into use in UK hospital information systems in 1979. It was superseded in Scotland by the 10th revision (ICD-10) from April 1996 (ISD 2000).

Table 7.1 ICD classification and mapping[1] of alcohol related codes 7th to 10th revision

	'Psychosis'	'Alcoholism'	Alcohol 'Abuse'
ICD-7	307 (Alcoholic psychosis)	322 (Alcoholism)	
ICD-8	291 (Alcoholic psychosis)	303 (Alcoholism)	
ICD-9	291 (Alcohol-induced mental disorders)	303.9 (Alcohol dependence syndrome)	303.0 305 (Alcohol abuse (incl. drunkenness, Excessive drinking, Hangover Inebriety)
ICD-10	F10.3-F10.9 (Withdrawal state (incl. with Delirium), Psychotic disorder, Amnesic syndrome, Residual and late-onset psychotic disorder, Other/unspecified mental and behavioural disorders)	F10.2 (Dependence syndrome)	F10.0 (Acute intoxication) F10.1 (Harmful use)

[1] Chikritzhs et al 2002

Between 1 January 1981 and 31 December 2007, 241,355 people, aged 15 years and over, admitted to hospitals in Scotland with an alcohol-related diagnosis, recorded in any diagnostic position, were identified. Patients who died (n=5,401) during their hospitalisation were identified and excluded from the cohort. The remaining episodes (n=236,154) were then linked to the Scottish Cancer Registry, with the aim of identifying cases of cancer that occurred among patients in the cohort after the first hospital discharge with an alcohol-related diagnosis. All cancers reviewed in chapter 2 were included and were defined according to ICD-9 (1981 to 1995) and ICD-10 (from 1996). Table 7.2 lists the cancers defined as 'alcohol-related' and their respective ICD-9 and ICD-10 codes (WHO 1976, 1992). Cancers of the oesophagus were further identified by histological code of the International Classification of Diseases for Oncology, Third Edition (ICD-O)[45] and grouped by histological types as oesophageal squamous cell carcinomas or oesophageal adenocarcinoma (Botterweck et al 2000).

Patients with a previous history of cancer (n= 6,995) diagnosed before the first alcohol related hospital admission were excluded. A further 435 patients were excluded at various steps of the linkage process because of inconsistencies of recording of gender, date of birth or death etc. in different sources of data. In addition, 8,807 patients were excluded because no information on area of residence of the patient was available on their hospital record to assign a deprivation score. The first year of observation, following the first alcohol related hospital discharge, was also excluded in order to reduce selection and detection bias which could occur if alcoholic patients with a yet undetected subclinical cancer are more likely to be hospitalised than other 'alcoholic' patients (Adami et al 1992, Boffetta et al 2001). This resulted in the exclusion of a further 18,987 patients who developed a cancer or died, within 1 year of the first alcohol hospital discharge. Of these, 9,186 (49.2%) died

[45] International Classification of Diseases for Oncology (ICD-O) is used principally in tumour or cancer registries for coding the site (topography) and the histology (morphology) of neoplasms (World Health Organisation, 1976, 2000a)

(including 1,137 cancer deaths) and 1,303 (7.0%) developed a cancer within a year of date of discharge.

Table 7.2 Cancers linked to alcohol consumption – ICD 9, ICD-10 and ICD-O classifications

NEOPLASM	ICD-9	ICD-10
Lip	140	C00
Oral cavity (incl. tongue)	141, 143-145	C01-C06
Oropharynx/tonsil	146	C09-C10
Hypopharynx	148.0, 148.2-148.9	C13
Oesophagus	150	C15
*Squamous Cell Carcinoma**	ICD-O M-8050-8078, 8083-8084	
*Adenocarcinoma**	ICD-O M-8140-8141, 8143-8145, 8190-8231, 8260-8263, 8310, 8401, 8480-8490, 8550-8551, 8570-8574, 8576*	
Colon	153	C18
Rectum (and rectosigmoid)	154.0-154.1	C19-C20
Liver	155	C22
Pancreas	157	C25
Larynx	161	C32
Lung	162,	C33-C34
Breast	174, 233.0	C50, D05
Ovarian	183.0 236.2,	C56
Prostate	185	C61
Bladder	188	C67
Kidney	189.0-189.1	C64-C65

Source: ISD (2010); * ICD-O classification

7.1.2 Statistical Analysis

Person-years at risk were calculated from the date of discharge of the index admission to hospital with an alcohol related diagnosis, to either occurrence of cancer, the date of death or 31 December 2007, whichever occurred first. Person-years at risk were calculated by summing the time each person in the cohort remained at risk of developing cancer during study period, taking into account each subject moving through age-groups until cancer, death or the end of the study. A further adjustment to these person years at risk was made by allocating a time effect to take into account the changes in cancer incidence over time. The expected number of cancers were calculated by multiplying the observed person-time (i.e. person years at risk) by cancer incidence rates specific for age (in 5-year groups), gender, and calendar year. The expected rates were derived from the entire Scottish population and aggregated into approximately 5-year intervals (1981-1986, 1987-1991, 1992-1996, 1997-2001 and 2002-2007) to ensure a sufficient number of observations in each cell. The standardized incidence ratio (SIR), estimated as the ratio of the observed to the expected number of cancers, was used to estimate relative risk.

In a second piece of analysis controlling for the effects of deprivation, this study utilises the area based Carstairs index of deprivation available on the ISD linked database and on the Scottish Health Survey (see Chapter 5.1.6 for more detailed information on the Carstairs Index). Cancer incidence

data by gender, age (eighteen five year age bands) and Carstairs quintiles[46] (from quintile one (least deprived) through to quintile 5 (most deprived)) was obtained from the Scottish Cancer registry for each of the cancers under investigation. Expected rates were obtained by multiplying gender, 5-year age group 5 year aggregated cancer incidence and Carstairs quintiles by the observed number of person years within each stratum of the cohort.

Confidence intervals for SIRs were calculated with the assumption that the observed number of events followed a Poisson distribution (Breslow and Day 1987). As incidence rates of the cancers studied were for the most part substantially different among men and women and there is still a lack of sufficient evidence of whether the risk of cancer from alcohol consumption varies by gender (see Chapter 2), all analyses were stratified by gender. Analyses were performed using Intercooled Stata version 11 (STATA statistical software, release 11; Stata Corporation, College Station, TX) and SPSS for Windows version 17 (SPSS, 2009).

7.2 Results

The alcohol related hospital cohort comprised 200,730 individuals, of whom 144,192 (71.8%) were men and 56,974 (27.9%) were women (Table 7.3). The mean age at index hospitalisation among the alcohol related hospital cohort was 43.6 years among men and 42.6 years among women. The patients in the cohort provided a total of 1,999,555 person-years at risk (men 1,423,645, women 569,910) for an average of 9.9 years of follow up (9.9 years for men and 10.1 years for women). Approximately, a quarter of men (29.1%) and a third of women (34.0%) had an alcohol related hospital condition recorded in the primary diagnostic position (see Section 5.1.1). Approximately, one in ten of men and women in the cohort lived in the least deprived quintile, compared to approximately a third or men and women living in the most deprived quintile.

[46] The Carstairs index scores for the whole of Scotland are ranked in order and can be divided into either five (quintiles) or ten (deciles) equal sized groups for comparison (McLoone 2004).

Table 7.3 Characteristics of the alcohol related hospital cohort followed up during 1–20 years through 2007

	Alcohol related hospital discharge		**Alcohol related hospital discharge as primary diagnosis**	
Characteristics	Males	Females	Males	Females
No. of patients	144,192	56,538	42,026	19,204
Mean age at entry (years)	43.6	42.6	42.1	41.3
Years of follow-up, mean	9.9	10.1	11.7	11.3
Person-years at risk	1,423,645	569,910	490,652	217,709
Number of alcohol related cancers	10,464	3588	3460	1427
Mean age at cancer diagnosis after first year of follow-up	65.0	62.6	63.0	62.0
Cohort subgroups (%)				
Alcohol abuse	67.6	67.6	34.5	42.1
Alcohol dependence	24.3	25.6	48.3	45.1
Alcohol psychosis	8.1	6.9	17.4	12.8
% with alcohol related condition as primary diagnosis	29.1	34.0	n/a	n/a
Socio-demographic* (%)				
% in least deprived quintile	9.3	10.7	9.6	11.0
% in most deprived quintile	36.0	32.7	33.6	31.4

* Based on quintiles derived from the 2001 Carstairs Index

Approximately two thirds (67.6%) of the alcohol related hospital cohort were admitted to hospital with a diagnosis of 'alcohol abuse' with the remaining third admitted to hospital for alcohol dependence or alcohol-related psychosis (Table 7.3). Those cohort members with a diagnosis of alcohol abuse were younger at index hospitalisation, compared to those with a diagnosis of alcohol dependence or alcohol psychosis (Table 7.4). There were gender differences in the mean age of index hospitalisation by alcohol diagnosis grouping. Women admitted for alcohol abuse were significantly younger than men. In contrast, women admitted for alcohol related psychosis were significantly older than men. There was no difference in age of index hospitalisation for alcohol dependence between men and women. Some caution is required in interpreting differences across the alcohol diagnosis categories. The introduction of ICD-10 in 1996 (in Scotland), to replace ICD-9, resulted in a number of additional alcohol diagnostic groupings providing increased specificity and accuracy of coding for alcohol related diagnoses from 1996 onwards (see Table 7.1). Although the changes in diagnostic categories introduced by ICD-10 have been shown to have a minimal effect on overall numbers, evidence exists of movements across categories particularly between diagnoses of 'alcohol abuse' and 'alcohol dependence' (Baker and Rooney 2003). The changes in diagnostic groupings, therefore, preclude any attempt to stratify cancer risk by alcohol abuse, alcohol dependence and alcohol psychoses due to the impact of measurement bias.

Table 7.4 Characteristics of the alcohol related hospital cohort by alcohol diagnosis category

Characteristics	Alcohol abuse		Alcohol dependence		Alcohol psychosis	
	Men	Women	Men	Women	Men	Women
Number	97,501	38,217	35,042	14,446	11,649	3,875
Mean age at cohort entry (years (SD))	42.1 (18.1)	40.0 (17.7)	46.1 (14.2)	46.6 (14.7)	49.2 (14.2)	52.5 (15.8)
Average length of follow-up (years)	9.3	9.7	11.8	11.7	8.5	8.4
Person-years	911,090	369,112	413,736	168,386	98,819	32,413
Mean age at diagnosis of alcohol related cancer (years (SD))	66.2 (11.8)	62.4 (13.6)	63.3 (10.4)	62.1 (11.8)	64.3 (10.5)	65.9 (11.6)

7.2.1 Primary cancer incidence in the alcohol related hospital cohort

Overall, 14,052 (7.0%) individuals with an alcohol-related hospital discharge, developed cancer during the study cohort period. Men accounted for 10,464 (7.3% of men in the cohort) of these cancers and women accounted for 3,588 cases (6.3% of women in the cohort).

Lung (32.8%), prostate (11.4%) and oral (8.1%) cancers accounted for over half of cancers diagnosed in men in the cohort (Table 7.5). Compared to the distribution of alcohol-related cancers among men in the Scottish general population aged 35-64 years in 1999 (the median year of an alcohol-related hospital discharge in the cohort), there were disproportionately more cases of oral cancer (8.1% vs. 4.9%), hypopharyngeal cancer (1.1% vs. 0.4%), liver cancer (4.2% vs. 1.7%) and lung cancer (32.8% vs. 26.3%) observed among men in the alcohol related hospital cohort (Table 7.5). Conversely, there were disproportionately fewer cases of kidney cancer (2.2% vs. 6.1%), colon cancer (7.4% vs. 10.4%) and rectal cancer (5.1% vs. 9.1%) among men in the cohort compared to the distribution among men aged 35-64 years in the general population.

Among women in the alcohol-related hospital cohort, lung (30.9%) and breast cancer (25.3%) accounted for over half of all cancers diagnosed. Other commonly diagnosed cancers in women included colon cancer (6.8%) and oral cancer (6.1%). There were considerably fewer cases of breast cancer observed in the alcohol-related hospital cohort, compared to the distribution in women aged 35-64 years in the general population (25.3% vs. 57.3%), whilst there were approximately twice as many lung cancer cases in women in the cohort, compared to the distribution in women in the general population (30.9% vs. 13.0%). Head and neck, oesophageal and liver cancers were also disproportionately more common in women in the cohort, compared to the distribution in the general population (Table 7.5).

Table 7.5 Primary cancer incidence in the alcohol related hospital cohort

	Men			**Women**		
Cancer	Observed cases	% of all cancers in cohort	% distribution in general population, 1999* (35-64yrs)[1]	Observed cases	% of all cancers in cohort	% distribution in general population, 1999* (35-64yrs)[1]
Lip	25	0.2	0.6	3	0.1	0.1
Oral	849	8.1	4.9	220	6.1	1.4
Pharynx	219	2.1	1.5	80	2.2	0.4
Hypopharynx	110	1.1	0.4	27	0.8	0.1
Larynx	602	5.8	5.1	102	2.8	0.8
Oesophagus	669	6.4	6.1	178	5.0	1.9
Gastric	465	4.4	5.7	83	2.3	2.1
Colon	775	7.4	10.4	244	6.8	7.3
Rectal	538	5.1	9.1	114	3.2	3.4
Liver	438	4.2	1.7	70	2.0	0.6
Pancreas	327	3.1	3.2	117	3.3	1.9
Breast	-	-	-	907	25.3	57.3
Prostate	1196	11.4	14.2	-	-	-
Lung	3430	32.8	26.3	1108	30.9	13.0
Ovary	-	-	-	165	4.6	6.8
Bladder	589	5.6	4.6	115	3.2	1.3
Kidney	232	2.2	6.1	55	1.5	1.6
Total	***10,464***	***100***	***100 (n=2,689)***	***3,588***	***100***	***100 (n=3,599)***

*Based on median year of alcohol related hospital discharge in cohort. [1] Scottish Cancer Registry, ISD (2010)

Of the two main types of oesophageal cancer, oesophageal squamous cell carcinoma and oesophageal adenocarcinoma, there were disproportionately fewer cases of oesophageal adenocarcinoma identified in men and women from the alcohol-related hospital cohort, compared to the expected distribution in the general population (Table 7.6). Over one in ten of oesophageal cancer cases could not be assigned to either histological sub-type.

Table 7.6 Oesophageal cancer incidence in the alcohol related hospital cohort by histological -type

	Men			**Women**		
Cancer	Observed cases	% of all oesophageal cancers in cohort	% distribution in general population, 1999* (35-64yrs)[1]	Observed cases	% of all oesophageal cancers in cohort	% distribution in general population, 1999* (35-64yrs)[1]
Squamous cell carcinoma	358	55.4	33.5	122	68.5	77.8
Adenocarcinoma	202	31.3	63.2	50	28.1	19.0
Unknown	86	13.3	3.2	29	16.3	3.2

Overall, women in the alcohol related hospital cohort were younger than men at entry into cohort (mean age difference 2.77 years, 95% CI 2.34-3.20, $p<0.001$) and at age of diagnosis (mean age difference 2.41 years, 95% CI 2.02-2.79, $p<0.001$) of an alcohol-related cancer (Table 7.7).

Among men and women, however, the mean age at index hospitalisation by cancer site varied considerably; in men, the mean age ranged from 50.9 years for cancer of the pharynx to 61.7 years for prostate cancer and in women from 52.7 years for ovarian cancer to 61.5 years for cancer of the colon (Table 7.7). Overall, men developing cancers of the head and neck (oral, pharyngeal, laryngeal and hypopharyngeal cancer) tended to be younger at discharge with an alcohol-related diagnosis than other alcohol related cancers. Women in the alcohol-related hospital cohort diagnosed with head and neck cancers and cancers of the breast and ovary were also younger at hospital discharge than other alcohol-related cancers (Table 7.7).

Table 7.7 Study characteristics by gender and cancer type

	Men			**Women**		
Cancer	**Person-years**	**Mean age (SD) on discharge**	**Mean age (SD) at diagnosis of primary cancer**	**Person-years**	**Mean age (SD) on discharge**	**Mean age (SD) at diagnosis of primary cancer**
Lip	155.4	54.6 (15.1)	60.3 (14.9)	14.2	70.6 (19.0)	75.0 (18.7)
Oral	7,045.0	51.6 (11.4)	59.7 (9.9)	1,950.7	51.1 (11.0)	59.6 (10.0)
Pharynx	1,876.7	50.9 (10.4)	59.3 (9.3)	713.5	52.9 (12.1)	61.6 (10.2)
Larynx	5,261.5	53.1 (11.2)	61.5 (9.6)	9,25.4	54.0 (12.1)	62.8 (10.8)
Hypopharynx	867.0	52.4 (10.5)	59.7 (9.1)	218.9	53.7 (13.8)	61.6 (11.2)
Oesophagus	5,256.4	56.9 (12.1)	64.6 (10.2)	1,589.8	56.5 (12.7)	65.2 (10.5)
Gastric	3,512.9	58.9 (12.6)	66.4 (11.3)	642.3	58.3 (14.1)	65.9 (12.8)
Pancreas	2,690.2	57.4 (12.6)	65.4 (11.0)	1,061.7	56.1 (12.9)	65.1 (11.0)
Liver	3,444.3	57.4 (11.7)	65.1 (10.4)	544.0	56.9 (11.7)	64.6 (10.6)
Colon	6,432.8	59.3 (12.5)	67. 3 (11.1)	2,034.1	58.8(14.9)	66.8 (13.0)
Rectal	4,384.4	58.5 (12.0)	66.5 (10.6)	924.8	58.3 (14.6)	66.2 (13.3)
Lung	27,119.8	58.4 (11.3)	66.1 (9.7)	9,817.8	56.9 (11.7)	65.5 (10.0)
Breast	-	-	-	7,603.5	51.3 (13.3)	59.5 (12.4)
Ovary	-	-	-	1,425.3	50.4 (14.1)	58.8 (13.0)
Prostate	9,982.2	61.7 (11.5)	69.8 (8.9)	-	-	-
Bladder	4,520.3	60.6 (12.2)	67.9 910.4)	952.7	58.1 (12.9)	66.2 (11.6)
Kidney	1,971.3	54.2 (11.8)	62.8 (10.3)	485.3	54.3 (11.5)	62.8 (10.5)
TOTAL	84,520.2	57.3(12.8)	65.0 (11.3)	29,978.6	54.5 (14.0)	62.6 (12.9)

SD- standard deviation

For men and women, the mean age of primary diagnosis of cancer was 65.0 (SD 11.3) years and 62.3 (SD 12.9) years old respectively (Table 7.7). The mean age of primary cancer diagnosis in the hospital varied by cancer type; men and women in the cohort diagnosed with head and neck cancers (i.e. cancers of the oral cavity, pharynx, larynx) and cancers of the breast and ovary (women only) were diagnosed at younger age (range 59-60 years old) compared to those diagnosed (range 65-68 years old) with gastrointestinal cancers (e.g. gastric, colon rectal, pancreas, liver) or urological cancers (e.g. bladder and kidney). The large standard differences in mean age, however, suggests some caution about interpreting differences in age at diagnosis by cancer type.

7.2.2 SIRs for cancers identified in the alcohol related hospital cohort

The age and age and deprivation standardised incidence ratios for cancer of the oral cavity, pharynx hypopharynx and larynx were significantly elevated for both men (Table 7.8) and women (Table 7.9) in the alcohol related hospital cohort, compared to the general Scottish population. For men, the incidence rates of cancer of oesophagus and liver were elevated with an age and deprivation standardised incidence ratio of 1.80 (95% CI 1.67-1.94) and 3.24 (95% CI 2.94-3.55), respectively. Among women, the incidence of cancer of oesophagus and liver were also significantly elevated with age and deprivation standardised incidence ratios of 3.30 (95% CI 2.84-3.83) for oesophagus and 3.99 (95% CI 3.11-5.05) for liver.

Although the age standardised incidence ratio (ASIR) for gastric cancer in men was significantly elevated (Table 7.8), further standardisation by deprivation quintile did not show an association between gastric cancer and alcohol related hospital discharge (SIR 1.04, 95% CI 0.95-1.14). For women, the incidence of gastric cancer was non-significantly elevated (age and deprivation standardised incidence ratio of 1.19, 95% CI 0.95-1.48) (Table 7.9). In this cohort, the incidence of colon cancer was not significantly increased in men with an alcohol related hospital discharge compared to the Scottish general population. The ASIR for rectal cancer in men was significantly elevated, but this association disappeared after further standardisation by deprivation (SIR 1.04, 95% CI 0.95-1.13). In women, ASIRs for colon and rectal cancer were not significantly elevated, but after further standardisation by deprivation, the risk of colon and rectal cancer was significantly increased, by 24% and 36% respectively, in women with an alcohol related hospital discharge, compared to the general population. For both men and women in the alcohol related hospital cohort, cancers of the pancreas and lung were significantly more frequent, compared to expected numbers in the general Scottish population.

The age, and age and deprivation standardised incidence ratios for bladder cancer were significantly elevated for both men (Table 7.8) and women (Table 7.9). The incidence rate of cancer of the kidney in women was not significantly higher than expected whilst, among men with an alcohol related discharge, kidney cancer was significantly less frequent, compared to that expected in the general population (SIR 0.85, 95% CI 0.74-0.96). The incidence rate of prostate cancer was significantly lower in men in the cohort with an alcohol related discharge, than in the general population. For women, the incidence of breast cancer was not higher than

Table 7.8 Standardised incidence ratio (SIR) with 95% confidence interval (CI) of developing alcohol related cancers among male patients with an alcohol related hospital discharge during 1-20 years of follow-up

Cancer Type	Obs.	Exp.	SIR[1]	95% CI	SIR[2]	95% CI
Head and neck						
Oral	849	173.7	**4.89**	4.57-5.23*	**4.37**	4.08-4.67*
Pharynx	219	37.5	**5.83**	5.09-6.66*	**4.10**	3.58-4.68*
Hypopharynx	110	13.3	**8.29**	6.81-9.99*	**7.28**	5.98-8.78*
Larynx	602	185.4	**3.25**	2.99-3.52*	**2.94**	2.71-3.18*
Digestive organs						
Oesophagus	669	344.6	**1.94**	1.80-2.09*	**1.80**	1.67-1.94*
Gastric	465	402.5	**1.16**	1.05-1.27*	**1.04**	0.95-1.14 *p=0.021*
Liver	438	120.9	**3.62**	3.29-3.98*	**3.24**	2.94-3.55*
Pancreas	327	214.1	**1.53**	1.37-1.70*	**1.40**	1.25-1.56*
Colon	775	783.6	**0.99**	0.92-1.06 *p=0.777*	**0.94**	0.88-1.01 *p=0.237*
Rectal	538	484.3	**1.11**	1.02-1.21**	**1.04**	0.95-1.13 *p=0.217*
Respiratory system						
Lung	3430	1976.4	**1.74**	1.68-1.79*	**1.54**	1.49-1.60*
Male genital organs						
Prostate	1196	1458.0	**0.82**	0.77-0.87*	**0.80**	0.75-0.84*
Urinary system						
Kidney	232	260.8	**0.89**	0.78-1.01 *p=0.076*	**0.85**	0.74-0.96**
Bladder	589	469.6	**1.25**	1.15-1.36*	**1.19**	1.09-1.28*

[1]age standardised [2]age and deprivation standardised. *P<0.05, ** P<0.001. Abbreviations: Obs= observed cases, Exp= expected cases

Table 7.9 SIR with 95% confidence interval (CI) of developing alcohol related cancers among female patients with an alcohol related hospital discharge during 1-20 years of follow-up

Cancer Type	Obs.	Exp	SIR[1]	95% CI	SIR[2]	95% CI
Head and neck						
Oral	220	29.8	**7.38**	6.43- 8.42*	**7.89**	6.88-9.01*
Pharynx	80	5.6	**14.17**	11.23-17.64*	**13.75**	10.90-17.12*
Hypopharynx	27	2.4	**11.33**	7.46-16.51*	**12.15**	8.00-17.70*
Larynx	102	15.4	**6.64**	5.41- 8.06*	**6.63**	5.40-8.05*
Digestive organs						
Oesophagus	178	59.5	**2.99**	2.57-3.46*	**3.30**	2.84-3.83*
Gastric	83	72.5	**1.14**	0.91-1.42 *p=0.242*	**1.19**	0.95-1.48 *p=0.024*
Liver	70	19.4	**3.61**	2.81-4.56*	**3.99**	3.11-5.05*
Pancreas	117	64.7	**1.81**	1.50-2.17*	**2.00**	1.65-2.40*
Colon	244	228.2	**1.07**	0.94-1.21 *p=0.311*	**1.24**	1.09-1.41**
Rectal	114	98.1	**1.16**	0.96-1.40 *p=0.125*	**1.36**	1.12-1.63**
Breast	907	944.3	**0.96**	0.90-1.03 *p=0.231*	**0.98**	0.91-1.04 *p=0.256*
Respiratory system						
Lung	1108	426.4	**2.60**	2.45-2.76*	**2.82**	2.66-2.99
Female genital organs						
Ovarian	165	116.7	**1.41**	1.21-1.65*	**1.24**	1.06-1.44**
Urinary system						
Kidney	55	53.4	**1.03**	0.78-1.34 *p=0.860*	**1.14**	0.86-1.49 *p=0.262*
Bladder	115	61.3	**1.88**	1.55-2.25*	**2.05**	1.70-2.47*

[1]age standardised [2]age and deprivation standardised. *P<0.05, ** P<0.001. Abbreviations: Obs= observed cases, Exp= expected cases

expected (SIR 0.98, 95% CI 0.91-1.04). There was, however, an elevated incidence of ovarian cancer with a SIR of 1.24 (95% CI 1.06-1.44

Table 7.10 provides ASIRs[47] for oesophageal cancer among men and women with an alcohol related hospital discharge, by the main histological types. The incidence of squamous cell carcinomas (SCC) of the oesophagus was three times higher in men, and four times higher in women with an alcohol related hospital discharge, compared to the general population in Scotland. Incidence ratios of oesophageal adenocarcinoma for men and women were smaller than those observed for SCC; compared to Scottish general population, men with an alcohol related hospital discharge had a small and non-significant increased risk (ASIR 1.14, 95 % CI 0.99-1.31) of oesophageal adenocarcinoma, whereas women with an alcohol related hospital discharge were not increased risk (ASIR 0.98, 95% CI 0.73-1.30).

Table 7.10 Age standardised incidence ratios, with 95% confidence intervals (CI) of oesophageal cancer among patients with an alcohol related diagnosis, by histological type

	Men			Women		
	Obs	SIR	95% CI	Obs	SIR	95% CI
Squamous cell carcinoma	358	3.17	2.85-3.52 *p<0.001*	122	4.08	3.39-4.87 *p<0.001*
Adenocarcinoma	202	1.14	0.99-1.31 *p=0.064*	50	0.98	0.73-1.30 *p=0.974*
Missing	86			29		

7.2.3 Variation in cancer risk by gender and Carstairs deprivation quintile

Age standardised incidence ratios (with 95% confidence intervals), for each cancer type, by gender and Carstairs (2001) deprivation quintiles are presented in Figures 7.1 to 7.16 (See Appendix I, for full data tables).

Overall, there was a statistically significant increased risk for head and neck cancers (i.e. cancer of the oral cavity pharynx, hypopharynx and larynx) across the majority of Carstairs quintiles (Figure 7.1 to 7.4) in both men and women with an alcohol related hospital discharge, compared to the Scottish general population. The highest ASIR for each of the afore-mentioned cancers was consistently observed in men and women with an alcohol related hospital discharge living in the most deprived quintile in Scotland. The risk ratio for oral and pharyngeal cancer in men increased with increasing levels of deprivation (Figures 7.1 and 7.2).

[47] Deprivation information was not available for histological types of oesophageal cancer

Figure 7.1 Age standardised incidence ratios, with 95% confidence intervals, for oral cancer, by gender and Carstairs (2001) deprivation quintiles (y axis in log scale)

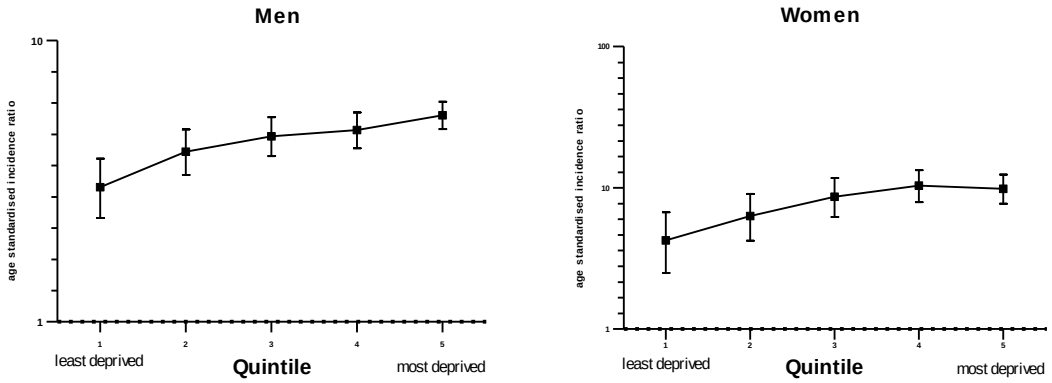


Figure 7.2 Age standardised incidence ratios, with 95% confidence intervals, for pharyngeal cancer, by gender and Carstairs (2001) deprivation quintiles (y axis in log scale)

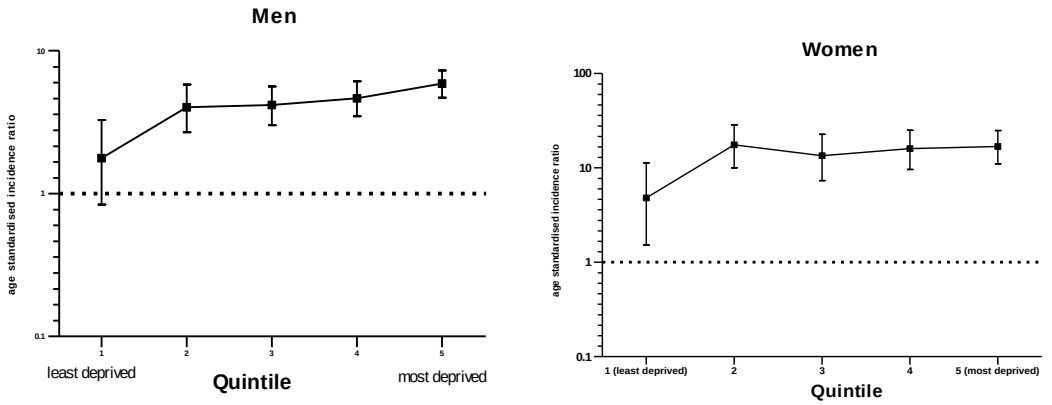


Figure 7.3 Age standardised incidence ratios, with 95% confidence intervals, for hypopharyngeal cancer, by gender and Carstairs (2001) deprivation quintiles (y axis in log scale)

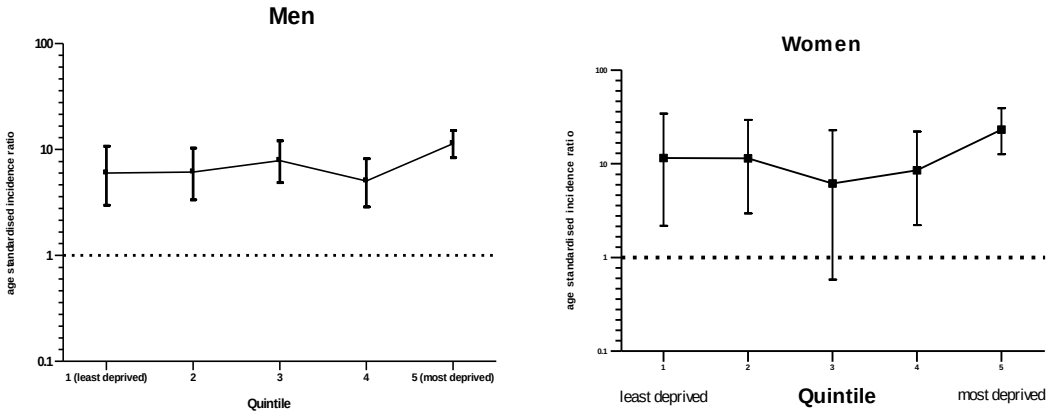
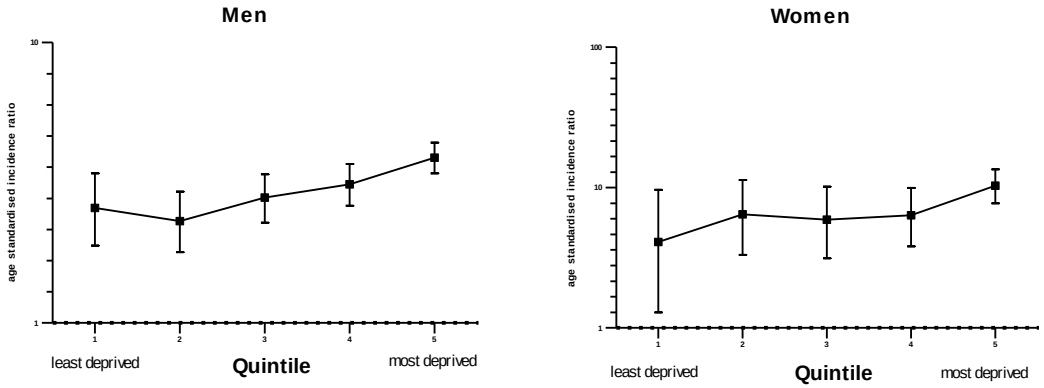


Figure 7.4 Age standardised incidence ratios, with 95% confidence intervals, for laryngeal cancer, by gender and Carstairs (2001) deprivation quintiles (y axis in log scale)



Overall, cancers of oesophagus (Figure 7.5) and liver (Figure 7.6) were significantly more frequent in men and women with an alcohol related hospital discharge, in each deprivation quintile, compared to the Scottish general population. The highest ASIR for oesophageal and liver cancers were observed for both men (ASIR 2.74, 95% CI 2.41-3.11, and ASIR 4.40, 95% CI 3.74-5.14, respectively) and women (ASIR 5.15, 95% CI 3.96-6.58 and ASIR 5.18, 95% CI 3.24-7.85, respectively) with an alcohol related hospital discharge and living in the most deprived quintile in Scotland. The risk ratio for oesophageal cancer in men, and for liver cancer in women, increased with increasing levels of deprivation (Figure 7.5 and 7.6).

Figure 7.5 Age standardised incidence ratios, with 95% confidence intervals, for oesophageal cancer, by gender and Carstairs (2001) deprivation quintiles (y axis in log scale)

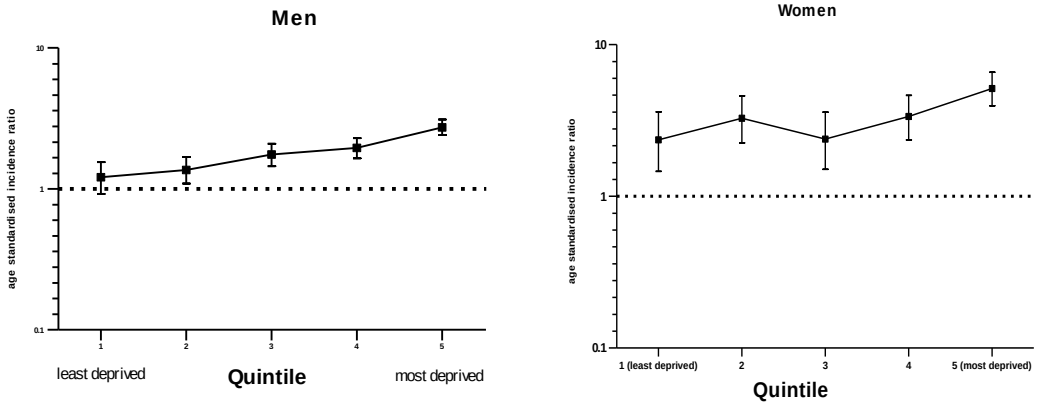
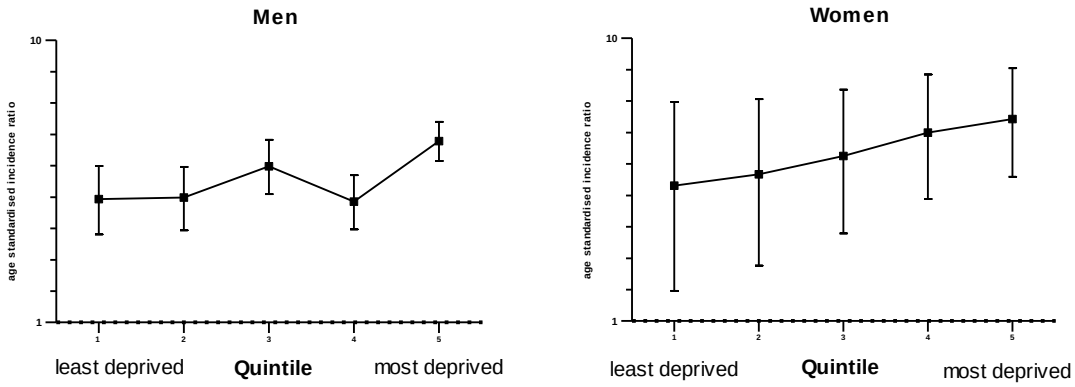


Figure 7.6 Age standardised incidence ratios, with confidence intervals, for liver cancer, by gender and Carstairs (2001) deprivation quintiles (y axis in log scale)



For both men and women in the alcohol related hospital cohort, living in Carstairs quintiles four and five, cases of pancreatic cancer were significantly more frequent, compared to expected numbers in the general Scottish population living in similarly deprived areas (Figure 7.7). The observed gastric cancer rates for men and women in the least deprived quintile were lower than expected, compared to the general population, but the differences were not statistically different (Figure 7.8). The incidence ratio for gastric cancer was only significantly elevated for men and women with an alcohol related hospital discharge, living in the most deprived quintiles of Scotland.

Figure 7.7 Age standardised incidence ratios, with 95% confidence intervals, for pancreatic cancer, by gender and Carstairs (2001) deprivation quintiles (y axis in log scale)

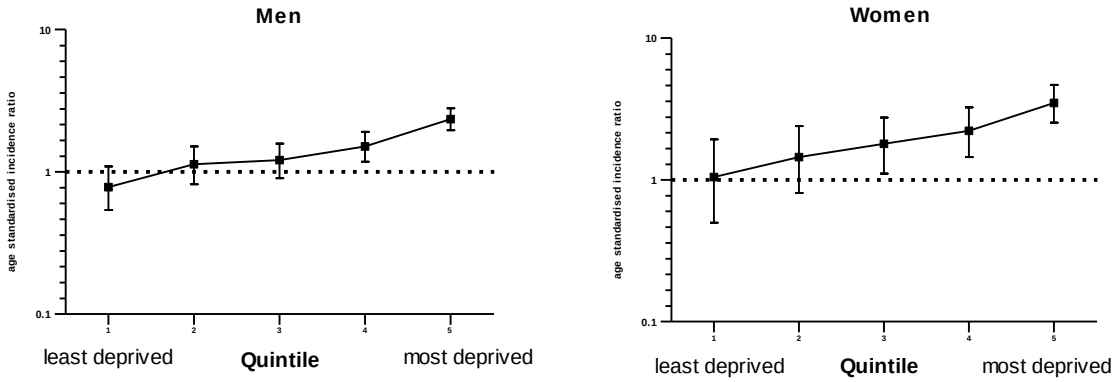
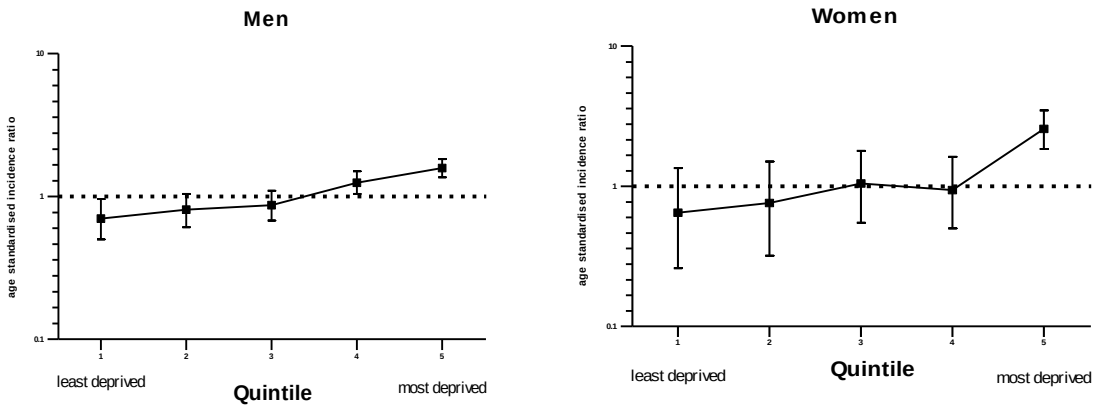


Figure 7.8 Age standardised incidence ratios, with 95% confidence intervals, for gastric cancer, by gender and Carstairs (2001) deprivation quintiles (y axis in log scale)



Men from the alcohol related hospital cohort had a statistically significant elevated risk of colon (ASIR 1.54, 95% CI 1.37-1.74) and rectal (ASIR 1.65, 95% CI 1.42-1.91) cancer, only if they were living in the most deprived Carstairs quintile (Figures 7.9 and 7.10 respectively). Conversely, men living in the least deprived quintile with an alcohol related hospital admission, were less likely to be at risk of developing colon (ASIR 0.56, 95% CI 0.45-0.69) or rectal (ASIR 0.55, 95% CI 0.41-0.72) cancer, compared to men in the general population from the same Carstairs quintile. A similar reduced, but non-significant, risk of colon cancer, but not rectal cancer, was also observed in women with an alcohol related discharge living in the least deprived quintile compared to women from the same quintile in the general population (Figures 7.9 and 7.10 respectively). For colon and rectal cancers in women, the risk ratio increased with increasing levels of deprivation, compared to that expected among women in the general population.

Figure 7.9 Age standardised incidence ratios, with 95% confidence intervals, for colon cancer, by gender and Carstairs (2001) deprivation quintiles (y axis in log scale)

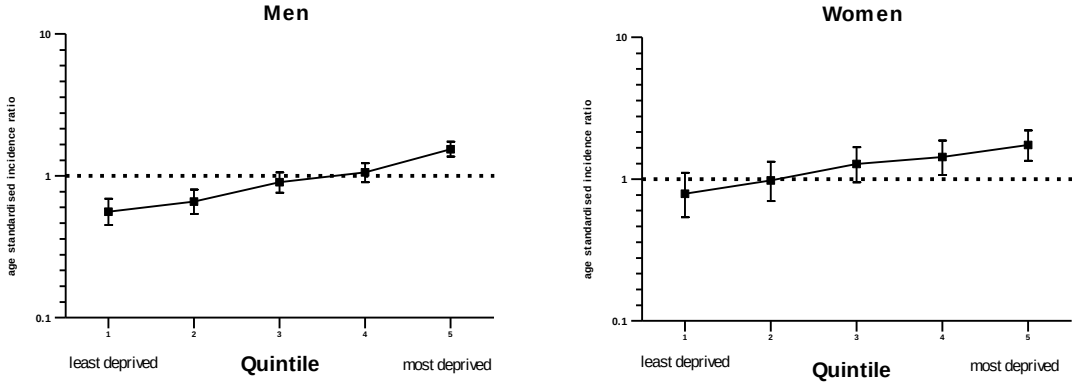
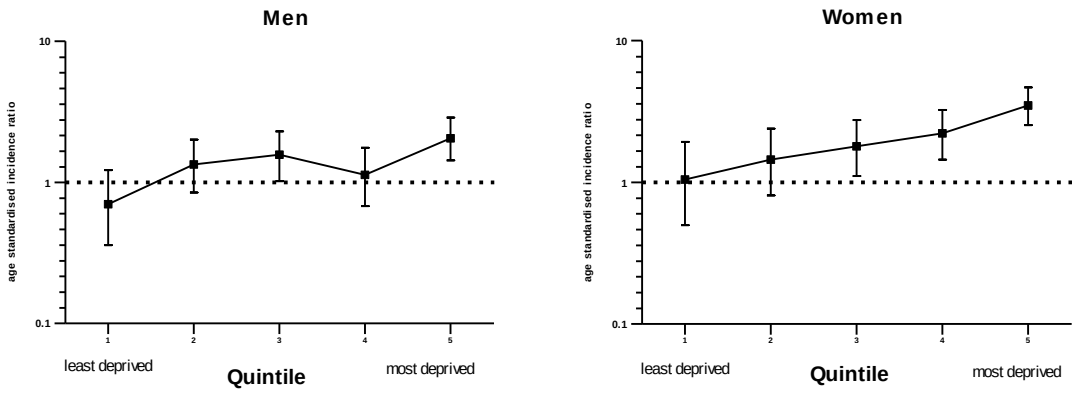
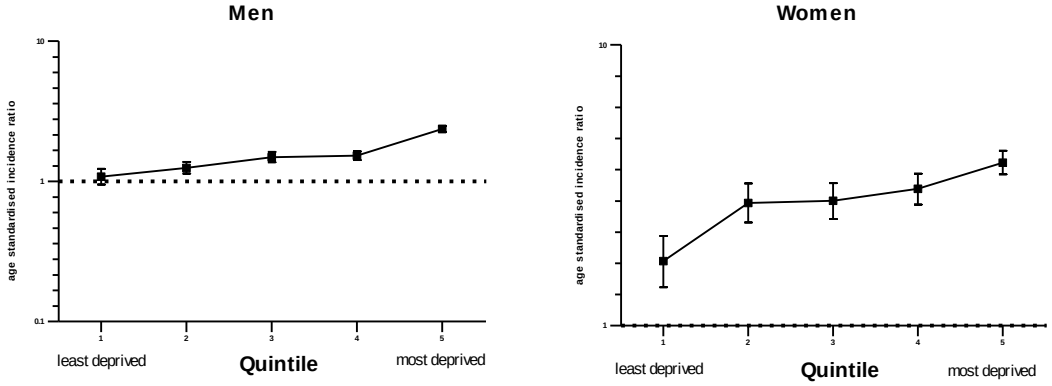


Figure 7.10 Age standardised incidence ratios, with 95% confidence intervals, for rectal cancer, by gender and Carstairs (2001) deprivation quintiles (y axis in log scale)



The relative risk of lung cancer among men and women with an alcohol related diagnosis was the highest for those living in the most deprived quintile (ASIR 2.37, 95% CI 2.25-2.49 and 3.81, 95% CI 3.46-4.20, respectively) and the relative risk increased with increasing levels of deprivation (Figure 7.11). There was no evidence of a significant association with risk of lung cancer (ASIR 1.08, 95% CI 0.95-1.23) for men from the alcohol hospital cohort living in the least deprived Carstairs quintile, compared to the Scottish general population.

Figure 7.11 Age standardised incidence ratios, with 95% confidence intervals, for lung cancer, by gender and Carstairs (2001) deprivation quintiles (y axis in log scale)



The standardised incidence ratio of alcohol related urological cancers increased with increasing levels of deprivation (Figures 7.12 and 7.13), however, compared to the Scottish general population only men and women living in the most deprived quintiles had a significantly elevated risk of cancer of the bladder (ASIR 2.02, 95% CI 1.77 2.30 and 3.66, 95% CI 2.69-4.85, respectively) and cancer of the kidney (ASIR 1.54, 95% CI 1.23-1.91 and 2.23, 95% CI 1.39-3.37, respectively). For women with an alcohol related hospital discharge living in the least deprived quintile, the incidence ratio for kidney cancer was lower and for bladder cancer, higher, than that among women in the general population,

but neither of these associations were statistically significant (*p* value= 0.555 and 0.125, respectively). In men, there was a statistically significantly reduced risk of developing kidney (SIR 0.44, 95% CI 0.23-0.75) cancer and bladder (SIR 0.72, 95% CI 0.54-0.94) cancer compared to men in the least deprived quintile in the general population.

Figure 7.12 Age standardised incidence ratios, with 95% confidence intervals, for kidney cancer, by gender and Carstairs (2001) deprivation quintiles (y axis in log scale)

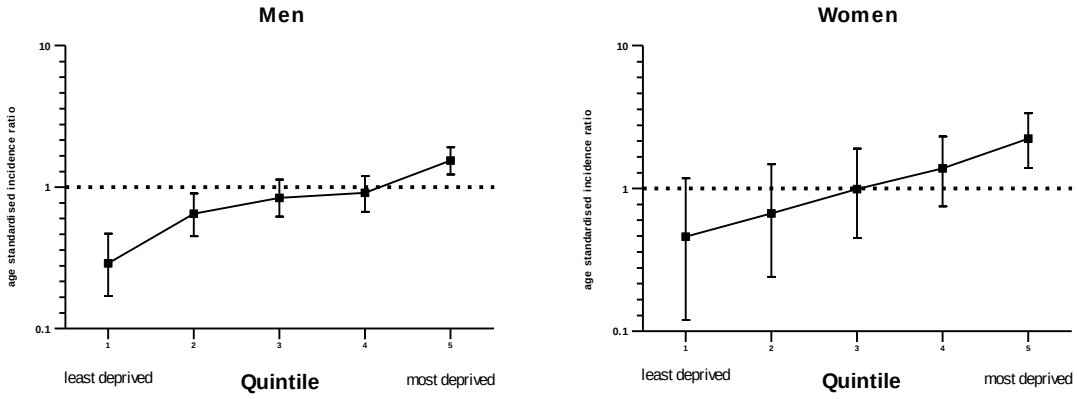
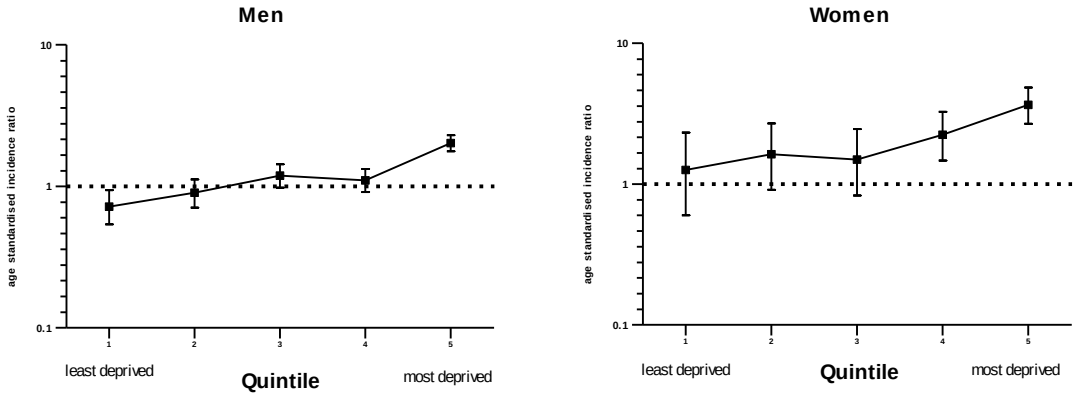
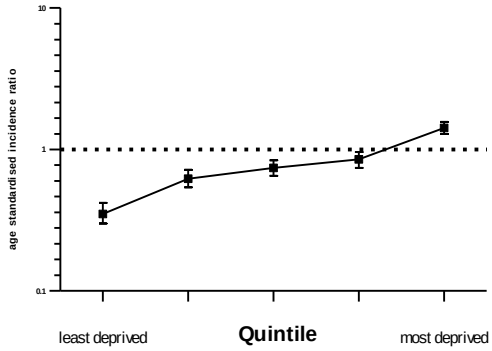


Figure 7.13 Age standardised incidence ratios, with 95% confidence intervals, for bladder cancer, by gender and Carstairs (2001) deprivation quintiles (y axis in log scale)



The incidence ratios for prostate cancer in men, with an alcohol related hospital discharge living in Carstairs quintiles one to four were significantly lower than those expected in the general population (Figure 7.14). Only among men living in the most deprived quintile was there a statistically significant increased association between alcohol and prostate cancer (SIR 1.42, 95% CI 1.29-1.57).

Figure 7.14 Age standardised incidence ratios with 95% confidence intervals for prostate cancer, in men by Carstairs (2001) deprivation quintiles (y axis in log scale)



The relative risk of breast cancer in women with an alcohol related hospital discharge increased with increasing levels of deprivation (Figure 7.15), however, compared to the Scottish general population, only women living in the most deprived quintiles had a significantly elevated risk of breast cancer (SIR 1.21, 95% CI 1.06-1.38 and SIR 1.64, 95% CI 1.46-1.84, in quintiles four and five respectively). There were significantly fewer cases of breast cancer observed in the present study among women with an alcohol related hospital discharge, living in the least deprived quintiles compared to that expected in the general population. Relative risk of ovarian cancer was at its highest for women in living in quintile five (SIR 2.15, 95% CI, 1.63-2.80), compared to women living in the most deprived quintile in the general population, with no evidence of a significant association in the remaining quintiles (Figure 7.16).

Figure 7.15 Age standardised incidence ratios, with 95% confidence intervals, for breast cancer (women), by gender and Carstairs (2001) deprivation quintiles(y axis in log scale)

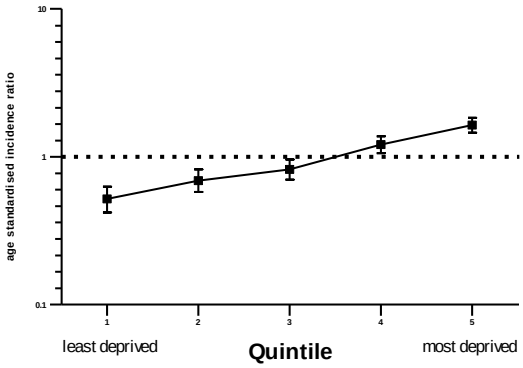
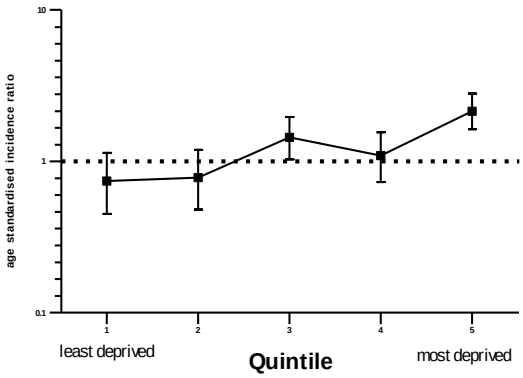


Figure 7.16 Age standardised incidence ratios, with 95% confidence intervals, for ovarian cancer (women), by gender and Carstairs (2001) deprivation quintiles (y axis in log scale)



7.3 Discussion

This study is the largest of its type to estimate cancer risk in a population admitted to hospital with an alcohol related diagnosis (Adami et al 1992, Boffetta et al 2001, Kuper et al 2000, 2001, Ye et al 2002) or with a diagnosis of alcoholism (Sigvardsson et al 1996, Ye et al 2003, Thygesen et al 2009). After controlling for the effects of age and deprivation, the incidence rates for cancers of the oesophagus, pancreas, bladder and lung were significantly increased in men and women with an alcohol-related hospital discharge, compared to the Scottish general population. An elevated incidence rate was found for colon and rectal cancer in women, but not in men. There was no significantly increased incidence of gastric, breast and kidney cancer in the alcohol related hospital cohort, compared to the general population. Ovarian cancer incidence rates were significantly higher, and prostate cancer cases significantly lower than expected among women and men respectively in the general population. In the present study, deprivation would appear to modify the association between an alcohol related hospital discharge and cancer incidence. For many of the cancers under investigation, the relative risk associated with a previous alcohol admission increased with increasing levels of deprivation.

A key innovation of this study is that, compared to other record linkage cohort studies (Adami 1992 et al, Boffetta et al 2001, Ye et al 2003, Thygesen et al 2009), it is the first to investigate the effects of deprivation both as a potential confounder and effect modifier of the association between a previous alcohol related hospital admission and subsequent cancer incidence. Although the relationship between alcohol consumption and area deprivation is complex with associations with amount drunk, either weekly or daily varying by gender and by age, there is a clear positive association between the number of people admitted to general hospitals in Scotland for an alcohol related diagnosis and increasing levels of deprivation. In 2007/08, people living in the most deprived areas of Scotland were

almost six times more likely to be admitted to a general hospital with an alcohol related diagnosis than those in the least deprived area; 7% (2,991 discharges) of all general hospital discharges in Scotland came from people living in the least deprived fifth of areas, compared to 42% (17,775 discharges) from those living in the most deprived fifth of areas (ISD Scotland 2009a). There is also a clear association between area deprivation and the incidence of most cancers**.** In England, between 2000 and 2004, there were 21% more diagnoses of cancer in men who live in the most deprived areas than in the least deprived (National Cancer Intelligence Unit 2010). The most deprived areas in Scotland have higher incidence and mortality rates for all cancers combined, but the effect of deprivation varies by cancer site. The incidence of head and neck cancers, for example, in Scotland and across Europe are strongly associated with increasing levels of deprivation (Conway et al 2007, Conway et al 2010), though previous studies have only found such an association for men and not for women (Conway et al 2010). On the other hand, women in the least deprived socioeconomic groups have higher breast cancer incidence rates (Brown et al 2007, Shack et al 2008, ISD Scotland 2009b). As a consequence, it is likely that deprivation could confound the association between alcohol related hospital admissions and cancer incidence and thus influence the interpretation of studies where its effect was not considered.

In the present study, there was a marked increase in relative risk of many of the cancers with increasing levels of deprivation among male and female patients in the alcohol related hospital cohort, compared to that expected in the Scottish general population. Consistently, men and women living in the most deprived quintile of Scotland had the highest incidence rates of each of the cancers under investigation compared to the Scottish general population living in the most deprived quintile. The link between an alcohol admission and relative risk of cancer with increasing levels of deprivation suggests that alcohol is contributing in some way to continuing inequalities in the incidence of many of the cancers under investigation in the present study in men and women with and alcohol related diagnosis compared to the Scottish general population. Another innovation of the study was to report the excess risk of the cancers under investigation by gender and to evaluate the excess risk of oesophageal cancer in patients with an alcohol related discharge, by histological subtype.

This study design also offers a number of strengths, including avoiding the risk of recall bias and virtually complete follow-up (>99%). Further, the high quality of Scottish national registers and the consistent use of the unique identifier numbers assigned to each person ensure correct linkage, thereby precluding selective loss to follow-up. Selection and information bias is therefore unlikely, especially since the first year of follow-up was excluded.

Despite these advantages, the study suffers from certain limitations. One potential concern is the possibility of biased ascertainment or detection of the cancer outcome. A lower diagnostic coverage among patients with an alcohol related diagnosis, than in the population at large, would entail

underestimation of the true relative risk (Ye et al 2003). However, the Scottish health-care system, with no patient fees and relatively equal access to hospital care for everyone, helps minimise this effect, although it is likely that people with alcohol related problems are less likely to participate in cancer screening programmes than those with no such problems. It is possible that this effect could be more marked in more than less deprived populations. A further limitation of the present study is the young age of the cohort, with a mean age at admission in men and women of 43.6 and 42.6 years respectively, which reduces the study's power to detect associations between alcohol related hospital admissions and cancer, particularly less common cancers.

Another concern is the lack of information about amount and type of alcohol intake, duration of alcohol abuse before index hospitalisation, and treatment, since it precludes a meaningful assessment of dose–response relationship. Using the diagnostic groupings (alcohol abuse, alcohol dependence and alcohol psychosis), which comprised the alcohol related hospital cohort as a proxy for increasing severity was considered, but rejected due to the broad and overlapping definitions within ICD for each of these groupings. This would introduce considerable measurement bias further accentuated by the change in ICD classifications in the 1990s which resulted in broader definitions and a shift in the trend within each of the groupings when the revised classification was introduced (Anderson and Robenberg 2003, Janssen and Kunst 2004, Quan et al 2008).

The most serious concern is the absence of information about lifestyle co-factors possibly related both to alcohol consumption and to the cancer outcome. In this study, as in other record linkage cohort studies, there was no information on exposure to potential confounders, of which tobacco smoking is likely to be the most important. Smoking is etiologically related to many cancers (IARC 2004), and there are numerous studies showing a positive association between cigarette smoking and alcohol drinking (Bien and Burge 1990, Dawson 2000), across a spectrum of drinking levels from light to heavy consumption (Cummins et al 1981, Adami et al 1992, King and Epstein 2005). The lack of information on smoking may partly result in the excess cancer risk if the alcohol related hospital cohort in this study contained a disproportionate number of smokers compared to the general population. Although no direct measure of smoking was available in the present study, the high incidence of lung cancer observed in both men and women in the alcohol related hospital cohort would suggest a higher prevalence of smoking compared to the Scottish general population. Given that cigarette smoking is a strong risk factor for bladder, pancreatic and lung cancer, it is possible that the excess risks observed for these cancers in the present study are entirely attributable to the confounding effects of smoking. Confounding from smoking may also explain some of the excess risk observed in the present study for liver cancer. Hepatitis B and hepatitis C virus infections and obesity have also been reported to be independent risk factors for liver cancer in a hospital population, interacting synergistically to increase the risk of liver cancer (Donato et al 2002, Marerro et al 2005).

Although the risk estimates for the head and neck cancers and cancers of the oesophagus identified in this study are also likely to be confounded by smoking, it is unlikely to account for all the excess risk of these cancers observed in the alcohol related hospital cohort compared to the Scottish general population. A carcinogenic effect of alcohol independently from that of smoking (i.e., an increased risk in non-smokers), has been observed as far back as 1961 (Boffetta and Hashibe 2006). Numerous studies since have shown a fairly consistent dose response relationship between alcohol consumption and risk of cancer in the oral cavity, pharynx and the larynx for non-smokers (Talamini et al 1990, Ng et al 1993, Fioretti et al 1999, Bosetti et al 2002) and oesophageal cancer in non-smokers (La Vecchia and Negri 1989, Castellsague et al 1999, Zambon et al 2000).

Alcohol consumption, especially heavy drinking, is also associated with additional risk behaviours and hazardous exposures. Since alcohol may account for a substantial proportion of total caloric intake, moderate to heavy drinkers are likely to have a different dietary composition and perhaps altered energy expenditure compared with abstainers and light drinkers (Boffetta et al 2001). Although confounding by diet may differ among cancer sites where diet is a recognised risk factor (e.g. colorectal, gastric), the most likely situation is one in which there is low intake of fruits, vegetables, fibre, and vitamins, which might increase rather than decrease cancer risk in most instances (Herbert and Kabat 1991). A positive association between alcohol intake and consumption of foods high in fat might also increase cancer risk among alcoholics (Adami et al 1992). The association between heavy alcohol drinking, smoking and diet has been shows to differ by socio-economic status (La Vecchia 1992, Pomerleau et al 1997, Ruidavets et al 2004, Mackenbach et al 2008). Helicobacter pylori infection also increases the risk of gastric cancer though it has been reported that moderate consumption of alcohol may lower the risk of Helicobacter pylori infection (Murray et al 2002). It is, therefore, feasible that risk estimates would be lowered if levels of H pylori infection were higher in the alcohol related hospital cohort than the general population and it were possible to adjust for this.

The use of comorbidity measures, to control for potential confounders of the alcohol-cancer association in the present study, was considered (Schneeweiss and McClure 2003). Comorbidity is the presence of a disease unrelated to the disease under study (Paleri and Wright 2002). This is particularly relevant in cancer where comorbidity has been found to have a significant impact on both survival and treatment selection in several types of cancer (Feinstein et al 1977, Wells et al 1984, Feinstein and Wells 1990, Piccirillo et al 1994, Singh et al 1998). A variety of comorbidity scoring indexes have been developed with individual characteristics and validity. The most commonly used validated indices include the Cumulative Illness Rating Scale, the Elixhauser scale, the Adult

Comorbidity Evaluation-27[48], the Index of Co-Existent Disease, the Alcohol and Tobacco Scale Washington University Head and Neck Comorbidity Index and the Charlson Morbidity Index (Charlson et al 1987, Hall 2006, Castro et al 2007).

The Charlson Morbidity Index, unlike other indices which are disease severity indices and cannot be implemented with routine data (Stockton 2004), has previously been adapted for use with administrative data as the information for the index (originally designed for a chart setting) can be extracted from clinically coded (e.g. ICD-9) databases (De Groot et al 2003). The Charlson index comprises of a list of 19 diseases (certain of them representing two degrees of severity of the same condition) with different weights attached (from 1: least severe to 6: most severe) (Table 7.11). Because the Charlson index is weighted and allows for additive scoring, it can take into account both the number and the severity of comorbidity to provide a summary of disease burden for each individual patient (Khan et al 2010). The index has been validated in several different populations, and has been widely used in studies involving cancer patients and survivors (Singh et al 1997, Reid et al 2002, Castro et al 2007, Cronin-Fenton et al 2007).

Table 7.11 Charlson comorbidity index

Comorbidity	***Notes***	***Points***
Myocardial infarction	alcohol related	1
Congestive heart failure	alcohol related (I42.6 alcoholic cardiomypathy) (10+ codes in this category)	1
Peripheral vascular disease		1
Cerebrovascular disease (except hemiplegia)	alcohol related	1
Dementia		1
Chronic pulmonary disease		1
Connective tissue (rheumatic) disease		1
Ulcer disease		1
Mild liver disease	alcohol related	1
Diabetes (without complications)	alcohol related	1
Diabetes with end organ damage		2
Hemiplegia		2
Moderate or severe renal disease		2
2nd solid tumour (non-metastatic)	cancer related	2
Leukaemia	cancer related	2
Lymphoma, multiple myeloma, etc	cancer related	2
Moderate or severe liver disease	alcohol related	3
2nd Metastatic tumour	cancer related	6
AIDS		6

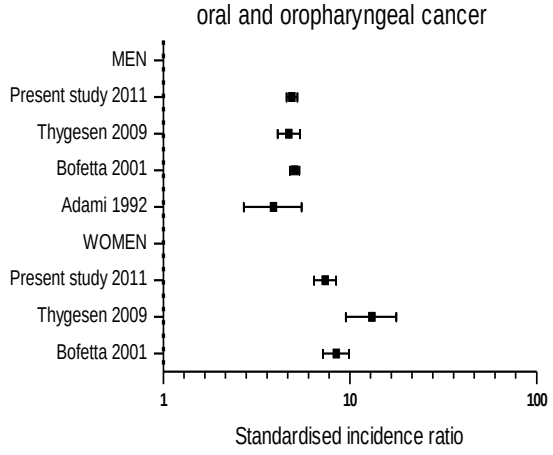
The Charlson Index was, however, developed from the study of outcomes for general medical patients, not patients with alcohol related conditions and/or cancer. While various comorbid ailments are common to all populations, the frequency distribution and the relative prognostic impact of each condition to the primary disease process may vary (Piccirillo et al 2002 Schneeweiss and McClure 2003). Furthermore, within a cohort of patients with cancer, the relative impact of individual comorbidities may vary across different cancer types. For example, head and neck cancer is primarily

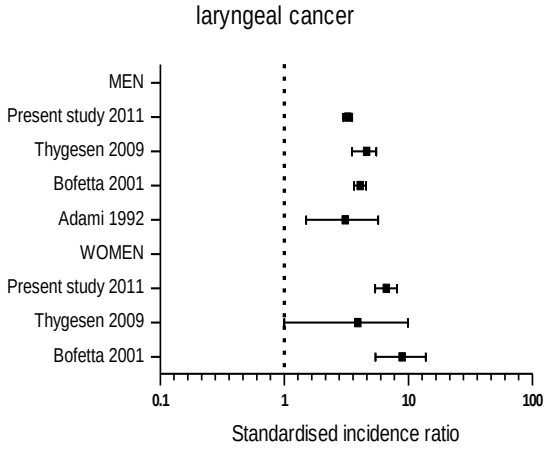
[48] Derived from the original Kaplan- Feinstein index (KFI) which was developed for assessing comorbidity in diabetes mellitus (Kaplan and Feinstein 1974), and subsequently modified and validated by Piccirillo (2000) to include terms relevant to cancer

a disease of the elderly, and the pattern of comorbidities in such a patient population may be quite different than that of patients with ovarian cancer which occurs at younger ages (Piccirillo et al 2002). This issue is amplified in the present study which involves the study of fifteen cancers, and in this context, it is unlikely that the Charlson Index would provide an adequate measure of co-morbidity in the present study, across all cancers under investigation. A further limitation of the Charlson Index, in respect of the present study, is that six and four of the disease items in the index, relate to alcohol and/or cancer respectively (Table 7.11) and, for the study of alcohol and cancer patients, these would be generally excluded from the score (Stockton et 2004). This leaves nine eligible disease items in the index, out of the original nineteen diseases. Excluding alcohol and related cancer conditions reduces the scoring power of the index, and neutralises the weights applied in the index by emphasising the less serious comorbidities. An alternative approach to the use of a validated tool like the Charlson index would be to derive co-morbidity measures from ICD-9 and ICD-10 codes specific to each cancer under investigation in the present study, but this would be complex to apply (Paleri and Wright 2002) and lay beyond the scope of the present study. For these afore-mentioned reasons, it was, therefore, considered inappropriate to use comorbidity measures in the present study to control for confounders of the alcohol-cancer association.

The findings of the present study are broadly consistent with previous studies of patients with an alcohol related hospital discharge or who were 'alcoholics'. This study found excess risks for all head and neck cancers under investigation (oral, pharyngeal, hypopharyngeal and laryngeal cancer) among the alcohol related hospital cohort compared to the Scottish general population. This is consistent with findings of previous record linkage studies (Adami et al 1992, Sigvardsson et al 1996, Boffetta et al 2001, Thygesen et al 2009; Figure 7.17) and with the results from high quality meta-analyses (Corrao et al 1999, 2004) and systematic reviews (IARC 1988, WCRF/AICR 2007) establishing alcohol as major risk for oral, pharyngeal and laryngeal cancer.

Figure 7.17 Comparison of standardised incidence ratios from previous record linkage studies, by gender and cancer type; oral, oropharyngeal and laryngeal cancer



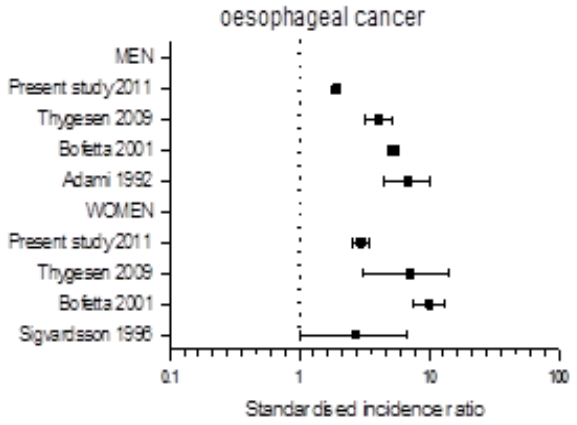


This study was also able to examine the association between patients with an alcohol related diagnoses and cancer of the hypopharynx compared to the Scottish general population. Hypopharyngeal cancer is a rare disease representing about 0.5% of all human malignancies with an annual incidence of less than 1 per 100 000 population and constituting only 3-5% of all head and neck cancers (Krstevska et al 2010). However, rising trends in hypopharyngeal cancer incidence rates in Scotland have been attributed to alcohol consumption (MacFarlane et al 1993). In this study, the SIRs for hypopharyngeal cancer observed in men and women were among the highest of the head and neck cancers in the alcohol related hospital cohort. The SIRs reported for head and neck cancers in the present study were two to three times higher than SIRs reported for other alcohol related cancers. These results offer further evidence consistent with the hypothesis of a carcinogenic effect of alcohol involving direct contact with oral and pharyngeal mucosa, which is also supported by epidemiological studies of moderate alcohol consumption (Tuyns et al 1988, Boffetta et al 1992, Franceschi et al 1994, Kjaerheim et al 1998).

The statistically significant excess SIRS for cancer of the oesophagus observed among both men and women in the alcohol related hospital cohort compared to the general population are consistent with those reported in other studies of 'alcoholics' (Adami et al 1992, Sigvardsson et al 1996, Boffetta et al 2001, Thygesen et al 2009; see Figure 7.18). Further analysis by histological sub-type revealed significantly raised risk for oesophageal squamous cell carcinoma, but no association with oesophageal adenocarcinoma. Boffetta et al (2001) reported similar findings in a cohort of Swedish patients admitted for 'alcoholism' compared to the general population in Sweden. There is a well-established dose response relationship between cancer of the oesophageal SCC and alcohol consumption (Chapter 2.12, WCRF/AICR 2007). Although associations between alcohol consumption and oesophageal adenocarcinoma have been inconsistent in past studies, the present

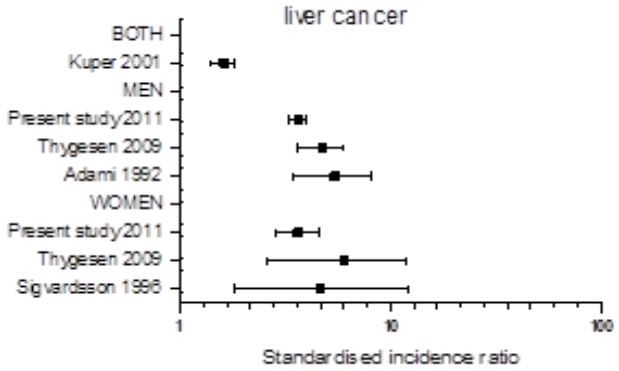
study adds further strength to the evidence that alcohol is not associated with an increased risk of oesophageal adenocarcinoma (Chapter 2.12, WCRN/AICR 2007, Freedman et al 2011).

Figure 7.18 Comparison of standardised incidence ratios from previous record linkage studies, by gender and cancer type; oesophageal cancer



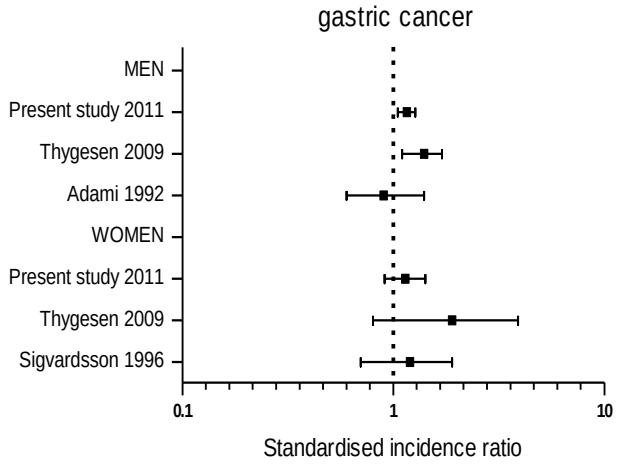
In the present study, a three to four fold statistically significant increased risk of liver cancer was observed in both men and women with an alcohol related hospital discharge, compared to the Scottish general population. This is consistent with the results of the majority of previous studies (Adami et al 1992, Sigvardsson et al 1996, Thygesen et al 2009). Kuper et al (2001), however, reported excess risks of liver cancer approximately three times lower than those reported in the present study (Figure 7.19). In this study, 'alcoholic patients", with a diagnosis of chronic viral hepatitis or cirrhosis, were excluded from the main cohort and their data were analysed separately. Patients with alcoholism in the absence of chronic hepatitis and without evidence of cirrhosis had an excess risk of liver cancer compared to the general population, but the increase was moderate (SIR 2.4, 95% CI 2.0-2.8) and could be explained by the presence of preclinical cirrhosis. Alcohol induced cirrhosis (SIR 40.7, 95% CI 33.9-48.9) and chronic hepatitis (SIR 34.4, 95% CI 18.3-58.9) on the other hand were strongly associated with liver cancer (Kuper et al 2001). Adami et al (1992) also observed a marked decrease in the SIR for liver cancer (from 6.0 to 3.1) when patients in their cohort with liver cirrhosis were excluded from the analysis. These results suggest that cirrhosis might be an important, or perhaps necessary, intermediary step in a causal pathway from alcohol to liver cancer. As the Scottish Morbidity Record (described in Chapter 5.1.1) does not record complete information on liver disease, it was not possible to examine the relationship between an alcohol related hospital admission, cirrhosis and subsequent liver cancer. Nevertheless, since Scotland has one of the highest mortality and morbidity rates for chronic liver disease including cirrhosis in Europe (Leon and Cambridge 2001, Scottish Public Health Observatory 2010b), it is highly likely that there will a high prevalence of liver disease in the present alcohol related hospital cohort.

Figure 7.19 Comparison of standardised incidence ratios from previous record linkage studies, by gender and cancer type; liver cancer



The present study found a small, statistically significant, increase in gastric cancer risk in men and a non-significant elevated risk in women, after controlling for the effects of age among peoples with an alcohol-related hospital discharge compared to the general population. This is consistent with the results of similar studies (Adami et al 1992, Thygesen et al 2009, see Figure 7.20). Further controlling for the effects of deprivation in the present study resulted in similar incidence ratios of gastric cancer in the alcohol related hospital cohort compared to the Scottish general population. This is consistent with the findings of the systematic review here and of those published in the literature (IARC 1988, Bagnardi et al 2001, WCRF/ACIR 2007) that alcohol has no causal role in the aetiology of stomach cancer.

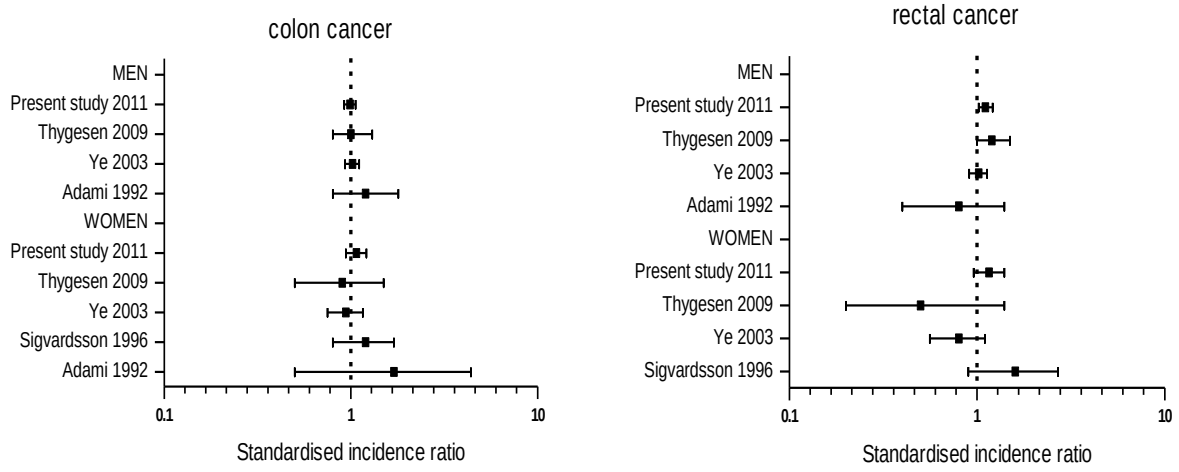
Figure 7.20 Comparison of standardised incidence ratios from previous record linkage studies, by gender and cancer type; gastric cancer



In the present study, the SIRs for colon and rectal cancer were not significantly elevated in men and

women with an alcohol related discharge, compared to the general Scottish population. These findings are broadly consistent with previous record linkage studies which have shown no difference in incidence rates for colon and rectal cancer in their study population, compared to those expected in the general population (Adami et al 1992, Sigvardsson et al 1996, Ye et al 2003, Thygesen et al 2009; see Figure 7.21). Controlling further for the effects of deprivation did not alter that association in the present study between colon and rectal cancer in men, but in women, however, a small and borderline statistically significant excess risk for both colon and rectal cancer, compared to the Scottish general population, was observed. In women with an alcohol related hospital discharge, however, SIRs were only significantly elevated in the most deprived Carstairs quintile. Although alcohol consumption has been considered a risk factor for colorectal cancer, the findings of the systematic review (Chapter 2.7) would suggest that this increased risk is only apparent for those drinking more than 30 grams per day (approximately 4 UK standard 'units'), but not at lower levels. A recent systematic review and meta-analysis also concluded that consumption of more than 30-40 grams of alcohol per day is a cause of colorectal cancer in men is convincing and probably also in women' (Cho et al 2004, WCRF/AIRC 2007). The lack of information on alcohol exposure levels in the present cohort precludes an investigation of a risk at certain alcohol intake levels.

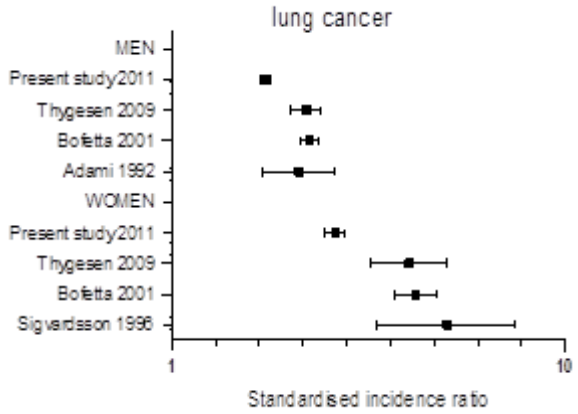
Figure 7.21 Comparison of standardised incidence ratios from previous record linkage studies, by gender and cancer type; colon and rectal cancer



The findings of an excess risk of lung and pancreatic cancer in men and women with an alcohol related discharge, compared to that expected in the general population is consistent with the findings reported in other studies of lung (Figure 7.22) and pancreatic (Figure 7.23) cancer risk in patients with an alcohol related hospital discharge. The small increase in risk of lung and pancreatic cancer in the present study among cohort members with an alcohol related diagnosis, which still remains after controlling for the effects of deprivation, is most likely to be attributable to smoking. A study of alcoholics in Canada found lung cancer risk was 1.7 fold greater than that of the general population,

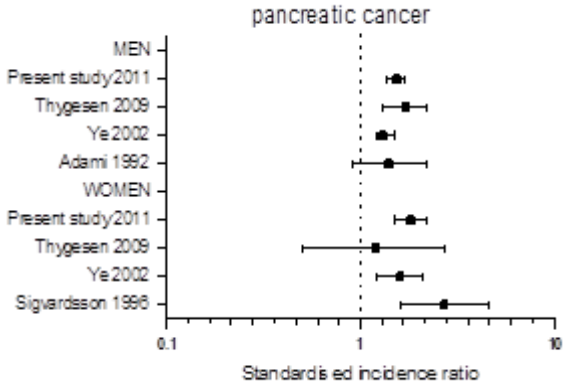
but no excess was found when compared with a population with similar smoking habits (Schmidt and Popham 1981). Bagnardi et al (2001) analysed the modifying effect of tobacco on the alcohol and lung cancer risk by comparing pooled estimates on unadjusted and adjusted RRs in their meta-analysis of alcohol and cancer risk. They observed that low (25 grams per day (g/d); unadjusted RR 1.58 (95% CI 1.12-2.24), adjusted RR 1.01 [95% CI 0.99-1.04)) moderate (50 g/d; unadjusted RR 2.50 (95% CI 1.25-5.01), adjusted RR 1.03 (95% CI 0.99-1.08)) and high (100 g/d; unadjusted RR 6.30 (95% CI 1.57-25.18), adjusted RR 1.07 (95% CI 0.98-1.17)) levels of alcohol consumption did not show significant effects on the risk of lung cancer when adjusted for smoking.

Figure 7.22 Comparison of standardised incidence ratios from previous record linkage studies, by gender and cancer type; lung cancer



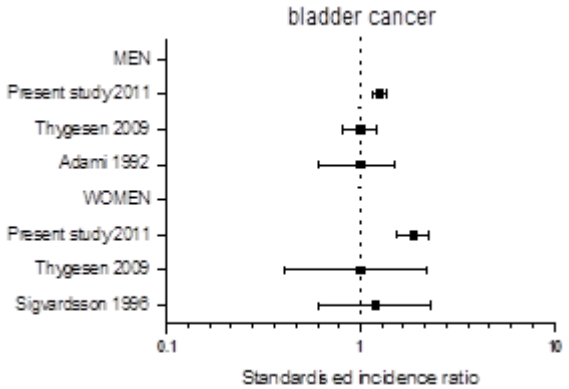
Heavy alcohol consumption is also known to be a major cause of chronic pancreatitis which is linked to pancreatic cancer (Go et al 2005, Lowenfels and Maisonneuve 2006). Ye et al (2002) reported SIRs for pancreatic cancer considerably lower among alcoholic chronic pancreatitis patients (2.2, 95% CI 0.9-4.5) than that among non-alcoholic chronic pancreatitis patients (SIR 8.7, 95% CI 6.8-10.9), compared to the general population. As information on chronic pancreatitis diagnosis was not collected as part of this study, it was not possible to examine the mediating effect of chronic pancreatitis.

Figure 7.23 Comparison of standardised incidence ratios from previous record linkage studies, by gender and cancer type; pancreatic cancer



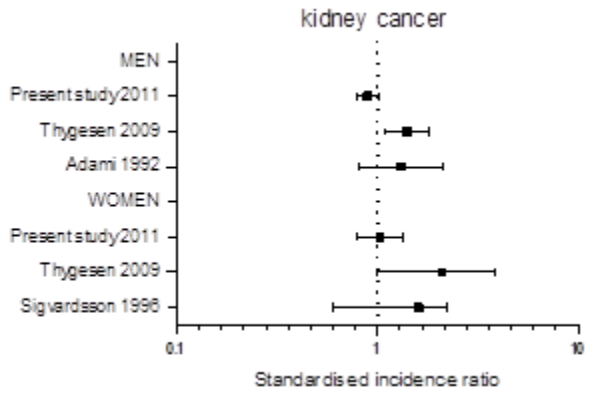
The finding of a significantly elevated risk for bladder cancer in men and women in the alcohol related hospital cohort compared to the Scottish general population is not in agreement with previous Swedish studies, similar in design to the present study (Adami et al 1992, Sigvardsson et al 1996, Thygesen et al 2009). These studies have observed comparable incidence rates of bladder cancer in their cohorts, compared to those in the Swedish general population (See Figure 7.24). Smoking, a major risk factor for bladder cancer, is, however, considerably more prevalent among men and women in Scotland than in Sweden (Taulbut et al 2008) and the difference in study results is likely to be attributable to a greater proportion of smokers in the present cohort, compared to those found in Swedish cohorts. Confounding from smoking will in turn account for the modest excess risk observed for bladder cancer in men and women in the alcohol related hospital cohort, compared to the Scottish general population. To date, the evidence of an association between levels of alcohol intake and risk of bladder cancer remains inconclusive as a result of too few studies, small sample sizes and the impact of residual confounding from smoking.

Figure 7.24 Comparison of standardised incidence ratios from previous record linkage studies, by gender and cancer type; bladder cancer



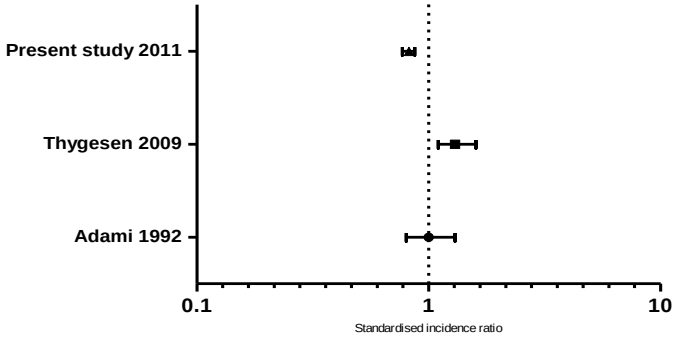
Previous studies have reported statistically significant increased risks of kidney cancer in cohorts of 'alcoholics" compared to the general population (Adami et al 1992, Sigvardsson et al 1996, Thygesen et al 2009). In the present study, however, women with an alcohol related discharge were not at increased risk of kidney cancer and the incidence ratio of kidney cancer in men was significantly lower in the alcohol hospital cohort, than would be expected in the Scottish general population (see Figure 7.25). These differences in study findings may be partly explained by the greater precision in the present study's estimates as a result of having approximately four to five times as many observed kidney cancer cases than previous studies. Two major systematic reviews have also concluded that there is insufficient evidence to attribute a causal role of alcohol in the development of kidney cancer (IARC 1988, WCRF/AICR 2007). This is also consistent with findings from a meta-analysis, albeit based on only two studies (Bagnardi et al 2001). It does not entirely rule out an effect of alcohol on kidney cancer risk since much of the evidence is based on a small number of studies, diverse population groups, small sample sizes and heterogeneous measures of alcohol consumption. Recent studies of reasonable methodological quality would seem to suggest that alcohol consumption may even offer some protection against the development of kidney cancer (Lee et al 2007), though the mechanism by which alcohol consumption might affect kidney cancer risk is unclear and it is unlikely that alcohol has a substantial effect on the risk of kidney cancer (WCRF/AIRC 2007).

Figure 7.25 Comparison of standardised incidence ratios from previous record linkage studies, by gender and cancer type; kidney cancer



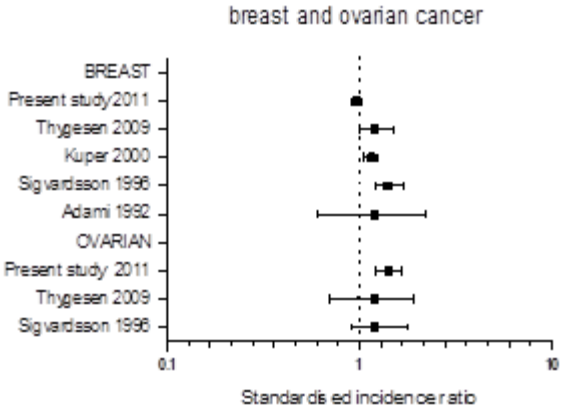
In the present study, cases of prostate cancer were significantly less frequent, after adjustment for age and deprivation, in the men with an alcohol related hospital discharge, compared to the expected numbers in the general Scottish population (see Figure 7.26). Previous studies of 'alcoholics' have reported mixed results from no association with prostate cancer in a cohort of patients admitted to hospital with alcoholism (Adami et al 1992) to a modest, but statistically significant excess risk of prostate cancer in men attending an alcohol treatment service (Thygesen et al 2009), compared to the general population. Neither of the afore-mentioned studies adjusted their estimates for the effects of deprivation and this is likely to explain the differences in results.

Figure 7.26 Comparison of standardised incidence ratios from previous record linkage studies, by gender and cancer type; prostate cancer



The finding of a slightly higher incidence ratio of ovarian cancer in women with an alcohol related hospital discharge, compared to the Scottish general population, is consistent with that reported by other studies of 'alcoholics' (Sigvardsson et al 1996, Thygesen et al 2009). Confounding by differences in smoking, parity, dietary pattern, use of oral contraceptives and hormone replacement therapy, reproductive history, prevalence of obesity, or diabetes mellitus, all of them associated with ovarian cancer risk are likely explanations of this excess. There is no available individual level information about these factors in this study.

Figure 7.27 Comparison of standardised incidence ratios from previous record linkage studies, by gender and cancer type; prostate cancer



In the present study, the age standardised incidence rates for breast cancer in women with an alcohol related hospital discharge were similar to those expected among women in the general Scottish population. Further controlling for the effects of deprivation strengthened the lack of association with breast cancer, but did not significantly alter the estimate. Modest excess risks of breast cancer of between 15% and 40% (without controlling for the effects of deprivation) have been reported in previous studies of women with an alcohol related hospital episode (Adami et al 1992, Kuper et al 2000) or in studies of 'alcoholic' women (Sigvardsson et al 1996, Thygesen et al 2009) though

incidence ratios were only statistically significantly higher, compared to those expected in the general population, in the study by Sigvardsson et al 1996). SIRS for the afore-mentioned studies are presented in Figure 7.27.

As with other hospital based record linkage cohort studies, the absence of information on confounders in the present study limits the interpretation of the findings of no excess risk of breast cancer. It is possible that women with an alcohol related diagnosis in the present study, compared to the background population, have an earlier age at first full-term pregnancy, more pregnancies, and - as a consequence of their higher smoking prevalence - an earlier menopause, as well as being generally of lower socioeconomic status, which may lower risk of breast cancer. Concerns about confounding by body mass index (BMI) cannot be ruled out since there is conflicting evidence for an association between alcohol intake and relative weight (Møller al 1994, Sayon-Orea et al 2011). Furthermore, a confounding effect of BMI in this present study may be likely given the high prevalence of obesity (i.e. BMI$\geq$ 30km/g^2) among women aged 16yrs and over in Scotland (Corbett et al 2010) though it would only act as a confounder if the prevalence of obesity was differentially associated in the exposed and unexposed groups. Another factor to consider in interpreting the present study's findings is the young age at which women entered the cohort. Women were considerably younger at entry into the present study's cohort (mean 42.6 years) compared to the age-ranges (50-74 years, mean, range from 57-63 years, see Table 2.6.1) covered by the majority of epidemiological studies on alcohol intake levels and risk of breast cancer. Evidence from the literature review discussed in Chapter 2.4 would suggest that the effects of alcohol consumption are more consistent and somewhat greater in post-menopausal women, than in pre-menopausal women.

In conclusion, the present study provides evidence that people who require in-hospital care for an alcohol related condition are at substantial subsequent relative risk of head and neck and upper gastrointestinal cancers and that the relative risk increases with increasing levels of deprivation. There were no significant differences in relative risk of these cancers between men and women. More modest increases in relative risk were observed for cancers of the liver, bladder and lung than for the previously named cancers. Deprivation may modify the effects of alcohol on risk of many of the cancers investigated, but does not explain fully the increased risk in head and neck and upper gastrointestinal cancers. Tobacco smoking is likely to contribute to some, but not all of the excess risk that appears to be associated with alcohol. There was no excess risk of breast cancer in women admitted to hospital with an alcohol diagnosis compared to the general population. Relative risks are greatest for cancers originating from mucous membranes that are in direct contact with alcohol. The inability to disentangle the effects of smoking and other major risk factors from those of alcohol consumption is an important limitation of the study.

Chapter 8 Conclusions

8.1 Introduction

In the first chapter of this thesis, historical and policy perspectives on alcohol, health and the alcohol-cancer association were discussed, and the aims and objectives were presented. In chapter two, a systematic review, including a detailed search protocol following guidelines developed by the Cochrane Collaboration, assessed the strength of evidence from epidemiological studies, published between 1999 and 2009, on the association between alcohol consumption and fourteen cancers. A detailed assessment of the strengths and limitations of the systematic review was provided in section 2.17.2. The epidemiology of alcohol consumption in Scotland was presented in chapter three and the strengths and weaknesses of individual and population level measures of alcohol consumption were discussed. Chapter 4 describes the recent trends in Scotland in the age-adjusted incidence rates for the alcohol-related cancers included in the systematic review. In the following three chapters the results from two separate Scottish prospective record linkage cohort studies are presented. Chapter 5 provides the background and a description of the data sources used in the analyses. The results of the first study, which comprised a sample of the general population in Scotland, are presented in chapter 6, and the results of the second study, comprising people admitted to hospitals in Scotland with an alcohol-related condition are presented in chapter 7, with a detailed discussion of the strengths and limitations of each study provided at the end of each chapter (sections 6.3.6-6.3.7 and 7.3.2-7.3.3 respectively).

The main conclusions that are drawn from this thesis as well as suggestions for future research and the implications for policy are presented in the following sections.

8.2 Conclusions

In the present study, a systematic review of the epidemiological literature supports the well-established association between alcohol consumption and an increased risk of cancers of the oral cavity, pharynx, larynx, and oesophagus. Strong evidence exists that alcohol consumption increases the risk of oesophageal squamous cell carcinoma, but not oesophageal adenocarcinoma. For these cancer sites, there is a dose-response relationship with alcohol consumption that persists after adjustment for potential confounders such as age, tobacco smoking and diet. These results appear to hold for both men and women, though many studies suffered from limited numbers of women drinkers, compared to men, especially those drinking heavily, to totally rule out an effect of gender. The effect of alcohol on head and neck cancers would appear to be stronger where alcohol comes in direct contact with the tissues (e.g. oral vs. laryngeal cancer). There is sufficient evidence that drinking ≥30g/d is associated with an increased risk of colorectal cancer. For liver cancer, there is

evidence of a threshold effect, whereby drinking ≥40 g/d increases the risk of liver cancer, compared to non-drinkers. Positive associations between alcohol consumption and an increased risk of breast cancer were in general only associated with alcohol consumption of approximately >15 g/d (i.e. approximately >1 'standard drink' or >2 UK 'units' per day). The risk estimates for breast and colorectal cancer were, however modest (the majority of relative risks in cohort studies being less than 1.5). Bias and confounding from unknown risk factors or residual confounding from existing risk factors could not be ruled out as an explanation for the small associations observed for breast and colorectal cancer. The weight of evidence would also suggest that low to moderate alcohol consumption is unlikely to be a risk factor for prostate and gastric cancer, though an increased risk from heavy alcohol consumption cannot be ruled out. Evidence of an effect on other cancers under investigation was inconclusive because of the small number and size of studies, and inconsistent findings.

The review suggests an effect by drink type in some cancers (e.g. oral, bladder, lung) though in the majority of studies positive associations between beverage type and cancer outcome generally reflected that fact that the beverage type identified as being associated with cancer was the most commonly consumed beverage in the population under study. Very few studies explored the impact of drinking frequency and/or drinking pattern, mostly because to do so would require a very large sample size (which few studies had) and some understanding of the complexity of people's individual drinking behaviour. This has only recently received attention among alcohol epidemiology and is lacking in medical epidemiology. Even within categories of low, moderate and heavy drinkers, there are patterns and frequency of drinking that may have different effects on the health outcome (Wetterling et al 1999, Poikolainen et al 2007).

The literature review in the present study also concluded that there were major weaknesses in the measurement of alcohol consumption in epidemiological studies. This precluded the use of meta-analysis in the present study because there was considerable heterogeneity of alcohol measures e.g. in use of reference periods, the definition of drinkers, non-drinkers, ethanol content and definition of standard drinks and questions used to elicit details of alcohol consumption. It is, therefore, the contention of this thesis that these shortcomings in measures of alcohol consumption represent a significant methodological limitation and restrict any collective assessment of the totality of evidence for the alcohol-cancer association, especially where there are weak or small associations. The implication of this is discussed below in relation to the current evidence and recommendations, from recent international reviews, on the association between alcohol and breast and colorectal cancer.

Investigation of these associations within the general Scottish population and within a population of people attending hospital with an alcohol related condition in the primary data analysis components of this thesis confirmed the positive associations between alcohol and an increased risk of UADT (oral

cavity, pharynx, larynx and oesophagus) cancers reported in other studies. These analyses, however, did not find that alcohol intake was associated with statistically significantly increased risk of breast and colorectal cancer at low levels of alcohol consumption. An association cannot be ruled out, however, for these cancers, for several reasons; in the general population cohort, very few of the study population were drinking at alcohol consumption levels associated with an increased risk of breast and colorectal cancer (approximately >15 g/d and >30g/d, respectively), and no adjustment was possible for other lifestyle risk factors (e.g. folate and fibre intake), associated with breast and colorectal cancer, which may or may not have masked a true association. Findings from the present study's hospital record linkage cohort study would seem to indicate that the risk of colorectal and breast cancer varies by level of deprivation, with the risk increasing with increasing levels of deprivation. It was not possible to investigate a possible modifying effect of deprivation on risk of cancer associated with alcohol, by cancer type, within the general population cohort sample because of small numbers of outcomes. This is an area requiring more attention in epidemiological studies as the effects of area measures of deprivation are generally not addressed, with the majority of studies relying on individual measures of socio-economic status e.g. by length or type of education, income or not considering the potential confounding effects of socio-economic status at all.

Overall, the findings of the thesis on the association between alcohol consumption and the fourteen cancers under investigation, both in terms of the conclusions of the review and the findings of the two cohort studies are supported by the findings of international systematic reviews, and meta- and pooled analyses. During the course of this thesis both IARC and WCRF/AICR updated their earlier reviews on alcohol and cancer, using an evidence base covering approximately forty years of published research (Baan et al 2007, WCRF/AICR 2007). Significantly, both these reviews concluded that the existing evidence was sufficient to consider alcohol a cause of both breast and colorectal cancer. These conclusions have important implications for both government policy and prevention strategies in the alcohol and cancer policy areas in Scotland and firmly place alcohol consumption as a significant risk factor for two cancers which are among the most common cancers in Scotland and which are projected to increase over the next twenty years (Stockton 2004).

8.2.1 Research and policy implications

On one level the assessment of alcohol as risk factor for breast and colorectal cancer is understandable, as even a small increase (relative risk of <1.5 for approximately 20 grams per day or 10-12% increase per 10 grams of alcohol) in risk of these very common cancers represents a very significant public health risk; in Scotland, for example, this would equate to alcohol consumption contributing to an additional 1000 incident cases of breast cancer and 500 incident cases of colorectal cancer in 2003 (Grant et al 2009). Yet on another level, the fact that the associations are small raises

the question of whether the observed increases in risk of breast and colorectal cancer could not be explained by bias and incomplete control of confounding factors (and a lack of control for unknown confounders) of the alcohol-cancer association. Evidence reviewed in the present study would suggest that these issues remain unresolved. Although many individual, and meta- and pooled studies, are rigorous in their attempts to control for confounders and interactions with other risk factors, the complexity of the 'web' of confounders (for example, weight, folate intake, other aspects of diet and nutrition, genes) of the alcohol and breast, and colorectal cancer associations makes this almost impossible to achieve in individual studies. This is even more difficult in combined studies because of differences in exposure measurement which may multiply the measurement bias inherent in individual studies. The presence of confounding in epidemiological studies still presents problems in interpreting the results of these studies. Fewell et al (2007), using simulation studies and logistic regression analyses to investigate the size of the apparent exposure-outcome association that can occur if the exposure has no causal effect on the outcome, concluded that the small effect sizes of the magnitude frequently reported in observational epidemiological studies of alcohol and breast, and colorectal cancer for example, can be generated by residual and/or unmeasured confounding alone.

The full spectrum of drinking behaviour has also not been extensively researched in the literature and it is possible further investigation of the full range of drinking behaviour may advance our understanding of the association between alcohol consumption and breast, and colorectal cancer. For example studies by Dal Maso et al (2008) and Kesse (2005) suggest that the effect of alcohol drunk with meals only, compared to drinking only between meals can modify the association between cancer and alcohol consumption; Thygesen et al (2008; 2009) has shown that the latency of cancer may modify the effect of alcohol consumption on breast and colorectal cancer.

Of perhaps more significance than the issue of confounding, in explaining the small associations reported for breast and colorectal cancer, is the potential impact of misclassification. This arises from the heterogeneity of alcohol consumption measures utilised in epidemiological studies; in particular, methods used to estimate typical beverage strength and beverage specific serving size, which not only makes comparisons across studies problematic, but also raise questions about the precision of risk estimates from meta-analyses which are derived from individual epidemiological studies. Greenfield and Kerr (2008) argue that the variation contributed by the 'ethanol [alcohol]' content of drinks however defined in a survey, may be of equal importance to all the other influences such as questionnaire type, reference periods, definition of reference groups and definitions of 'current' and lifetime drinking from the perspective of accuracy of consumption and drinking pattern measurement. Most surveys of alcohol consumption are phrased in terms of "drinks", meaning standard drinks of the respective country or area surveyed, yet the use of the 'standard drink' concept is complicated by different standards across countries and even within countries. In turn these differences will affect the precision and the statistical significance of risk estimates derived from meta-analyses of international

studies potentially producing positive associations where there are none or vice-versa. The issue of alcohol content/standard drinks not only presents a methodological challenge for epidemiological studies, but also presents some specific challenges for researchers and policy makers in Scotland (and the UK).

Against a background of rising levels of alcohol consumption up to end of the last century, alongside a rise in the incidence in Scotland of many cancers strongly linked to alcohol consumption, it is of no surprise that the findings of epidemiological studies are of great interest to researchers, policy makers and the media. Summary relative risks derived from individual and pooled epidemiological studies are now increasingly used to estimate the cancer burden attributable to alcohol consumption in Scotland (Grant et al 2009) and England and Wales (Jones et al 2008), with some moves towards routine monitoring of alcohol caused cancer burden underway in England and at a European wide level (Rehm and Scafato 2011). Nevertheless, as described above, these risk estimates are based on 'standard drinks' consumed, often converted to grams per day/week, but with different drink-gram equivalencies depending on a study's country of origin.

What makes this challenging and confusing for UK researchers and policy makers is that in the UK there is no 'standard drink' measure since the alcohol unit, which varies by drink type and serving size, is the mainstay measure used in population surveys, the majority of research and for public health messages on safe and excessive drinking levels. In addition, the UK standard unit measure is seen as being equivalent to 8 grams, lower than the gram equivalencies (range 12-26 g) of standard drinks in epidemiological studies, yet methods used to calculate the cancer burden in the UK assume the 'unit' and the 'standard drink' are comparable when they are not. In international studies, calculating the cancer burden attributable to alcohol consumption, the categorisation of alcohol is based on gram intake per day so, for example, men drinking between 0.25 and 39.99 grams per day are considered low level drinkers. However, if this category is converted into units using the 8 gram equivalency, the range would be 0.1 to 4.99 units per day. This exceeds the recommended safe daily drinking levels for men in the UK, of no more than 3 units per day, and which in no way could be considered as 'low levels of drinking'. The likely effect of this is that the current estimates of the cancer burden attributable to alcohol consumption in Scotland probably underestimate the true burden.

The uncertainty concerning the interpretation of 'standard drinks' in the epidemiological literature, on the association between alcohol consumption and cancer, may also explain the confusion and ambiguity in current government advice on alcohol consumption and cancer. In the current Scottish Government cancer strategy, 'Better Cancer Care, An Action Plan', drinking more than three units a day is highlighted as increasing the risk of cancer of the 'oral cavity, pharynx, larynx, oesophagus, breast and large bowel' (Scottish Government 2008). The threshold of 'three units' (e.g. equivalent to

24 grams in Scotland/UK or 2 medium sized (175ml) glasses of wine) is, however, misleading, and for a number of the cancers mentioned, not supported by the published literature or by the findings of the present thesis and may overestimate the levels of alcohol consumption at which the risk of cancer is increased. For example, it is well established in the international literature, that drinking one or more 'standard drinks' (equivalent to approximately 12-14 grams) increases the risk of oral, pharyngeal and laryngeal cancer. In the present study (Chapter 6), an increased risk of cancers of the upper aero digestive tract was also found in the Scottish general population, for those drinking approximately >2 units per day (equivalent to 16 grams per day, or 1 medium sized (175ml) glasses of wine). Equally the suggestion that drinking more than three units (24g) increases the risk of breast cancer, is also not consistent with the international evidence which shows an increased risk of breast cancer associated with drinking >15 g/d (approximately >2 'UK' units).

It is now over a hundred years since a link between alcohol and cancer was first postulated and despite the library of research that has built up over that time, it is still sobering to think that alcohol's role in cancer aetiology is still, for many cancers, clouded with uncertainty. That said there is still sufficient knowledge, and evidence, to enable a more precise message to be delivered, in Scotland, about the dangers of alcohol consumption in relation to the risk of certain cancers. With the incidence of many of the cancers associated with alcohol consumption increasing in Scotland (and which are expected to continue to do so, well into the next decade), combined with high levels of excessive drinking in the Scottish population, the link between alcohol consumption and cancer needs to be an integral component of public health policy making. Past and future policy developments offer some encouragement; McKee et al (2009) reported that one year after the implementation, in 2006, of smoke free policy in indoor public venues in Scotland, the heaviest drinking smokers (i.e. those most at risk of head and neck cancers) had reduced their alcohol consumption in pubs by about six drinks. Drinking behavior overall, and particularly among low to moderate drinkers, however, did not change significantly in Scotland compared with the rest of the United Kingdom. Although Mckee et al (2009) reported that overall drinking behaviour was not displaced from pubs to the home, no evidence was presented on possible displacement occurring for the heaviest drinking smokers. Purshouse et al (2010) also reported a small reduction in the prevalence of the cancer cases 10 years after the implementation of an alcohol minimum price per unit of £0.50 though as the authors acknowledged themselves an analysis of the supply-side response to pricing policies should be undertaken, because it is plausible that policies that have a large effect on beverage prices might lead to market restructuring, and supply-side responses are unlikely to be straightforward.

8.3 Recommendations

1. To establish a consensus on a minimum standard for the assessment and measurement of alcohol consumption in epidemiological studies. In particular, this should include a move towards an internationally agreed definition of alcohol measures what constitutes a standard drink. The recent launch of the European Commission's Alcohol Measures for Public Health Research Alliance (AMPHORA) offers some hope that a common set of standard definitions of alcohol measurement can be achieved.

2. Given that the magnitude of the association between alcohol consumption and breast and colorectal cancer risk appears to be relatively modest, resolution of the nature of the dose-response relationship may require further pooling of data particularly from prospective studies (though only if consensus can be reached regarding the definition of exposure categories). This would also assist with clarification of whether the association between alcohol consumption and breast and colorectal cancer risk is modified by other factors by increasing a study's power to adjust for measured confounders. Furthermore, to better understand the biological mechanisms involved, more studies on alcohol intake and studies on interactions between alcohol intake and other lifestyle factors, nutritional factors and genetic factors (e.g. alcohol dehydrogenase gene) with adjustment for potential confounding factors are needed.

3. To increase the evidence base in Scotland and the UK. There is currently only a small pool of epidemiological evidence of the alcohol–cancer association in Scotland and across the UK despite both high levels of alcohol consumption and incidence of many cancers linked to alcohol consumption. Further studies in Scotland and the UK are therefore required, with a large sample and a long follow-up to further explore associations between alcohol and related cancers particularly the effect of heavy drinking and variation by gender, ideally with repeated measures of alcohol intake and complete recording of confounding factors

4. Epidemiological studies of alcohol and cancer (and all disease) outcomes should consider the relationship between exposure and outcome more than simply in terms of volume of alcohol drunk. Analytical strategies should attempt where possible; to incorporate attempts to combine patterns and/or frequency of drinking with average volume consumed; and to stratify by gender where possible as opposed to simply adjusting results for gender differences - overall women drink far less than men and estimates of risk should be presented separately.

5. Researchers and policy makers in the UK need to consider the long term validity of the alcohol unit as a measure of alcohol consumption. At a minimum, consideration should be given to upgrading the unit equivalency in the UK to 10 or 12g. A precedent has already been established to facilitate this when conversion factors for converting amount consumed into units were updated by ONS to take

into account the increased strength of alcohol drinks over the last 20 years and the different drink sizes now available.

This would be a step towards providing some homogeneity of a standard measure at least in North American and European studies as well allowing researchers to estimate more accurately the cancer burden due to alcohol.

6. Government strategies and health promotion campaigns on 'alcohol' and 'cancer' need to deliver a more coherent and accurate message about the threshold at which alcohol consumption may increase the risk of cancer.

7. Develop specific health promotional material, for dissemination through the local framework of alcohol and drug partnerships (consisting of regional health boards, local authorities and alcohol and drug treatment services), in Scotland, which provide rapid access to holistic care from health and social care professionals for individuals who have alcohol problems and who are at high risk of developing severe health problems including many alcohol associated cancers.

8. Policy estimates of the cancer burden attributable to alcohol consumption need to be updated to take into account the current evidence and should take into account the variation in risk by tumour type (oesophageal squamous cell carcinoma and adenocarcinoma) and the threshold effect of alcohol consumption on an increased risk of liver and colorectal cancer.

8.4 Dissemination of study results

The results of the present thesis will be disseminated through conference presentations, workshops and journal papers. This will involve the following outputs:

1. Conference paper, *'Risk of cancer in an alcohol-related hospital admission cohort – a Scottish record linkage study'* presented at the 'Health, Culture and Scotland: new challenges, new opportunities, Annual Public Health Conference, 11 & 12 November 2010, Faculty of Public Health.

2. Journal papers to be written on;

a) The association between alcohol consumption and risk of UADT, colorectal, lung and prostate cancer in a representative sample of the Scottish population.
b) Cancer incidence in a cohort of people hospitalised for alcohol related problems in Scotland.
c) Alcohol and cancer – the effect of deprivation on the association between alcohol and cancer.
d) Review of alcohol measurement in epidemiological studies.

3. Findings from present study will be discussed in 'alcohol and cancer' seminar in December 2011, organised by Scottish Health Action on Alcohol Problems, for general practitioners, consultants and public health policy makers and researchers.

4. Oral and poster abstracts to be submitted to relevant conferences and seminars

8.5. Developing PhD research aims

Chapter 2 Literature review

- Review and appraise the units of alcohol measurement and the ethanol content of drinks and corresponding gram equivalencies used in papers included in systematic review
- Carry out meta-analysis of the association between alcohol and selected cancers where number and quality of papers allow

Chapter 6 Self-reported alcohol consumption and subsequent cancer risk in a sample of the Scottish population

- To analyse whether the association between alcohol and breast and colorectal cancer varies by drink type i.e. wine, beer and spirits
- To explore whether demographic differences between the 1995 and 1998 surveys and the 2003 survey will have an effect on the risk estimates reported
- As a result of the numerous tests for statistical significance undertaken consideration be given for correction for multiple testing by using the Bonferroni method

Chapter 7 Cancer risk in a Scottish alcohol related hospital cohort

- Patients with multiple alcohol related hospital admissions – do they have an even higher risk of alcohol-related cancers?
- Does the risk of an alcohol related cancer vary by type of alcohol admission i.e. alcohol abuse, alcohol dependence and alcohol psychoses?
- Investigate the development of an alcohol –cancer co-morbidity index to control for potential confounders of the alcohol-cancer association in the present study.

Appendix A: Search strategy terms

Full details of the search strategy, applied to each of the bibliographic databases, are listed below:

MEDLINE

1. exp alcohol drinking/ or exp drinking behaviour/ or exp alcoholism/ or exp alcoholic beverages/
2. alcohol consumption.tw.
3. 1 or 2
4. exp Pharyngeal Neoplasms/ or exp Laryngeal Neoplasms/ or exp Colonic Neoplasms/ or exp Stomach Neoplasms/ or exp Rectal Neoplasms/ or exp Colorectal Neoplasms/ or exp Esophageal (and oesophageal) Neoplasms/ or exp Liver Neoplasms/ or exp Mouth Neoplasms/ or exp Breast Neoplasms/ or exp Pancreatic Neoplasms/ or exp Bladder Neoplasms/ or exp Kidney Neoplasms/ or exp Prostrate Neoplasms/ or exp Ovarian Neoplasms/ or exp Endometrial Neoplasms/
5. (carcinoma or cancer or tumour or tumor or malignan$).tw.
6. (laryn$ or pharyn$ or colorec$ or colon$ or stomach or liver or mouth or oesophag$ or esophag$ or rectal or breast or pancreas or hepatic or oral or gastric or hepatic or ovary or ovarian or kidney or bladder or prostrate or endrometrial or endometrium).tw.
7. 4 or (5 and 6)
8. 3 and 7
9. limit 8 to humans
10. limit 9 to yr="1999-2009"

EMBASE

1. exp Drinking Behavior/ or exp ALCOHOLISM/ or exp Alcohol Abuse/ or exp Alcohol Consumption/ or exp alcoholic beverages/
2. alcohol consumption.tw.
3. 1 or 2
4. exp PANCREAS CANCER/ or exp BREAST CANCER/ or exp MOUTH CANCER/ or exp LIVER CANCER/ or exp ESOPHAGUS (and oesophageal)CANCER/ or exp COLORECTAL CANCER/ or exp RECTUM CANCER/ or exp STOMACH CANCER/ or exp COLON CANCER/ or exp PHARYNX CANCER/ or exp LARYNX CANCER/ or exp OVARY CANCER/ or exp BLADDER CANCER/ or exp KIDNEY CANCER/ or exp ENDOMETRIUM CANCER/ or exp PROSTATE CANCER/
5. (carcinoma or cancer or tumour or tumor or malignan$).tw.
6. (laryn$ or pharyn$ or colorec$ or colon$ or stomach or liver or mouth or oesophag$ or esophag$ or rectal or breast or pancreas or hepatic or oral or gastric or ovary or ovarian or bladder or kidney or edometrium or endometrial or prostate).tw.
7. 4 or (5 and 6)
8. 3 and 7
9. limit 8 to humans
10. limit 9 to yr="1999 - 2009"

CINAHL

1. exp Alcohol Drinking/ or exp Drinking Behavior/ or exp ALCOHOLISM/ or exp Alcohol Abuse/ or exp alcoholic beverages/
2. alcohol consumption.tw.
3. 1 or 2
4. exp Pharyngeal Neoplasms/ or exp Laryngeal Neoplasms/ or exp Colonic Neoplasms/ or exp Stomach Neoplasms/ or exp Rectal Neoplasms/ or exp Colorectal Neoplasms/ or exp Esophageal (and oesophageal) Neoplasms/ or exp Liver Neoplasms/ or exp Mouth Neoplasms/ or exp Breast Neoplasms/ or exp Pancreatic Neoplasms/ or exp Bladder

Neoplasms/ or exp Kidney Neoplasms/ or exp Prostrate Neoplasms/ or exp Ovarian Neoplasms/ or exp Endometrial Neoplasms/
5. (carcinoma or cancer or tumour or tumor or malignan$).tw.
6. (laryn$ or pharyn$ or colorec$ or colon$ or stomach or liver or mouth or oesophag$ or esophag$ or rectal or breast or pancreas or hepatic or oral or gastric or hepatic).tw.
7. 4 or (5 and 6)
8. 3 and 7
9. alcohol.tw.
10. 1 or 9
11. 10 and 7
12. limit 11 to yr="1999 - 2009"

PsycINFO

1. exp alcohol abuse/ or exp alcohol drinking attitudes/ or exp alcohol drinking patterns/ or exp alcohol intoxication/ or exp alcoholic beverages/
2. alcohol consumption.tw.
3. 1 or 2
4. exp NEOPLASMS/
5. (carcinoma or cancer or tumour or tumor or malignan$).tw.
6. (laryn$ or pharyn$ or colorec$ or colon$ or stomach or liver or mouth or oesophag$ or esophag$ or rectal or breast or pancreas or hepatic or oral or gastric or ovary or ovarian or prostate or bladder or kidney or endometrial or endometrium).tw.
7. 4 or (5 and 6)
8. 3 and 7
9. alcohol.tw.
10. 1 or 9
11. 10 and 7
12. limit 12 to yr="1999 - 2009"

Appendix B: Newcastle - Ottawa quality assessment scale

Cohort and cross-sectional studies
Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average adult population in the community □
   b) somewhat representative of the average adult population in the community □
   c) selected group of users e.g. nurses, doctors, teachers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort □
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) structured questionnaire administered by trained interviewer□
   b) self completed questionnaire□
   c) other
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes □
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor*) e.g. smoking, body mass index, vegetable and fruit consumption*□
   b) study controls for any additional factors - please list □

Outcome

1) Assessment of outcome
   a) secure record (histological confirmation)□
   b) record linkage □
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) □
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for □
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > 80 % follow up, or description provided of those lost) □
   c) follow up rate < 80% and no description of those lost

d) no statement

Case Control Studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation □
   b) yes, e.g. record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases □
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls □
   b) hospital or clinic controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) □
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) *) e.g. smoking, body mass index, vegetable and fruit consumption* □
   b) study controls for any additional factors - please list□

Exposure

1) Ascertainment of exposure
   a) structured interview where blind to case/control status □
   b) self administered questionnaire □
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes □
   b) no

3) Non-Response rate
   a) same rate for both groups □
   b) non respondents described
   c) rate different and no designation

Study quality

Please score the appropriate Newcastle-Ottawa form, referring to the manual, and enter the number of stars for each section in the box below:-

	SELECTION	COMPARABILITY	EXPOSURE	OUTCOME
CASE CONTROL				
COHORT				

Study findings

Crude (and stratified) effect sizes with CIs/SEs *(use a table if possible and continue in Notes if you need more space)*

List factors adjusted for in the design and/or analysis and state method used for adjustment e.g. stratification, statistical modelling.

(If more than one adjustment – report the effect which is adjusted for the most confounders)

Notes:-

Appendix C: References included in literature review

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Appendix D, Descriptive tables

Descriptive tables for bladder cancer: cohort studies

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Allen 2009 **Country:**United Kingdom **Study aims:** to describe the relationship of low to moderate levels of alcohol intake, with subsequent risk of cancer, overall and at particular sites, in a large cohort of women **Source of funding:** Cancer Research UK, UK Medical Research Council,	**Population:** *Source:* middle-aged women who attended breast cancer screening clinics in the United Kingdom completed between 1996 and 2001 *Exclusion criteria*:none specified *Study pop*: 1 280 296 women, average age of 55 yrs **Observation time:** From 1996-2001 to 31 December 2006, followed up for cancer incidence over 9.2 millionperson-years, for an average of 7.2 years per woman 928 incident cases of bladder cancer	**Exposure:** *Questionnaire:* no details provided *Repeated during follow-up:* Yes, three years after baseline interview *Reference period:* n/s *Drink type:* wine (red and white specified), beer, and spirits **Measure:** drinks per week; **Reference group**: drinking less than 2 drinks per week (n=258) **Results:** *ca* Non-drinkers 271 1.06 (0.94 - 1.21) 3-6 206 1.05 (0.92- 1.21) 7-14 151 0.91 (0.77 - 1.07) ≥15 42 0.96 (0.63 - 1.17) *p*trend =0.2

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Djoussé 2004 **Country:** USA **Study aims:** to evaluate whether total and beverage specific alcohol consumption are associated with an increased risk of bladder cancer in the Framingham Heart Study (FHS) **Source of funding:** n/s	**Population:** *Source:* Cohort started in 1948 in Framingham, Massachusetts. Original cohort included 5209 participants. In 1971, children of original cohort and their spouses formed the Offspring study (n=5124) *Exclusion criteria:*missing alcohol consumption data and prevalent cases of bladder cancer *Study pop*: =9821 **Observation time:** From baselines (1948 and 1971), mean follow up 27.3 +/-10.1yrs. Loss to follow up: n/s; 126 incident cases	**Exposure:** *Questionnaire:* no details provided *Repeated during follow-up*: every 4 years from both cohorts *Reference period:*usual consumption in previous month *Drink type:* beer, wine spirits and cocktails **Measure:**grams per day, **Reference group**: Non drinkers (0 g/day), n=14 **Results:** *ca* 0.1-6.0 43 0.9 (0.5-1.8) 6.1-12 21 0.9 (0.4-1.9) 12.1-24.0 14 0.6 (0.3-1.3) 24.1-48.0 22 0.9 (0.5-1.9) >48 8 0.5 (0.2-1.2) *p*trend=0.3 *Beer* *Wine* *Spirits* <1d/w 0.6 (0.3-1.2) 0.9 (0.5-1.6) 1.0 (0.5-2.0) 1-4d/w 0.7 (0.4-1.3) 0.6 (0.3-1.2) 1.4 (0.7-2.9) >4d/w 0.5 (0.2-0.8) 0.8 (0.3-1.7) 1.6 (0.9-3.1) *p*trend= 0.03 0.7 0.2

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Zeegers 2001 **Country:** Netherlands **Study aims:** to explore the influence of quantity and types of alcohol beverages consumed on risk of bladder cancer' **Source of funding:** Dutch Cancer Society	**Population:** *Source:* from 204 municipal population registries throughout Netherlands, cohort includes 58,279 men and 62,573 women who were aged 55-69 yrs at baseline (1986) *Exclusion criteria:*prevalent bladder cancer cases *Study pop*: A sub cohort of 3,500 subjects was randomly sampled from the cohort after baseline exposure measurement and used in analysis **Observation time:** from baseline (1986), analysis was restricted to 6.3 years of follow-up Loss to follow up: <5% 594 incident cases (517 men and 77 women)	**Exposure:** *Questionnaire:* Self-administered questionnaire with food-frequency section *Repeated during follow-up*: baseline only *Reference period:* during the year before the study. *Drink type:* beer, wine spirits **Measure:**grams per day; **Reference group**: non drinkers (less than once a month), n=62 (men), 25 (women) **Results:** *ca* *Males* *ca* *Females* <5 108 1.49 (1.00-2.21) 29 0.97 (0.56-1.69) 5--<15 136 1.52 (1.04-2.21) 33 0.75 (0.41-1.37) 15->30 109 1.16 (0.78-1.71) ≥30 102 1.63 (1.08-2.47) *p*trend = 0.13 alcohol increment for 10g/day - 1.04-0.98,1.10 (men), 0.85 0.60, 1.20 (women) *Beer* *Wine* *Spirits* <5 1.35 (0.94-1.95) 1.54 (1.06-2.23) 1.44 (0.98-2.11) 5--<15 1.44 (0.95-2.18) 1.23 (0.80-1.90) 1.38 (0.92-2.08) 15->30 1.70 (0.90-3.23) 1.14 (0.65-2.00) 1.25 (0.81-21.91) ≥30 1.09 (0.46-2.57) 1.73 (0.74-4.05) 1.94 (1.17-3.22)

Descriptive tables for bladder cancer: case control studies

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Benedetti 2009 **Country:** Canada **Study aims:** 'to investigate the association between lifetime consumption of alcoholic beverages and cancer risk' **Source of funding:** n/s	**Population:** *Cases:* were males living in Montreal area with histologically confirmed cancer at 20 different sites newly diagnosed at any Montreal-area hospital N= 425 bladder cancer cases, aged 35-70yrs *Controls:* randomly selected from electoral lists N= 507 controls, aged 35-70yrs ***Exclusion criteria:*** *patients with any other cancers* ***Observation time:*** *between January 2001 and January 2006* *Response rate: n/s*	**Exposure:** *Questionnaire:* food frequency questionnaire, *(no other details provided)* *Interviewers blinded*: n/s *Reference period:* any period when alcohol drunk at least once a week or nearly every day *Drink type:* beer, wine and spirits **Measure:** drinks per week; **Reference group**: never weekly drinkers (Total alcohol n=78 cases) **Results:** *ca* *Total alcohol* *ca* *Beer* 1-6 weekly 138 1.14 (0.78-1.66) 129 0.91 (0.66-1.49) 7+ weekly 209 1.10 (0.77-1.56) 40 0.98 (0.70-1.37) *ca* *Wine* *Spirits* 1-6 weekly 149 1.38 (1.02-1.86) 163 1.09 (0.82-1.46) 7+ weekly 60 0.91 (0.59-1.36) 74 1.12 (0.76-1.65)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Demirel 2008 **Country:** Turkey **Study aims:** 'To analyse the effect of Turkish coffee and black tea consumption, alcohol intake and smoking on bladder cancer' **Source of funding:** n/s	**Population:** *Cases:* were patients treated in the Second Urology Clinic of Ankara Diskapi Training Hospital N= 164 cases (median age 63), *Controls:* selected sequentially from patients without bladder tumours and hematuria of unknown aetiology attending the same hospital. N= 324 controls, aged 25 to 79 years (median age 60) **Exclusion criteria:** patients with any other cancers **Observation time:** between January 2001 and January 2006 Response rate: n/s	**Exposure:** *Questionnaire:* face-to-face interviews, *(no other details provided)* *Interviewers blinded*: n/s *Reference period:* n/s *Drink type:* Turkish raki **Measure:** drinking status (yes/no); **Reference group**: never drinker (n=124/176) **Results:** *ca/co* yes 40/48 1.85 (1.15-2.96)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Jiang 2007 **Country:** USA **Study aims:** To investigate the relationship between alcohol consumption and bladder cancer, and the potential interaction between alcohol consumption and other exposures. **Source of funding:** National Cancer Institute & National Instituteof Environmental Health Sciences	**Population:** *Cases:* identified through the Los Angeles County Cancer Surveillance Program (SEER registry) and diagnosed between January 1, 1987 and April 30, 1996 N= 1,586 *Controls:* matched neighbourhood controls N= 1,586 *Exclusion criteria:*n/s **Observation time:** between January 1, 1987 and 1999 Response rate: cases 83% controls 69%	**Exposure:** *Questionnaire:* In-person, structured interviews *Interviewers blinded*: n/s *Reference period:* within the previous two years. *Drink type:* beer, wine, and hard liquor **Measure:**drinks/day, duration and age at first use; **Reference group**: 0 drinks per day and never drinkers for age at first use (n=432) **Results:** *d/d ca/co Total alcohol* *Duration (yrs)* <1. 364/385 0.85 (0.68-1.06) 1-20 311/303 0.83 (0.65-1.05) 1–4 512/505 0.77 (0.62-0.96) 21-30 275/292 0.72 (0.56-0.92) >4 265/234 0.68 (0.52-0.90) 31-40 376/338 0.87 (0.68-1.10) *p*trend0.003 41+ 188/199 0.66 (0.48-0.89) *p*trend 0.017 *Beer* *Wine* *Spirits* <1 d/d 0.81 (0.61-1.07) 0.84 (0.64-1.09) 1.18 (0.90-1.55) 1–4 0.68 (0.49-0.95) 0.65 (0.44-0.95) 1.01 (0.72-1.41) >4 0.54 (0.35-0.83) 0.91 (0.41-2.02) 1.01 (0.63-1.62)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Pelucchi 2002 **Country:** Italy **Study aims:** 'investigating any potential relation between alcohol drinking and bladder cancer risk' **Source of funding:** Italian Association for Research on Cancer	**Population:** *Cases:* recruited from the National Cancer Institute and major general hospitals and university clinics in Northern Italy N= 727 cases (617 males, 110 females), (median age 63), *Controls:* as per cases 1,067 controls (769 males, 298 females), aged 25 to 79 years (median age 60) **Exclusion criteria:**admitted to hospital for chronic conditions, associated with smoking and alcohol drinking and alcohol-related traumas **Observation time:** between 1985 and 1992 Response rate: >98% for cases and controls.	**Exposure:** *Questionnaire:* Structured questionnaire administered by trained interviewer *Interviewers blinded*: n/s *Reference period:*n/s *Drink type:* wine, beer, and spirits **Measure:** drinks/day, drinking duration' **Reference group**: non-drinkers, all and drinking duration(n=117/152), non-drinkers, wine (n=126/172) **Results:** d/d *ca/co* *Total alcohol* *years* *Duration of alcohol drinking* <3 207/329 0.80 (0.57-1.11) 1–24 65/157 0.68 (0.45-1.05) 3 to <6 175/261 0.90 (0.54-1.10) 25–39 199/400 0.73 (0.51-1.02) ≥6 217/304 0.77 (0.58-1.22) ≥40 342/351 1.00 (0.71-1.41) *p*trend=0.52 *p*trend =0.67 *d/d* *Wine* <3 0.90 (0.66-1.25) 3 to 5 0.78 (0.55-1.11) >5 0.86 (0.60-1.23) *p*trend=0.37

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Pohlabeln 1999 **Country:** Germany **Study aims:** 'to analyse the relation between occupation, lifestyle and risk of bladder cancer in Germany **Source of funding:** Bundesanstalt fur Abreitschutzn	**Population:** *Cases:* drawn from four hospitals in Hessen (State of the Federal Republic of Germany) N=300 cases *Controls:* as per cases N=209 controls **Exclusion criteria:**patients with neoplastic conditions **Observation time:** between 1989-1992 Response rate: 93% for cases and 98% for controls	**Exposure:** *Questionnaire:* Standardised questionnaire by trained interviewer *Interviewers blinded*: n/s *Reference period:*10 to 15 years prior to survey baseline *Drink type:* beer wine and other beverages*(n/s)* **Measure:** grams per day; **Reference group**: no daily alcohol intake (n=102/117) **Results:** *ca/co* 1-20 74/67 1.10 (0.70-1.73) 21-40 35/40 0.83 (0.46-1.47) >41 21/15 1.71 (0.78-3.73)

Descriptive tables for breast cancer: cohort studies

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Baglietto 2005 **Country:** Australia **Study aims:** to evaluate the effect of dietary folate intake on the relation between alcohol consumption and breast cancer risk **Source of funding:** None specified	**Population:** *Source:* Melbourne collaborative cohort study of 41 528 people (24 479 women) aged between 40-69yrs at baseline. Participants recruited through electoral rolls, advertisements, and community announcements *Exclusion criteria:* diagnosis before baseline of invasive breast cancer, angina, heart attack, or diabetes, missing data on alcohol intake and dietary factors *Study pop*: 17 447 women born in Australia, New Zealand, or the UK Kingdom **Observation time:** 1990-1994, to 31 December 2003, average of 10.1 follow up years, LFU 6%, 537 cases of invasive breast cancer	**Exposure:** *Questionnaire:* structured interview *Repeated during follow-up*: baseline *Reference period:* in the previous week *Drink type:* n/s *Quest validated:* n/s **Measure:** grams per day, **Reference group**: Abstainers **Results:** *cases* Ex-drinkers 16 1.03 (0.62 to 1.73) 1-19 g/day 286 1.12 (0.93 to 1.36) 20-39 g/day 43 0.87 (0.62 to 1.22) ≥40 g/day 21 1.41 (0.90 to 2.23)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Chlebowski 2007 **Country:** USA **Study aims:** to evaluate performance of Breast Cancer Risk Assessment Tool for estimating invasive breast cancer risk by receptor status in postmenopausal women. **Source of funding:** National Heart,Lung and Blood Institute, NIH	**Population:** *Source:* women recruited at 40 clinical centres in US through direct mailings Postmenopausal women, 50-79 yrs, unlikely to move or die within 3 yrs, were eligible.. *Exclusion criteria:*women with previous invasive breast cancer, previous non-invasive breast cancer, previous mastectomy, or less than 5 years follow-up *Study pop*: 147, 916 **Observation time:** 3236 developed invasive breast cancer within 5years	**Exposure:** *Questionnaire:* interviewer-administered questionnaire *Repeated during follow-up*: n/s *Reference period:* n/s *Drink type:* n/s *Quest validated:* n/s **Measure:** drinks per day, **Reference group**: <1 drink per day (cases = 127,608) **Results:** *ER-positive* >1 359 1.17 (1.02-1.33) *ER-negative* >1 50 1.06 (0.75-1.49)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Chen 2002 **Country:** USA **Study aims:** To examine the relation between concurrent use of alcohol and postmenopausal hormones and invasive breast cancer. **Source of funding:** National Institutes of Health	**Population:** *Source:* from Nurses' Health Study cohort (established in 1976, when 121 700 female registered nurses 30 to 55 years of age completed a baseline questionnaire) *Exclusion criteria:*Women who left 10 or more food items blank (4%), implausibly high or low scores for total food intake (2.7%), diagnosis of cancer (except non-melanoma skin cancer) before 1980 *Study pop*: Postmenopausal women (n= 44,186, aged 54-56yrs) **Observation time:** 1980-1986 , 557 984 person-years of follow-up, 1722 cases of invasive breast cancer identified; LFU = 5%	**Exposure:** *Questionnaire:*semi-quantitative FFQ *Repeated during follow-up* Baseline questionnaire 1980, then updated with responses from 1984, 1986, and 1990 questionnaires *Reference period:* within last 12 months prior to survey. *Drink type:* yes *Quest validated:* n/s **Measure:** grams per day, **Reference group**: none (0 g/d) **Results:** *g/d* *ca* 0.1-4.9 538 1 07 (0.95-1.20) 5.0-9.9 166 0 99 (0.83-1 18) 10-19.9 257 1 22 (1.06-1.42) ≥20.0 167 1.33 (1.12-1 58)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Dumeaux 2004 **Country:** Norway **Study aims:** To examine how oral contraceptive use or oestrogen dose from oral contraceptives interact with alcohol on breast cancer risk **Source of funding:** None specified	**Population:** *Source:* Between January 1991 and January 1997, 179,388 women from general population of Norway, 30-70 yrs, sampled according to birth year from the national population register102,443 included in study (response rate 57.1%) *Exclusion criteria:*prevalent cancer; women recruited in 1997 (n = 5,933) because questionnaire did not ask for alcohol intake; ever users of oral contraceptives for whom duration of use was not stated *Study pop*: After exclusions, cohort = 86,948 **Observation time:** between 1991 and 2001; 618,638 person-years of follow-up, LFU, n/s; 1,130 cases of breast cancer	**Exposure:** *Questionnaire:* Self–completed questionnaire (91-92) *Repeated during follow-up*: baseline only, *Reference period:* over the preceding year. *Drink type:* beer, wine, and spirits *Quest validated:* **Measure:** grams per day, **Reference group**: none (0g/d) **Results:** *ca* 0.1-4.9 554 1.24 (1.06-1.44) 5.0-9.9 188 1.35 (1.11-1.64) ≥10.0 96 1.69 (1.32-2.15) *p*trend<0.0001

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Feigelson 2001 **Country:**USA **Study aims:** To investigate the hypothesis that alcohol consumption increases the risk of breast cancer mortality. **Source of funding:** None specified	**Population:** *Source:* selected from the 676,306 female participants of CPS-II, a prospective mortality study in all 50 States, the District of Columbia, and Puerto Rico *Study pop*: includes 242,010 women **Exclusion criteria:** missing or poorly quantified alcohol consumption data (n=369,326); women reporting a history of cancer (other than non-melanoma skin cancer) (n=57,107); women reporting a history of cirrhosis (n=314); former drinkers (n=7,549). **Observation time:** 1982 through 31 December 1996 After 14 years of follow-up, 1,442 eligible breast cancer deaths were observed	**Exposure:** *Questionnaire:* self-administered questionnaire *Repeated during follow-up*: baseline *Reference period:*in the past 10 years *Drink type:*Beer, wine, and liquor **Measure:** drinks per day, **Reference group**: none (0 d/d) **Results:** *Ca* *All* *ca* *Premenopausal* *ca* *Postmenopausal* <0.25 132 1.1 (0.88-1.3) 40 0.94 (0.66-1.3) 92 1.1 (0.89-1.4) 0.26-<1 273 1.2 (1.0 -1.4) 70 0.99 (0.74 -1.3) 203 1.3 (1.1 -1.6) 1-<2 177 1.3 (1.1-1.6) 42 1.1 (0.75-1.5) 135 1.4 (1.2-1.7) 2-<3 162 1.4 (1.2-1.7) 37 1.2 (0.82-1.7) 125 1.5 (1.2-1.9 3+ 130 1.2 (1.0-1.5) 34 1.1 (0.74-1.6) 96 1.3 (1.0-1.6) *p*trend 0.08 0.37 0.16

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Feigelson 2003 **Country:** USA **Study aims:** to evaluate a possible interaction between folate and alcohol on incident breast cancer **Source of funding:** None specified	**Population:** *Source:* selected from 97,787 female participants in the CPS-II Nutrition Cohort, a prospective study of cancer incidence and mortality among United States men and women established in 1992, *Exclusion criteria:* women with prevalent cancer (except non-melanoma skin cancer) at baseline (n=11,601); women with cirrhosis (n=36); women with unknown menopausal status (n=604) or who were not postmenopausal (n =4,247); daily energy intake outside range of 550-3500 kcal/day or missing ≥15% of dietary questions; missing alcohol data. *Study pop:* After exclusions cohort = 66,561 **Observation time:** 1992 to 31 August 1997, lost to follow-up (n=7,592), 1,303 incident breast cancer cases	**Exposure:** *Questionnaire:* Mailed questionnaire. A follow-up questionnaire mailed between September 1997 and August 1998 (response rate >90%). a semi-quantitative 68-item FFQ, *Repeated during follow-up:* baseline *Reference period:* in the past 10 years *Drink type:* Beer, wine, and liquor **Measure:** grams per day, **Reference group:** none (0d/d n=598) **Results:** *ca* 0.1 to <5 353 1.00 (0.88–1.15) 5 to <10 109 0.94 (0.77–1.16) 10 to <15 109 1.18 (0.96–1.46) ≥15 134 1.26 (1.04–1.53). *p*trend0.01

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Garland 1999 **Country:** USA **Study aims:** To examine alcohol consumption in various time periods in relation to breast cancer risk in a large cohort of mostly premenopausal women. **Source of funding:** National Institutes of Health	**Design**: prospective cohort **Population:** *Source:* Female registered nurses (Nurses' Health Study II) who were 25-42 years old and living in one of 14 states in the United States when they responded to a baseline questionnaire in 1989. *Exclusion criteria:* Women who reported cancer at enrolment (with the exception of non-melanoma skin cancer, hydatidiform mole, or cervical cancer/dysplasia) *Study pop*: After exclusions cohort of 116,671 women **Observation time:** 619,691 person-years of follow-up between 1989 and 1995, LFU n/s; 445 cases of invasive breast	**Exposure:** *Questionnaire:* baseline questionnaire, participants asked about alcohol consumption during 5 different periods: from 15 to 17 yrs of age, from 18 to 22 yrs of age, from 23 to 30 yrs of age, from 31 to 40 yrs of age, and during the previous year. *Repeated during follow-up*: baseline and three follow-up questionnaires (1991, 1993, and 1995), response rate among participants was >90%. *Reference period:*over the previous year *Drink type:* beer, wine, and liquor *Quest validated:* n/s **Measure:** grams per day (in last year) and drinks per week (average lifetime), **Reference group**: none (0g/d) **Results:** *In the last year* >0–1.5 68 0.99 (0.74–1.31) >1.5–5 79 0.81 (0.62–1.06) >5–10 45 1.08 (0.77–1.50) >10–20 34 1.20 (0.83–1.74) >20 12 1.30 (0.73–2.34) *pt*rend =0.85 *Average lifetime alcohol consumption* <1 125 0.82 (0.61–1.10) 1–<1.5 46 1.01 (0.69–1.47) 1.5–<4.5 136 1.02 (0.76–1.38) 4.5–<6.5 28 1.03 (0.66–1.60) 6.5–<10.0 18 1.01 (0.60–1.71) ≥10 15 1.20 (0.68–2.11) *pt*rend =0.18

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Horn-Ross 2004 **Country:** USA **Study aims:** to evaluate the effects of patterns of alcohol use (including age at drinking and ''sporadic'' versus ''daily'' drinking) on invasive breast cancer risk **Source of funding:** National Cancer Institute	**Population:** *Source:* California Teachers Study cohort, established in 1995-1996 when 133,479 active and retired female teachers and administrators participating in the California State Teachers Retirement System returned questionnaire *Exclusion criteria:*not residing in California at baseline (n=8,866); having been diagnosed (incl. past history) with breast cancer before baseline questionnaire, (n=6,267); aged 85 or older at baseline (n=1,994);missing or unreliable alcohol consumption data (n=12 892) *Study pop*: After exclusions 103,460 women included in analysis **Observation time:** 1995–1996 to December 31, 2000; LFU, n/s; 1,742 diagnosed with invasive breast cancer	**Exposure:** *Questionnaire:* mailed questionnaire *Repeated during follow-up*: baseline only *Reference period:* assessed for three time periods: age 18-22 yrs, 30-35 yrs, and previous year *Drink type:* beer wine, champagne wine cooler cocktail *Quest validated: n/s* **Measure:** grams per day, **Reference group**: non-drinkers **Results:** *Previous year* *pre/perimenopausal* / *Age 30– 35* / *Age 18– 22* <5 53 0.93 0.66-1.30 / 47 0.98 0.67-1.43 / 54 0.97 0.70-1.34 5-9 55 1.05 0.75-1.47 / 67 1.27 0.90-1.79 / 59 1.12 0.81-1.53 10-14 42 1.09 0.75-1.57 / 43 1.23 0.84-1.82 / 39 1.10 0.76-1.60 15-19 27 1.28 0.83-1.97 / 21 1.15 0.70-1.89 / 9 0.72 0.37-1.43 ≥20 23 1.21 0.76-1.92 / 17 0.91 0.53-1.57 / 12 0.62 0.34–1.13 *Lifetime* *pre/perimenopausal* / *Age 30– 35* / *Age 18– 22* *g/d ca* <5 181 1.03 0.86-1.24 / 196 1.22 1.01-1.47 / 171 1.03 0.86-1.23

Study and Aims	Study and sample characteristics	Exposure measurement and main results
		5-9 150 1.04 0.86-1.27 177 1.04 0.84-1.26 104 0.85 0.68-1.05 10-14 126 1.08 0.88-1.33 130 1.28 1.03-1.59 82 1.17 0.92–1.48 15-19 82 0.91 0.71-1.16 75 1.17 0.90-1.51 25 1.01 0.68-1.52 ≥20 123 1.32 1.06-1.63 79 1.20 0.93-1.55 27 1.07 0.72-1.58 *Patterns (referent group: non-drinkers*) ''Sporadic'' 282 0.99 0.84-1.17 ''Daily'' <20 g/day 116 1.07 0.86-1.32 ''Daily'' ≥20 g/day 110 1.34 1.07-1.67

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Jain 2000 **Country:** Canada **Study aims:** To evaluate the impact of alcohol on mortality from breast cancer **Source of funding:** Medical Research Council of Canada	**Population:** *Source:* Eligible population were women participating in controlled trial of (primarily) mammographic screening for breast cancer in women 40-59yrs in Canada between 1980 and 1985 (n= 89,835) *Exclusion criteria:*dietary questionnaires not available; extreme values for energy intake *Study pop*: 58,926 women returned lifestyle **Observation time:** Between 1980 and 1985 to 31 December, 1993, LFU n/s. 241 deaths from breast cancer identified.	**Exposure:** *Questionnaire:* self-administered quantitative FFQ *Repeated during follow-up*: baseline only *Reference period:*in one month period prior to completion of questionnaire *Drink type:*beer, wine, and spirits **Measure:** grams per day, **Reference group**: 0g/day **Results:** *ca* >0-≤10 113 1.008 (0.986-1.032) >10-≤20 35 1.039 (1.009-1.071) >20 26 1.063 (1.029-1.098) ptrend <0.0001 per10g/unit; 223, 1.012 (1.005-1.019)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Kuper 2000 **Country:** Sweden **Study aims:** To investigate the risk of breast cancer among female patients with a discharge diagnosis of alcoholism, **Source of funding:** Swedish Cancer Society	**Population:** All in-patients (n=196,803) with a discharge diagnosis of alcoholism admitted to all Swedish hospitals between 1965 and 1994. After exclusions final cohort size = 182,667 patients and of these 36,856 were women, mean age at index hospitalisation was 42.7 years, **Exclusion criteria:** (1) erroneous or incomplete national registration numbers; (2) inconsistencies uncovered during record linkage; (3) patients who died during the index hospitalisation; (4) of patients with prevalent cancers at entry. **Observation time:** mean follow up 9.6 yrs, 353,596 years at risk'; no loss to follow up; 514 incident cases	**Exposure:** consumption defined by specified ICD-7,8,9 codes (ICD-7=307, 322; ICD-8=291, 303; ICD-9=291, 303, 305A), into category 'alcoholism' **Measure:** Standardised Incidence, **Reference group**: 0g/day **Results:** *Years of follow-up* 1–30 514 1.15 1.05-1.25 < 1 40 1.09 0.78-1.49 1–9 331 1.21 1.08-1.35 ≥10 183 1.06 0.91-1.22 *Age at follow-up (years)* <50 143 1.11 0.93-1.30 50–59 153 1.16 0.98-1.36 60–69 129 1.14 0.95-1.35 >70 89 1.24 0.99-1.52

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Lew 2009 **Country:** USA **Study aims:** To examine among postmenopausal women whether alcohol was associated with the risk of breast cancer defined by tumour characteristics and whether the association of alcohol with breast cancer was modified by folate intake, body mass index, and MHT use. **Source of funding:** National Institutes of Health	**Population:** *Source:* 50-71 yrs and residing in 1 of 6 states (California, Florida, Louisiana, New Jersey, North Carolina, Pennsylvania) or 2 metropolitan areas (Atlanta, or Detroit). 617,119 returned baseline questionnaire *Exclusion criteria:*did not answer substantial portions of the questionnaire, had more than 10 recording errors or reported consuming less than 10 foods; cancer, other than non-melanoma skin cancer, at baseline; were premenopausal or of uncertain menopausal status *Study pop*: 184,418 post-menopausal women **Observation time:** 1995–2003; LFU: n/s; 5,461 breast cancer cases (3,531 ductal, 550 lobular, 424ductal-lobular, 956 other tumours)	**Exposure:** *Questionnaire:* self-administered 124-item FFQ *Repeated during follow-up*: *Reference period:*over the past year *Drink type:* beer, liquor or mixed drinks wine or wine coolers **Measure:** grams per day, **Reference group**: 0 grams per day (n=1493) **Results:** *All* / *ER+/PR+* / *ER+/Pr-* >0-5: 531, 1.04 (0.97, 1.10) / 759, 1.07 (0.95, 1.21) / 15, 1.08 (0.83, 1.42) >5-10: 395, 1.04 (0.93, 1.16) / 131, 1.13 (0.93, 1.38) / 27, 1.15 (0.74, 1.78) >10-20: 550, 1.13 (1.02, 1.25) / 65, 1.07 (0.89, 1.29) / 45, 1.39 (0.96, 2.02) >20-35: 265, 1.23 (1.08, 1.41) / 89, 1.34 (1.06, 1.69) / 28, 1.13 (0.73, 1.77) >35: 227, 1.35 (1.17, 1.56) / 67, 1.46 (1.12, 1.91) *p*trend: <0.001 / 0.003 / 0.51

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Lin 2005 **Country:** Japan **Study aims:** To evaluate the association between alcohol consumption and breast cancer risk **Source of funding:** Ministry of Education, Culture, Sports, Science andTechnology of Japan	**Population:** *Source:* Original cohort included 110,792 people (46,465 men, 64,327 women) aged 40-79 years, enrolled from 45 areas throughout Japan, analysis included 38,600 women whose incident data were available from 24 areas where cancer registry systems existed *Exclusion criteria:*previous diagnosis of breast cancer (165); women who gave no information on drinking status (2,591) *Study pop*: = 35,844 **Observation time:** Average follow-up of 7.6 years, 271,412 person-years of follow-up, LFU = <3%; 151 cases of breast cancer	**Exposure:** *Questionnaire:* self-administered questionnaire *Repeated during follow-up*: baseline only *Reference period:*drinking in last week *Drink type:*Japanese sake, Japanese spirits, beer, whiskey and wine] **Measure:** grams per day, frequency, age started, **Reference group**: non-drinkers (n=103) **Results:** *ca* Ex-drinkers: 3, 0.82 (0.20-3.33) Current drinkers: 45, 1.27 (0.87-1.84) 0.1– 4.9 (g/day): 13, 1.07 (0.57-2.00) 5.0–14.9: 5, 0.83 (0.34-2.04) ≥15.0: 11, 2.93 (1.55-5.54) *p*trend = 0.01 *Current drinkers only* *Years*: <25: *ca* 3, 1.02 (0.32-3.24); 25–35: 5, 0.93 (0.34-2.25); >35: 7, 1.33 (0.78-2.28) *Age started drinking* *Frequency of consumption (times/week)*: <1: 13, 1.46 (0.81-2.61); 1–2: 11, 1.08 (0.54-2.14); 3–4: 7, 1.17 (0.54-2.53); 5–7: 11, 1.51 (0.80-2.83)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Mattison 2004 **Country:** Sweden **Study aims:** To examine *(i)* if breast cancer risk in post-menopausal women is associated with intakes of total alcohol, specific alcoholic beverages *(ii)* genuine effects of total alcohol and fat intakes when adjusted for each other. **Source of funding:** Swedish Cancer Society	**Population:** *Source:* source population included all men and women (n= 74,138) born in city of Malmo, between 1923-50, 28,098 participants had completed questionnaire by October 1996. *Exclusion criteria:*Inadequate Swedish language skills; mental incapacity; all prevalent cancer cases, except cervical cancer *in situ* and non-malignant melanoma skin cancer *Study pop:* Eligible participants were women 50 years or older at baseline examination, 11,726 post-menopausal women were included **Observation time:** end of follow up (31December 2001), average follow-up time, 7.6 years, 89,602 person-years LFU <1%; 342 incident (312 invasive and 30 *in situ*) cases,	***Exposure:*** *Questionnaire:* interview-based, modified diet history method combines *(i)* a 7-day menu book for registration of lunch and dinner meals, including cold drinks and alcohol, and *(ii)* a questionnaire for assessment of meal patterns, consumption frequencies and portion sizes *Repeated during follow-up*: baseline only *Reference period:* during the previous year *Drink type:* n/s **Measure:**grams per day, **Reference group:** group 0-15 g/day (n=257) **Results:** *ca* Abstainers 22 0.89 (0.57–1.39) >15 to ≤30 39 0.88 (0.62–1.24) >30 11 1.68 (0.91–3.12)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Nielsen 2008 **Country:** Denmark **Study aims:** to determine whether alcohol interactswith hormone use on risk of breast cancer **Source of funding:** Danish Ministry of Interior and Health	**Population:** *Source:* Copenhagen City Heart Study **(see Petri below)** *Exclusion criteria:* none specified *Study pop*: 5,035 **Observation time:** Baseline year n/s, end of period 31 December 1996, mean follow up 6.1 yrs, LFU <1	**Exposure: SEE PETRI BELOW** **Measure:** drinks per week, **Reference group**: <1 drink/wk (n=107) **Results:** 1–7 101 1.19 (0.90–1.57) 8–14 5 36 1.28 (0.87–1.89) 15–21 14 1.61 (0.92–2.84) >21 9 1.54 (0.77–3.10) *p*trend0.06

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Petri 2004 **Country:** Denmark **Study aims:** To examine the influence of alcohol intake and type of beverage on breast cancer risk in relation to menopausal status. **Source of funding:** Danish Ministry of Interior and Health, The Health Insurance Foundation.	**Population:** *Source:* Copenhagen Centre for Prospective Population Studies (comprising data from various Danish cohort studies: the Copenhagen City Heart Study and the Research Centre for Prevention and Health *Exclusion criteria:*none specified *Study pop*: included 13,074 age-stratified women ≥20yrs who completed questionnaires **Observation time:** Baseline year n/s, end of period 31 December 1996, mean follow up 6.1 yrs, LFU <1%; 76 incident cases in pre-menopausal, women	**Exposure:** *Questionnaire:* Self-administered questionnaires *Repeated during follow-up*: *Reference period:* in preceding year. *Drink type:* beer, wine, and spirits *Quest validated:*n/s **Measure:** drinks per week, **Reference group**: 1-6 d/w **Results:** <1 1.17 (0.66-2.07) 7–13 1.22 (0.66-2.25) 14–27 0.86 (0.33-2.21) >27 3.49 (1.36-8.99)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Rohan 2000 **Country:** Canada **Study aims:** To study the association between alcohol consumption and breast cancer risk **Source of funding:** National Cancer Institute of Canada	**Population:** *Source:* Conducted as a case-cohort study within a cohort of 56,837 women participating in controlled trial of mammographic screening for breast cancer in women 40-59yrs in Canada between 1980 and 1985 *Exclusion criteria:*dietary questionnaires not available; extreme values for energy intake *Study pop*: Sub-cohort of 5681 women selected by random sampling from cohort of 56,837 women **Observation time:** 1980-1985 to 31 December 1993, median follow-up time for cohort-approx. 10 years; 1,469 cases of invasive breast cancer, 144 in sub-cohort	**Exposure:** *Questionnaire:* self-administered quantitative FFQ *Repeated during follow-up*: baseline only *Reference period:* n/s *Drink type:*beer, wine, and spirits **Measure:** grams per day, **Reference group**: 0 g/d **Results:** >0-≤10 1.01 (0.84-1.22) >10-≤20 1.16 (0.91-1.47) >20-≤30 1.27 (0.91-1.78) >30-≤40 0.77 (0.51-1.16) >40-≤50 1.00 (0.57-1.75) >50 1.70 (0.97-2.98) *p*trend 0.35

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Sellers 2002 **Country:** USA **Study aims:** To examine interactions of alcohol and low folate intake on the risk ofpostmenopausal breast cancer stratified by tumour receptor status for oestrogen (ER) and progesterone (PR) **Source of funding:** None specified	**Population:** *Source:* Iowa Women's Health Study, cohort represents 41,836 licensed drivers ages 55-69 yrs who responded to a mailed survey *Exclusion criteria:*not postmenopausal (*n*=569) or total or partial mastectomy (*n*=1,870); dad any cancer other than skin cancer (*n*=2,293);if >30 items on FFQ left blank; extreme energy intake values (<600 or ≥5,000 kcal/day; *n*=2,712). *Study pop*: Final cohort size = 34,393 **Observation time:** 1986-1999, 14 yrs of follow-up, LFU n/s; identified 1875 breast cancer cases (1,633 invasive and 242 *in situ*)	**Exposure:** *Questionnaire:* Food frequency questionnaire *Repeated during follow-up*: baseline only *Reference period:* over the previous year *Drink type:* yes **Measure:** grams per day, **Reference group** 0g/d **Results:** *g/d* *ER+* *ER-* *PR+* *PR-* ≤4 1.06 (0.91–1.22) 1.40 (1.00–1.96) 1.04 (0.89–1.23) 1.24 (0.95–1.62) >4 1.07 (0.90–1.26) 1.64 (1.14–2.35) 1.12 (0.93–1.34) 1.28 (0.96–1.71)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Stolzenberg-Solomon 2006 **Country:** USA **Study aims:** to better understand the association between folate intake (food folate, the natural polyglutamate forms in foods, synthetic folic acid supplements, and total folate), alcohol consumption, the interaction of these factors, and postmenopausal breast cancer **Source of funding:** National Institutes of Health	**Population:** *Source:* Women 55-74yrs recruited between 1993 and 2001 in 10 US centres to the intervention arm (randomly assigned) of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Of 77,376 women in screening trial, only those in intervention arm given dietary questionnaire at baseline (*n*=38,660 women); of that group, 31,411 (81%) completed the questionnaire *Exclusion criteria:* history of any cancer other than non-melanoma skin cancer (*n*=2,338); >8 items missing from FFQ (*n*=319); extreme values for energy intake (lowest or highest, *n*=544); missing data on multivitamin use (*n*=2,810) *Study pop*: = 25,400 **Observation time:** follow-up to June 2003 (median 4.94 y; 127,261 person-years; LFU n/s;500 cases	**Exposure:** *Questionnaire:* self-administered FFQ *Repeated during follow-up*: baseline only *Reference period:* within past year *Drink type:* beer, wine, and spirits, *Quest validated:* n/s **Measure:** grams per day, **Reference group**: ≤0.01g/d **Results:** >0.01-≤0.43 138 1.21 (0.94, 1.57) >0.43- ≤1.39 158 1.18 (0.92, 1.51) >1.39-≤7.62 118 0.94 (0.72, 1.22) >7.62 173 1.30 (1.02, 1.67) *p*for trend =0.065

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Suzuki 2005 **Country:** Sweden **Study aims:** To investigate whether association of alcohol with increased risk of postmenopausal breast cancer differs across ER+/− and PR+/− tumour subtypes, and whether there are interactions between alcohol intake and other known risk factors, on the risk of ER- and PR-defined postmenopausal breast cancer **Source of funding:** Swedish Cancer Society	**Population:** *Source:* All women born between 1917 and 1948 in Västmanland County and between 1914 and 1948 in Uppsala County, Sweden, invited to a mammography screening between 1987-1990 (response rate 74%, n= 66 651). *Exclusion criteria:*missing or incorrect national identification numbers (n=1,122); born before 1914 or after 1948 (*n*=165); incomplete questionnaires (*n*=2,994); pre- and peri-menopausal women at the start of follow-up (*n*=27,722), but subsequently re-entered women who become postmenopausal during follow-up if cancer-free and living in the study area (*n* = 23 888);>70 years old at baseline (*n*=2,364) *Study pop*: 51,847 post-menopausal women **Observation time:** November 1997,to June 30, 2004, average 8.3-year follow-up, 43,0583, person-years, LFU < 1%; 1284 invasive cases	**Exposure:** *Questionnaire:* FFQ *Repeated during follow-up*: at baseline, follow-up FFQ in 1997 (response rate 70%) *Reference period:*during the past 6 months *Drink type:* light beer, medium beer, strong beer, wine, and hard liquor *Quest validated:* Spearman rank correlation coefficient, *r* = .9 for alcohol intake estimated by the FFQ-87 and alcohol intake calculated from four 1-week diet records obtained 3–4 months apart **Measure:** grams per day, **Reference group**: non-drinkers (n=138) **Results:** *All invasive tumors* / *ER+PR+* <3.4: 476 1.08 (0.94-1.25) / 269 1.07 (0.89-1.30) 3.4 -9.9: 343 1.10 (0.94-1.29) / 186 1.09 (0.88-1.35) ≥10: 151 1.43 (1.16-1.76) / 77 1.35 (1.02-1.80), *p*trend.0012 / *p*trend .049 *ER+PR −* / *ER+PR* / *ER − PR −* <3.4: 90 1.10 (0.78-1.55) / 21 1.27 (0.63 to 2.57) / 56 1.11 (0.72 to 1.71) 3.4 -9.9: 81 1.30 (0.91-1.87) / 14 1.30 (0.58 to 2.89) / 42 1.09 (0.68 to 1.75) ≥10: 54 2.36 (1.56-3.56) / 2 0.62 (0.13 to 2.90) / 10 0.80 (0.38 to 1.67) *p*trend <.001 / *p*trend .57

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Tjønneland 2004 **Country:** Denmark **Study aims:** To examine the relationship between postmenopausal breast cancer incidence rate and alcohol consumption in different life periods **Source of funding:** Danish Cancer Society	**Population:** *Source:* Between December 1993 and May 1997, all 79,729 women aged 50-64 yrs living in specific municipality-defined areas in Denmark invited to participate in study.Total of 29,875 women enrolled in study, i.e. 37% of the women invited *Exclusion criteria:p*revious history of cancer (326); Incomplete lifestyle information (8); women reporting at least one natural menstruation >12 months before entry and no use of HRT (4,798); lifetime history of no menstruation (9);missing information about present or previous alcohol consumption (177); no information on reproductive events or length of schooling, (837) *Study pop:* After exclusions cohort = 23,683 **Observation time:**	**Exposure:** *Questionnaire:* Mailed questionnaire *Repeated during follow-up*: no *Reference period:* mean alcohol consumption during four different periods of life, i.e., their twenties, thirties, forties and from age 50 until 1 y before study entry *Drink type:* wine, fortified wine, beer and spirits. **Measure:** per each additional 10 g/d of alcohol intake, **Reference group**: non-drinkers **Results:** Twenties 0.94 (0.79–1.11) Thirties 0.95 (0.84–1.06) Forties 0.99 (0.90–1.08) Fifties—baseline 1.01 (0.91–1.13) *Cumulative intake* 0.99 (0.96–1.03) Baseline 1.10 (1.03–1.16) *Early maximum drinking period before age 50 with the highest maximum intake of alcohol (ref group forties*)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
	Follow-up until 31 December 2000; 423 cases of breast cancer identified during a median of 4.7 y of follow-up, LFU 0%	Twenties 17 1.03 (0.63–1.69) Thirties 32 0.92 (0.64–1.33)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Tjønneland 2007 **Country:** Norway, Sweden, Denmark, United Kingdom, Germany, The Netherlands, France, Spain, Italy, and Greece**,** **Study aims:** to describe the associations between alcohol intake and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) **Source of funding:** Europe Against Cancer programme of the European Commission	**Population:** *Source:* consists of sub cohorts recruited in 23 centers in ten European countries. Participants recruited from the general population residing in a specific geographical area. Exceptions were most of the Oxford cohort, UK (based on vegetarian volunteers and healthy eaters), the Utrecht cohort, the Netherlands and the Florence cohort, Italy (based on women attending breast cancer screening), the French cohort (based on female members of the health insurance for state school employees living throughout France), the Ragusa cohort, Italy, and most of the Spanish cohort (based on blood donors and their spouses), n=368,010 *Exclusion criteria:* Women with a prevalent cancer diagnosis (19,953) and with missing data for variables considered in the analysis (67,055 subjects) as well as 6,314 who were in the lowest and highest 1% of the distribution of the ratio of reported total energy intake to energy requirement *Study pop*: 274,688 female participants aged 35-70 yrs. were excluded, **Observation time:** 1,695,876 person years (PY) of follow up, during which time 5,054 cases (1,114 pre-, 969 peri-, and 2,962 postmenopausal) were diagnosed.	**Exposure:** *Questionnaire:* food frequency questionnaire *Repeated during follow-up*: no *Reference period:* 12 monthly 24-h recalls *Drink type:* beer and/or cider, wine, liquor, spirits, or fortified wine *Quest validated:* dietary questionnaires used in the different cohorts were all validated or are currently being validated **Measure:** grams per day, **Reference group**: >0–1.5 g/day (n=50,979 incl. 701 cases) **Results:** *Cases/ cohort* — *incidence rate ratio* Abstainers 612/46,939 1.01 (0.91–1.13) >1.5–4.7 723/51,087 0.98 (0.89–1.09) >4.7–10 731/48,585 0.97 (0.88–1.08) >10–19 759/40,931 1.07 (0.96–1.19) >19–23.6 211/10,724 1.08 (0.92–1.26) 23.6–29.9 154/8,156 1.03 (0.86–1.23) 29.9–37.1 194/7,795 1.36 (1.15–1.60) >37.1 206/9,492 1.09 (0.93–1.28)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Thygesen 2008 **Country:** Denmark **Study aims:** to determine the influence of both baseline and updated alcohol intake on the risk for breast cancer and also the modifying influence of latency. **Source of funding:** National Institute of Public Health	**Population:** *Source:* Copenhagen City Heart Study initiated in 1976in which 19,698 individuals from central Copenhagen invited to a health examination and to fill in a questionnaire concerning health behaviour sample was randomly selected by age strata from a population of 90,000 inhabitants At the first examination, 14,223 persons participated (72%) *Exclusion criteria:*- no diagnosed malignant disease *Study pop*: 9,318 women **Observation time:** until December 31, 2002, 476 primary breast cancers	**Exposure:** *Questionnaire:* questionnaire concerning health behaviour *Repeated during follow-up*: baseline and 1981-83, 1991-94 and 2001-04 *Reference period:* n/s, *Drink type:* beer wine liquor **Measure:** grams per day, **Reference group**:<1.71 grams per day **Results:** *ca* *Baseline alcohol intake* *ca* *Updated alcohol intake* 1.71–12 236 1.00 (0.80–1.24) 164 0.98 (0.78–1.21) 13–24 79 1.36 (1.01–1.81) 84 1.19 (0.91–1.56) 25–48 8 1.71 (0.82–3.57) 29 1.12 (0.75–1.68) >48 4 4.64 (1.67–12.9) 7 1.05 (0.46–2.40) *Intake and length of latency time* *0 years* *4 years* *8 years* 1.71–12 0.98 (0.79-1.21) 1.14 (0.91-1.44) 1.05 0.81-1.37) 13–24 1.19 (0.91-1.56) 1.30 (0.97-1.75) 1.59 1.16-2.18) 25–48 1.12 (0.75-1.68) 1.28 (0.83-2.00) 1.38 0.83-2.28) >48 1.05 (0.46-2.40) 1.17 (0.48-2.89) 1.35 0.49-3.70) - *12 years* *16 years* *20 years* 1.71–12 1.29 (0.96-1.74) 1.33 (0.93-1.91) 1.74 (1.00-3.05) 13–24 1.49 (1.01-2.19) 1.67 (1.06-2.64) 2.48 (1.28-4.81) 25–48 1.65 (0.91-3.01) 1.31 (0.55-3.09) 6.25 (2.36-16.5) >48 2.39 (0.86-6.63) 2.19 (0.52-9.13) 0.50 (1.34-82.6)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Zhang 1999 **Country:** USA **Study aims:** To examine relation of average alcohol consumption and of different beverages to the risk of breast cancer **Source of funding:** Institute on Lifestyle & Health, Boston University School of Medicine	**Population:** *Source:* Cohort started in 1948 in Framingham, Massachusetts. Original cohort included 2,873 women, aged 28-62 years;. In 1971, female children of original cohort and their spouses formed the Offspring study (n=2,641, aged 12-60 years) *Exclusion criteria:* missing alcohol consumption data and history of prevalent cases of breast cancer *Study pop:* Final cohort for analysis = 5,048 **Observation time:** Cohort I follow up median, 34.3 years; Cohort II follow up median 19.3 years; Loss to follow up n/s; 287 incident cases (221 cohort I, 66 cohort II)	**Exposure:** *Questionnaire:* n/s *Repeated during follow-up*: every 4 years from both cohorts *Reference period:* n/s *Drink type:* beer, wine and cocktails **Measure:** grams per day, **Reference group:** Non-drinker(0g/d) **Results:** *g/d* *ca* 0.1-<5.0 110 0.8 (0.6-1.1) 5.0-<15 55 0.7 (0.5-1.1) >15.0 53 0.7 (0.5-1.1)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Zhang 1999 **Country:** USA **Study aims:** To examine relation of average alcohol consumption and of different beverages to the risk of breast cancer **Source of funding:** Institute on Lifestyle & Health, Boston University School of Medicine	**Population:** *Source:* Cohort started in 1948 in Framingham, Massachusetts. Original cohort included 2,873 women, aged 28-62 years;. In 1971, female children of original cohort and their spouses formed the Offspring study (n=2,641, aged 12-60 years) *Exclusion criteria:* missing alcohol consumption data and history of prevalent cases of breast cancer *Study pop:* Final cohort for analysis = 5,048 **Observation time:** Cohort I follow up median, 34.3 years; Cohort II follow up median 19.3 years; Loss to follow up n/s; 287 incident cases (221 cohort I, 66 cohort II)	**Exposure:** *Questionnaire:* n/s *Repeated during follow-up*: every 4 years from both cohorts *Reference period:* n/s *Drink type:* beer, wine and cocktails **Measure:** grams per day, **Reference group:** Non-drinker(0g/d) **Results:** *g/d* *ca* 0.1-<5.0 110 0.8 (0.6-1.1) 5.0-<15 55 0.7 (0.5-1.1) >15.0 53 0.7 (0.5-1.1)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Zhang 2007 **Country:** USA **Study aims:** To assess the association between moderate alcohol consumption and breast cancer risk **Source of funding:** None specified	**Population:** *Source:* Women's Health Study, a randomized trial evaluating the benefits and risks of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer among 39,876 US female health professionals *Exclusion criteria:*- none specified *Study pop*: 39,345 (98.7 percent) of the randomized participants whocompleted and returned a self-administered **Observation time:** end of the trial, March 31, 2004, average duration of follow-up was 10 years 1,484 cases of total breast cancer	**Exposure:** *Questionnaire:* 131-item food FFQ *Repeated during follow-up*: baseline only *Reference period:* preceding 12 months *Drink type:* beer, wine, and liquor **Measure:** grams per day, **Reference group**: 0 g/day (n=516) **Results:** *Total alcohol intake* 0.1_4.9 549 1.02 (0.90-1.15) 5.0_9.9 181 1.13 (0.95-1.34) 10.0_14.9 109 1.14 (0.92-1.40) 15.0_29.9 88 1.16 (0.92-1.45) ≥30.0 41 1.32 (0.96-1.82) 10 g/day increment 1.09 (1.03-1.15) *ca* *ER+/PR+* *ca* *ER+/PR-* *ca* *ER-PR-* 0.1_4.9 295 1.00 (0.84-1.18) 49 1.13 (0.74, 1.72) 69 1.17 (0.82, 1.67) 5.0_9.9 84 0.96 (0.75-1.24) 16 1.21 (0.67, 2.18) 18 1.04 (0.60, 1.78) 10.0_14.9 66 1.29 (0.98-1.70) 8 1.01 (0.47, 2.17) 10 1.02 (0.52, 2.01) 15.0_29.9 50 1.23 (0.91-1.68) 9 1.39 (0.67, 2.90) 10 1.25 (0.63, 2.47) ≥30.0 23 1.39 (0.90-2.15) 2 0.69 (0.17, 2.88) 4 1.15 (0.41, 3.19)

Descriptive tables for breast cancer: case control studies

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Althuis 2003 **Country:** USA **Study aims:** To assess risk factors for breast cancer among very young compared to older premenopausal women **Source of funding:** US government	**Population:** *Cases:*women newly diagnosed with breast cancer aged 20-54yrs and living in New Jersey, Seattle and Atlanta N=1,750, *Controls:*selected by random-digit dialing (90.5% screening response rate) N=1,557 **Exclusion criteria:** did not have a residential telephone; previous diagnosis of breast cancer; post-menopausal women **Observation time:** 1990-1992; response rate: cases (86%) controls (78%)	**Exposure:** *Questionnaire:* interviewed in person *Interviewers blinded*: n/s *Reference period:* n/s *Drink type:* n/s **Measure:**drinks per week, **Reference group**non-drinker **Results:** *d/w* *ca/co* *<35 yrs* *35-44yrs* *45-54yrs* <3 74/78 1.33 (0.8-2.2) 414/344 1.04 (0.8-1.3) 80/106 1.98 (1.2-3.2) 3-6.9 50/64 0.99 (0.6-1.7) 229/186 1.00 (0.8-1.3) 92/66 1.95 (1.1-3.4) 7-13.9 27/22 1.29 (0.6-2.7) 101/80 1.04 (0.7-1.5) 53/39 1.84 (1.0-3.5) 14+ 20/13 1.71 (0.7-4.0) 59/26 1.95 (1.2-3.30) 34/28 4.24 (1.2-14.6)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Berstad 2007 **Country:** USA **Study aims:** To examine the association between total intake and intake of different types of alcoholic beverages at different time periods and breast cancer risk in a case-control study of women younger than 50 years **Source of funding:** None specified	**Population:** *Cases:* US-born English-speaking, white (including Hispanic) or African-American, female residents of Los Angeles County, and 20-49 years old N=1,794 *Controls:*identified using a neighbourhood walk algorithm, in which that field staff conducted walks according to predefined pattern in neighbourhoods where case patients lived at time of their diagnoses N=444 **Exclusion criteria:** never diagnosed with invasive or in situ breast cancer or any other cancer **Observation time:** between 1998 and 2003 Response rate: cases (62%) controls (74%)	**Exposure:** *Questionnaire:* structured questionnaire *Interviewers blinded*: n/s *Reference period:* lifetime histories: calendar of life events was used to assist the recall. *Drink type:* beer, wine, liquor **Measure:** drinks per week, **Reference group**: never drinker (561/141) **Results:** *Lifetime intake (from age 15 years* *Early intake (15–20 years age)* <3 740/192 1.09 (0.84-1.41) <3 407/113 0.99 (0.73-1.34) 3–<7 248/67 0.97 (0.68-1.39 3–<7 100/31 0.78 (0.48-1.25) 7+ 177/34 1.26 (0.81-1.96) 7+ 61/14 0.95 (0.50–1.82) *Recent intake (average intake in the 5 years before the alcohol reference date)* <3 482/129 1.06 (0.80–1.42) 3 – <7 217/56 1.05 (0.73–1.53) 7 – <14 126/24 1.36 (0.82–2.24) 14+ 113/15 1.82 (1.01–3.28)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Bessaoud 2008 **Country:** France **Study aims:** to examine the association between drinking pattern of alcoholic beverages,particularly wine, and breast cancer using different statistical approaches **Source of funding:** National Cancer Institute of France,	**Population:** *Cases:* Eligible case subjects were French-speaking women, residing in Southern France (Hérault only), identified from both surgical ward and medical information department records N= 437 *Controls:* were randomized from the list of residents supplied by the electoral roll N= 922 **Exclusion criteria:**- no former history of breast cancer **Observation time:** 2002–2004; response rate: n/s	**Exposure:** *Questionnaire:* structured questionnaire administered by two trained interviewers *Interviewers blinded*: n/s *Reference period:* ‘‘usual drinking’’ habits *Drink type:* wine, aperitifs, beer, spirits **Measure:** drinking status, grams per day, **Reference group**: never, 0 g/day (41/73) **Results:** Sporadic 239/499 1.03 (0.62-1.71) Frequent 155/350 0.75 (0.40-1.41) 0- ≤5 211/421 0.75 (0.20-2.88) 5-≤10 57/141 0.36 (0.10-1.53) 10- ≤15 43/130 0.21 (0.10-0.91) >15 83/157 0.97 (0.23-4.10), Total intake (10 g/d) 0.94 (0.75–1.17)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Enger 1999 **Country:** USA **Study aims:** the association of alcohol and risk of breast cancer according to joint oestrogen receptor and progesterone receptor status **Source of funding:** National Institutes of Health	**Population:** *Cases:* all patients aged ≤40 yrs and aged 55-64yrs, living in Los Angeles County and first diagnosed between 1 July 1983 and 1 January 1989, with breast cancer N=744 ≤40yrs, 1,579 55-64yrs *Controls:* selected from housing units in a pre-defined walk pattern in neighbourhood where cases lived at the time of breast cancer diagnosis N=744 ≤40yrs, 1,579 55-64yrs **Exclusion criteria:** women no longer menstruating; did not know family history of breast cancer because they had been adopted **Observation time:** 1983-1989 Response rate: cases (72%), controls (73%)	**Exposure:** *Questionnaire:* face-to-face interview *Interviewers blinded*: n/s, *Quest validated: n/s* *Reference period:*at ages 18, 25 and the reference age (women aged 40 years or younger) and at ages 25, 40 and the reference age (women aged 55-64) *Drink type:* beer, wine and liquor **Measure:** grams per day, **Reference group:** 0g/d **Results:** *Pre-menopausal* *con/ca* *ER+/PR+* *ER+/PR–* *ER–/PR–* 1–5 135/30 0.73 (0.46-1.15) 135/6 0.45 (0.18-1.10) 20 0.68 (0.40-1.16) 6–13 118/37 1.07 (0.69-1.65) 118/2 0.16 (0.04-0.69) 23 0.90 (0.53-1.51) 14+ 88/28 1.10 (0.67-1.80) 88/7 0.71 (0.30-1.68) 21 1.04 (0.60-1.81) *p*trend 0.56 *p*trend 0.21 *p*trend 0.84 *Post-menopausal* *con/ca* *ER+/PR+* *ER+/PR–* *ER–/PR–* 1–13 329/122 0.97 (0.74-1.27) 329/38 0.75 (0.49-1.14) 33 0.81 (0.52-1.26) 14–26 109/46 1.18 (0.80-1.75) 109/21 1.36 (0.80-2.33) 12 0.91 (0.47-1.75) 27+ 63/43 1.76 (1.14-2.71) 63/10 1.10 (0.53-2.26) 11 1.37 (0.68-2.76) *p*trend0.03 *p*trend 0.65 *p*trend0.77

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Deandrea 2008 **Country:** Italy **Study aims:** investigated the role of alcohol according to ER and progesterone receptor (PR) status in a case-control study on breast cancer **Source of funding:** Italian Association for Cancer Research, the Italian League Against Cancer,	**Population:** *Cases:* from hospitals in six Italian areas: N= 989 *Controls:* admitted to hospitals in the same catchment areas for acute, non-neoplastic, non-gynaecologic diseases: non–alcohol related trauma; orthopaedic disorders; eye diseases; acute surgical disorders; and other miscellaneous diseases related to ear, nose and throat, skin, and teeth. N=1,350 **Exclusion criteria:**none specified **Observation time:** from 1991 to 1994; response rate: >95% in cases and controls	**Exposure:** *Questionnaire:* Information was collected in the hospital by trained Interviewers using a validated FFQ questionnaire *Interviewers blinded*: n/s *Reference period:*lifetime *Drink type:* wine, beer, herb liquors, grappa, whisky/brandy, and other spirits **Measure:**grams per day, **Reference group**: Never drinkers (491 cases/244 controls) **Results** *All* *ER-* *ER+* < 13.8 429/337 1.55 (1.24-1.93) 429/90 1.57 (1.09-2.26) 429/247 1.51 (1.18-1.93) ≥ 13.8 430/408 1.96 (1.57-2.47) 430/72 1.36 (0.93-2.01) 430/336 2.16 (1.68-2.76) per 10 g 1.11 (1.05-1.17) per 10 g 1.13 (1.07-1.20)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Kinny 2000 **Country:** USA **Study aims:** to investigate the effects of alcohol consumption on breast cancer risk in black and white women. **Source of funding:** n/s	**Population:** *Cases:* were women 20-74yrs residing in North Carolina. Predetermined sampling probabilities based on race and age used to randomly recruit approx. equal numbers of black and white women, as well as equal numbers of women <50yrs and women ≥50 yrs N=890 *Controls:*randomly selected from computerized databases: For women <65yrs from list of licensed drivers in North Carolina , women age ≥65 yrs from those eligible for Medicare N=841 **Exclusion criteria:**previous history of breast cancer **Observation time:** between May 1993 and May 1996 Response rate: Cases (77%) Controls (68%)	**Exposure:** *Questionnaire:* Nurse-interviewer administered questionnaire *Interviewers blinded*: n/s *Reference period:* lifetime (during three age periods up to time of the interview: < 25yrs, 25-49yrs, and ≥50 yrs) *Drink type:*beer, wine and liquor *Quest validated:* n/s **Measure:** grams per week (g/w), **Reference group**: lifetime non drinker **Results:** *g/w* *All women* *Black women* *White women* <13 0.9 (0.7-1.2) 0.6 (0.4-1.0) 1.0 (0.7-1.5) 13-90.9 0.9 (0.7-1.3) 0.8 (0.5-1.4) 1.0 (0.7-1.5) 91-181.9 1.4 (0.9-2.1) 2.2 (0.9-5.2) 1.1 (0.6-1.9) ≥182 1.0 (0.6-1.6) 0.8 (0.3-1.8) 1.2 (0.6-2.3) *p*trend 0.60 0.75 0.71

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Kropp 2001 **Country:** Germany **Study aims:** to evaluate theeffect of low-to-moderate doses on breast cancer risk among premenopausal women **Source of funding:** n/s	**Population:** *Cases:* German-speaking women who resided in one of two geographic areas in southern Germany and who were <51 yrs at time of diagnosis of breast cancer. all incident breast cancer diagnoses in 38 hospitals in the two regions N=706 *Controls:* selected from random lists of residents supplied by the population registries N=1,381 **Exclusion criteria:** previous history of breast cancer; non-German speaking **Observation time:** between January 1, 1992, and December 31, 1995 Response rate: cases (70.2%) controls (61.2 %)	**Exposure:** *Questionnaire:* self-administered questionnaire *Interviewers blinded*: n/s *Reference period:* three time periods: ages 15–20 years, ages 20–30 years, and ages 30–50 years *Drink type:* beer, wine, aperitifs, liqueur, and spirits **Measure:**Lifetime average ethanol intake grams per day, **Reference group**: non-drinkers (0.g/d) **Results:** *ca/co* 1–5 257/577 0.71 (0.54-0.91) 6–11 124/295 0.67 (0.50-0.91) 12–18 69/150 0.73 (0.51-1.05) 19–30 59/84 1.10 (0.73-1.65) ≥31 44/36 1.94 (1.18-3.20)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Lenz 2002 **Country:** Canada **Study aims:** To determine the association between postmenopausal breast cancer and prior consumption of alcoholic beverages **Source of funding:** Canadian Breast Cancer Initiative	**Population:** *Cases:*women 50-75yrs at time of breast cancer diagnosis, residents of Montreal area, identified from records of pathology departments and cancer registries from all 18 major hospitals in area, N=556 *Controls:* selected from the same set of hospitals as the cases, N=577 **Exclusion criteria:** certain sites of cancer excluded because of association with particular chemical or physical exposures (i.e. liver, pancreas, lung, bronchus and trachea, brain and central nervous system, and leukemia); women with non-melanoma skin cancer, and with cancers of the oral cavity, esophagus, and larynx **Observation time:** between 1996 and 1997, Response rate: Cases (81.1%) Controls (75.7%)	**Exposure:** *Questionnaire:* interviewer administered structured questionnaire, *Interviewers blinded*: unaware of cancer site of subject *Reference period:*ever drank in lifetime *Drink type:*beer, wine, cider or liquor **Measure:** drinking frequency, **Reference group**: never drinkers **Results:** Ever 1.2 (0.9-1.7) Infrequent drinker 1.2 (0.8-1.8) Ever regular drinker 1.3 (0.9-1.8) Current regular drinker 1.5 (1.0-2.2) (i.e. daily or weekly)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Li 2003 **Country:** USA **Study aims:** to assess the relationship between alcohol use and risk of invasive breast cancer by histology and hormone receptor status **Source of funding:** National Cancer Institute,	**Population:** *Cases:* women, 65-79yrs living in three counties in Washington state, with a diagnosis of invasive breast cancer and who had a Health Care Financing Administration record N=975 *Controls:* identified from Health Care Financing Administration records and frequency matched on age to cases to serve as controls N=1,007 **Exclusion criteria:**- prior history of *in situ* or invasive breast cancer **Observation time:** between April 1, 1997, and May 31, 1999, Response rate: Cases (80.6%) Controls (73.8%).	**Exposure:** *Questionnaire:* interviewed in-person *Interviewers blinded*: n/s *Reference period:* 20 years before diagnosis/reference date. life events calendar was used to enhance recall of times when patterns of alcohol use changed *Drink type:* beer, wine, and spirits **Measure:** grams per day, **Reference group**: women who drank <12 alcohol beverages during past 20 years, or who did not consume at least one beverage containing alcohol a month for 6 months during the past 20 years **Results:** *All* *ER+* *ER-PR+* *PR-* Current 1.3 (1.1-1.6) 1.1 (0.7-1.8) 1.4 (1.1-1.7) 1.1 (0.8-1.5) <1.5 1.3 (0.9-1.8) 1.5 (0.7-3.2) 1.3 (0.9-1.9) 1.3 (0.8-2.2) 1.5–4.9 1.3 (0.9-1.8) 1.0 (0.4-2.1) 1.4 (1.0-2.1) 0.8 (0.5-1.4) 5.0–14.9 1.2 (0.9-1.7) 0.8 (0.4-1.6) 1.3 (0.9-1.8) 0.9 (0.5-1.4) 15.0–29.9 1.2 (0.8-1.7) 1.5 (0.7-3.0) 1.2 (0.8-1.8) 1.2 (0.7-2.1) ≥30. 1.9 (1.2-3.1) 1.5 (0.5-4.0) 2.0 (1.2-3.2) 1.7 (0.9-3.3) *p*trend0.386 0.902 0.508 0.462

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Li 2006 **Country:** USA **Study aims:** To evaluate the relationships between established breast cancer risk factors and other histologic types **Source of funding:** National Institute of Child Health and Human Development and NationalCancer Institute	**Design:** population case-control **Population:** *Cases:* aged 35-64yrs identified with breast cancer in 5 metropolitan sites in the United States (Atlanta, Detroit, Los Angeles, Philadelphia, and Seattle) N= ductal (n=3,463), lobular (n=274), ductal-lobular, (n=261), medullary (n=91), tubular (n=77), comedo (n=70), and mucinous (n=61) *Controls:* selected using random digit dialling techniques from among eligible women enumerated during telephone screening, N=4,682 **Exclusion criteria:** without a history of breast cancer **Observation time:** between July 1994 and April 1998, Response rate:76.5% cases and 78.6% controls	**Exposure:** *Questionnaire:* in-person interviews *Interviewers blinded*: interviewers not blinded but unaware of study hypothesis *Reference period:* consumed ≥12 alcoholic drinks in lifetime and ≥1 drink per month for ≥6 months. *Drink type:* n/s *Quest validated:* n/s **Measure:** drinks per week, **Reference group**: never drank **Results:** SEE TABLE IN MAIN TEXT PAGE 20

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Marcus 2000 **Country:** USA **Study aims:** to examine the relationships of cigarette smoking, alcohol consumption, environmental tobacco smoke exposure, and medical treatment with ionizing radiation during adolescence with subsequent breast cancer risk. **Source of funding:** None specified	**Population:** *Cases:*women 20-74yrs residing in 24-county area of North Carolina and diagnosed with invasive breast cancer N=864 *Controls:*randomly selected from computerized databases: For women <65yrs from list of licensed drivers in North Carolina, women age ≥65 yrs from those eligible for Medicare N=790 **Exclusion criteria:**previous history of breast cancer **Observation time:** between May 1993 and May 1996 Response rate: cases (77%) controls (68%)	**Exposure:** *Questionnaire:* Nurse-interviewer administered questionnaire *Interviewers blinded*: n/s *Reference period:* n/s *Drink type:* n/s **Measure:** Age at first alcoholic beverage, **Reference group**: non-drinkers **Results:** Age at first alcoholic beverage 10-15 44/29 1.1 (0.6-1.8) 16-19 244/211 1.0 (0.7-1.3) ≥20 326/317 1.0 (0.8-1.3)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
McDonald 2004 **Country:** USA **Study aims:** To explore associated biological outcomes and clarify the role of timing of exposure in the alcohol breast cancer relationship **Source of funding:** National Institute of Child Health and Human Development,	**Population:** *Cases:* all those aged 35-64yrs identified with breast cancer in five metropolitan sites in the United States (Atlanta, Detroit, Los Angeles, Philadelphia, and Seattle). N=4,575 *Controls:* Using random digit dialling techniques, selected from among eligible women enumerated during telephone screening N=4,682 **Exclusion criteria:** without a history of breast cancer **Observation time:** between July 1994 and April 1998, Response rate: cases (76.5%) controls (64.7%)	**Exposure:** *Questionnaire:* in-person interviews *Interviewers blinded*: not blinded but unaware of study hypothesis *Reference period:* consumed ≥12 alcoholic drinks in lifetime and ≥1 drink per month for ≥6 months *Drink type:* n/s *Quest validated:* n/s **Measure:** drinks per week, **Reference group**: 0 d/w **Results:** *Overall 2 y before reference age* *1-10 y before reference age* <7 1490/1511 1.0 (0.9-1.1) 1811/852 1.0 (0.9-1.1) ≥7 34/470 1.2 (1.0-1.3) 550/506 1.1 (1.0-1.3) 7-<14 322/285 1.2 (1.0-1.4) 345/312 1.1 (1.0-1.3) ≥14 212/185 1.2 (1.0-1.5) 205 194 1.1 (0.9-1.4) *Ages 35-49, 2 y before reference age* *Ages 50-64, 2 y before reference age* <7 824/852 1.0 (0.9-1.1) 666/659 1.0 (0.9-1.1) ≥7 249/248 1.0 (0.9-1.3) 285/222 1.3 (1.1-1.6) 7 to <14 154/146 1.1 (0.8-1.4) 168/139 1.2 (1.0-1.6) ≥14 95/102 1.0 (0.7-1.3) 117/83 1.5 (1.1-2.0).

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Newcomb 2009 **Country:** USA **Study aims:** evaluated overall alcohol aswell as red and white wine consumption to examinebeverage-specific effects on breast cancer **Source of funding:** National Cancer Institute	**Population:** *Cases:* enrolled breast cancer cases identified from population-based registries in Wisconsin, Massachusetts (excluding metropolitan Boston), and New Hampshire, age 20 to 69 yrs. N=6,327 *Controls:* frequency matched to cases by 5-yr age groups, selected from lists of licensed drivers (<65 yrs) or a roster of Medicare beneficiaries (≥65 yrs) N=7,558 **Exclusion criteria:**n/s **Observation time:** between 1995 and 2000 Response rate: cases (80%) controls (76%)	**Exposure:** *Questionnaire:* Telephone interviews *Interviewers blinded*: n/s *Reference period:* during the year previous to the reference date *Drink type:* beer, red wine, white wine, or liquor (distilled spirits) **Measure:**drinks per week, **Reference group**: Non-drinkers (1,122 /1,379) **Results:** *All women* / *Postmenopausal women* / *Premenopausal women* <1 2129/2712 0.94 (0.85-1.04) 1106/1480 0.90 (0.79-1.02) 894/1045 1.02 (0.86-1.22) 1-3.4 1450/1731 0.99 (0.88-1.10) 745/863 1.03 (0.89-1.19) 592/767 0.90 (0.75-1.08) 3.5-6.9 702/793 1.02 (0.90-1.17) 345/384 1.05 (0.88-1.26) 306/363 0.96 (0.78-1.19) 7-13.9 619/658 1.11 (0.97-1.28) 355/395 1.07 (0.89-1.28) 221/223 1.17 (0.92-1.48) ≥14 305/285 1.24 (1.03-1.49) 189/164 1.37 (1.08-1.73) 98/103 1.10 (0.80-1.52) 1-drink increase p/d 1.01 (1.00-1.02) 1.02 (1.01-1.03) 1.00 (0.99-1.01)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Terry 2006 **Country:** USA **Study aims:** to investigate whether association between alcohol and breast cancer risk is affected by timing of alcohol exposure, modified by other risk factors such as BMI menopausal status, and HRT **Source of funding:** NationalCancer Institute	**Population:** *Cases:* English-speaking women (20-98yrs) living in Long Island, New York with newly diagnosed breast cancer N=1,508 *Controls:* randomly selected through random digit dialling methods (for subjects under 65 years) and Health Care Finance Administration lists (for subjects ≥65yrs) N=1,556 **Exclusion criteria:** none specified **Observation time:** August 1, 1996 to July 31, 1997 Response rate:cases 82.1%controls62.8%	**Exposure:** *Questionnaire:* In-person interview *Interviewers blinded*: n/s *Reference period:* for time periods: <20 yrs, 20 to 29 yrs, 30 to 39 yrs, 40 to 49 yrs, 50 to 59 yrs, and ≥60yrs *Drink type:* beer, wine, and liquor **Measure:** grams per day, **Reference group**: non-drinkers **Results**: *g/d* *ca/co* *Current* / *g/d* *ca/co* *Lifetime* <0.5 137/184 0.67 (0.50-0.91) <15 691/735 1.12 (0.88-1.42) 0.5–5 192/217 0.83 (0.63-1.11) 15–30 147/119 1.35 (0.96-1.91) 5–15 215/206 0.99 (0.75-1.31) > 30 72/94 0.81 (0.55-1.19) > 15 152/139 1.04 (0.74-1.45) *p*trend0.20.5

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Wrensch 2003 **Country:** USA **Study aims:** examines generally recognized breast cancer risk factors and years of residence in Marin County, California, an area with high breast cancer incidence and mortality rates **Source of funding:** California BreastCancer Research Program	**Population:** *Cases:* any female resident of Marin County California with a diagnosis of primary breast cancer between July 1997 and June 1999 if under 50 years of age, and between July 1997 and March 1999 if 50 years old or older at diagnosis N=285 *Controls:* ascertained through random digit dialling conducted by two survey research companies N=286 **Exclusion criteria:** without breast cancer **Observation time:** Cases from December 1999 to September 2001 and controls from April 2000 to September 2001 Response rate: cases (98%) controls (88%)	**Exposure:** *Questionnaire:* in-person interviews *Interviewers blinded*: n/s *Reference period:* n/s *Drink type:* n/s **Measure:**drinks per week and day, **Reference group**: <1 d/week **Results:** *Average drinks after age 21* *All Women* *ca/co* *aged 50 years and over* *under 50 years of age* ≥1 d/w-<2 d/d 137/149 1.1 (0.7-1.8) 90/106 0.63 (0.36-1.1) 47/43 3.5 (1.2-10.1**)** 2d/d 52/27 2.3 (1.2-4.4) 42/22 1.50 (0.70-3.3) 10/5 3.6 (0.79-16.5) ≥3d/d 15/6 3.6 (1.2-11.5) 13/5 2.90 (0.80-10.9) 2/1 n/s *p*trend 0.004 *p*trend0.090 *p*trend 0.030

Descriptive Tables for colorectal cancer: cohort studies

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Akhter 2007 **Country:** Japan **Study aims:** to further address the hypothesis that alcohol drinking is associated with an increased risk of colon and rectal cancer by separating anatomical sub-sites **Source of funding:** Ministry of Health, Labour and Welfare of Japan	**Population:** *Source:* 51,921 subjects (25,279 men and 26,642 women) aged 40 to 64 yrs living in14 municipalities of Miyagi Prefecture in rural northern Japan. 47,605 subjects responded (22,836 men and 24,769 women = response rate of 91.7% *Exclusion criteria:* already had cancer at the baseline; did not fully answer the questions on the frequency or amount of alcohol consumed and on alcohol drinking status *Study pop*: 21,199 men (Since the number of current drinkers was small among women (n = 4,995), analysis limited to men) **Observation time:** June 1, 1990, to March 31, 2001, 216,494pys, 179 colon, 131 rectum cases, LFU <5%;	**Exposure:** *Questionnaire:* self-administered questionnaire *Repeated during follow-up*: baseline only *Reference period:* n/s *Drink type:* sake, shochu, beer, whisky, wine, or others **Measure:**grams per day, **Reference group**: never drinkers (36) **Results:** *ca* *Colon* *ca* *Rectum* < 22.8 29 1.15 0.65–2.03 29 1.40 0.76–2.59 22.8–45.5 36 1.61 0.93–2.80 18 0.996 0.51–1.96 ≥45.6 79 2.03 1.23–3.33 61 1.84 1.05–3.21 *p*trend 0.0008 0.02 *ca* *Proximal colon* *ca* *Distal colon* < 22.8 13 0.82 0.37–1.80 10 1.68 0.57-4.92 22.8–45.5 12 0.89 0.40–1.99 18 3.30 1.22-8.91 ≥45.6 33 1.40 0.72–2.75 40 4.17 1.63-10.66 *p*trend 0.16 0.0002

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Bongaerts 2008 **Country:**Netherlands **Study aims**:' associations betweentotal alcohol consumption, specific alcoholic beverage consumptionand the risk of CRC according to anatomical sub-site and sex' **Source of funding:** European Research Advisory Board	**Population:**Netherlands Cohort Study on diet and cancer *Source:* cohort includes 58,279 men and 62,573 women, aged 55–69 at baseline and originating from 204 municipal population registries throughout The Netherlands *Exclusion criteria***:** Prevalentcancer cases other than non-melanoma skin cancer *Study pop*: sub-cohort, consisting of 5,000 randomly sampled men and women **Observation time:** 13.3 yrs follow-up; 2,323 cases,	**Exposure:** *Questionnaire:* self-administered questionnaire *Repeated during follow-up*: no *Reference period:*during the year preceding the startof the study, *Drink type:* beer; red wine; white wine; sherry and other fortified wines; liquor types, containing on average 16% alcohol and (Dutch) gin, brandyand whiskey. **Measure:** grams per day,**Reference group**: Abstainers **Results:** *Colorectal* *Colon* *Rectal* 0–<5.0 652 1.06 (0.91-1.23) 455 1.03 (0.87-1.22) 141 1.10 (0.83-1.45) 5.0–<15.0 507 0.97 (0.82-1.14) 341 0.93 (0.78-1.13) 117 1.00 (0.74-1.34) 15.0–<30.0 383 1.00 (0.83-1.20) 242 0.93 (0.75-1.14) 92 1.04 (0.75-1.44) 30.0 294 1.32 (1.06-1.65) 184 1.24 (0.96-1.59) 82 1.50 (1.05-2.16

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Chen 2005 **Country:** China **Study aims:** To assess association between alcohol consumption and the risk of colorectal cancer in Chinese population **Source of funding:** National Natural ScienceFoundation of China	**Population:** *Source:* all residents aged ≥30 yrs in 10 small towns invited to participate in CRC screening in, Zhejiang Province, China. 84.84% of 75,842 eligible individuals, responded *Exclusion criteria:* None specified *Study pop*: 64,343 (31,087 men, 33,256 women), **Observation time:** 10.6 years of follow-up from May 1990 to January 2001; 242 cases of CRC, (colon 107) (rectal 135)	**Exposure:** *Questionnaire:* face-to-face questionnaire *Repeated during follow-up*: n/s *Reference period:* n/s *Drink type:*n/s **Measure:** drink status, **Reference group**: non drinker **Results:** Daily (RR) Colorectal 1.11 0.74-1.67 Colon 0.97 0.52-1.78 Rectal 1.24 0.71-2.14

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Ferrari 2007 **Country:**Europe **Study aims:** '…to better elucidate the role of alcohol drinking oncolorectal carcinogenesis…' **Source of funding:** ''Europe Against Cancer'' Programme of the European Commission	**Population:**EPIC for further details of study sample and characteristics see Section 2.2, Box 2.1 **Observation time:** between 1992and 2000 were followed up for an average of 6.2 years, during which 1,833 CRC cases	**Exposure:** *Questionnaire:* various *Repeated during follow-up*: baseline only *Reference period:*over the 12 months before enrolment *Drink type:*beer, cider, wine, sweet liquor,distilled spirits or fortified wines **Measure:** grams per day, **Reference group**: 0.1-4.9 g/d (colorectal n=433), colon (n=299), rectal (n=134) **Results:** *Colorectal* *Colon* *Rectal* non-drinkers 110 0.98 (0.72-1.33) 83 1.03 (0.72-1.48) 27 0.85 (0.48-1.52) 4.9-14.9 444 1.05 (0.90-1.21) 298 1.06 (0.88-1.26) 146 1.02 (0.78-1.32) 15-29.9 246 1.07 (0.89-1.29) 156 1.07 (0.85-1.34) 90 1.09 (0.79-1.49) 30-59.9 40 1.23 (0.98-1.55) 82 1.17 (0.87-1.56) 58 1.33 (0.91-1.94) >60 74 1.98 (1.46-2.70) 38 1.62 (1.07-2.46) 36 2.59 (1.62-4.13) *pt*rend = 0.001, 0.374, 0.002

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Flood 2002 **Country:** USA **Study aims:** investigated the associations of folate, methionine, and alcohol intake, as well as combinations of these factors, with risk of colorectal cancer **Source of funding:** None specified	**Population:** *Source:* 64,182 women selected for entry into study cohort from a breast cancer screening programme (1973-1980) in US. 96% of women completed baseline questionnaire (1979-1981) and were eligible for further participation in study *Exclusion criteria:* prior colorectal cancer; missing (>30) items on the FFQ; implausible or unusually high intakes of folate *Study pop*: = 45,264 **Observation time:** 1987-1989 through to 1995-1998, LFU 10%, 490 Incident cases of colorectal cancer	**Exposure:** *Questionnaire:* 62-item Block/NCI FFQ *Repeated during follow-up*: baseline only *Reference period:*over the previous year *Drink type:* **Measure:** drinks per day, **Reference group**: 0 drinks per day **Results:** d/d Colorectal 0.01-0.50 0.92 0.73-1.16 0.51-1.00 1.00 0.74-1.35 1.01-2.00 0.94 0.62-1.42 <2.00 1.16 0.63-2.14 *p*trend 0.84

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Otani 2003 **Country:** Japan **Study aims:** investigated the association of alcohol consumption, smoking, and their joint effect with colorectal cancer and estimated the population-attributable fraction (PAF) to clarify their public health impact, based on a study **Source of funding:** Ministry of Health, Labor and Welfare of Japan	**Population:** *Source:* subjects (n= 57,591men and 59,103 women) identified by population registries in Osaka and Tokyo, maintained by local municipalities to form the Japan Public Health Centre-based prospective study on cancer and cardiovascular disease. 45,452 men (79%) and 49,924 women (84%) returned baseline questionnaire *Exclusion criteria:* Self reported medical history of cancer; Previous diagnosis of colorectal cancer; incomplete alcohol and/or smoking items *Study pop*: 42,540 men and 47,464 women **Observation time:** From baseline (1990-1993) until December 31, 1999. Loss to follow up 5%, 772 incident cases	**Exposure:** *Questionnaire:* self-administered validated questionnaire *Repeated during follow-up*: n/s *Reference period:*n/s *Drink type:* yes **Measure:** grams per week, **Reference group**: never drinkers **Results:** Colon Rectal 1-149 1.0 (0.7-1.4) 1.6 (0.9-2.6) 150-299 1.3 (0.9-1.8) 1.7 (1.0-2.8) 300+ 1.9 (1.4-2.7) 2.4 (1.5-4.0) *p*trend <0.001 <0.001

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Pedersen 2003 **Country:** Denmark **Study aims:** To investigate the relationship between amount and type of alcohol and the risk of colon and rectal cancer. **Source of funding:** Danish National Board of Health and Danish Ministry of Health	**Population:** *Source:* male participants from 3 longitudinal studies in Copenhagen, Denmark between 1976 and 1986, two random samples of general population, the other collected from 14 large workplaces *Exclusion criteria:*subjects with a history of cancer at baseline, except for non-melanoma skin cancer or carcinoma in situ *Study pop*:= 24, 496 **Observation time:** During a total of 426 934 person years (LFU <1%), 411 colon cancers (159 proximal colon, distal colon) and 202 rectal cancers. Mean follow up 14.7 years (range 2–23	**Exposure:** *Questionnaire:* self administered questionnaire *Repeated during follow-up*: yes *Reference period:* n/s *Drink type:* yes **Measure:** drinks per week, **Reference group**: <1 drink per week **Results:** Colon Rectum 1-6 1.0 0.8-1.3 1.5 0.9-2.3 7-13 0.9 0.7-1.2 1.5 0.9-2.5 14-27 0.9 0.6-1.2 1.7 1.0-2.8 28-40 1.1 0.7-1.7 2.1 1.1-4.0 ≥41 0.8 0.5-1.5 2.2 1.0-4.6 *p*trend =*0.58* *p*trend=*0.03*

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Shimizu 2003 **Country:** Japan **Study aims:** 'We have therefore conducted a prospective study, among Japanese people, of colorectal cancer in relation to height, BMI, alcohol consumption, and smoking habit' . **Source of funding:** Ministry of Education, Culture, Science, and Technology, Japan	**Population:** *Source:* cohort established in September 1992 with residents in Takayama, Japan, who were 35 years old or older *Exclusion criteria:*Participants who did not report their height; those who reported cancer other than non-melanoma skin cancer or colorectal adenoma at baseline; subjects who left four out of nine two page spreads of questionnaire or more all blank, and those who inadequately reported to the questionnaire *Study pop*: 29,051 **Observation time:** 1 January 1993 to 31 December 2000 198 (105 men, 93 women) with colon and 97 (56 men, 41 women) with rectal cancer.	**Exposure:** *Questionnaire:* semi quantitative FFQ *Repeated during follow-up*: *Reference period:* *Drink type:* sake, beer, light beer, shochu (distilled from sweet potatoes, rice, or buckwheat), wine, and hard liquor **Measure:**grams per day, **Reference group**:non-drinkers **Results:** Men Colon Rectal ≤36.7 1.79 0.71-4.55, 0.59 0.25-1.42 >36.7 2.67 1.06-6.76 1.17 0.50-2.73 *p*trend0.01 *p*trend0.06 Women Colon Rectal ≤36.7 1.07 0.58-1.96, 1.20 0.44-3.26 >36.7 1.78 1.00-3.18 1.80 0.70-4.62 *p*trend0.03 *p*trend0.17

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Su 2004 **Country:** USA **Study aims:** to examine effects of alcohol consumption on the risk of colon cancer and the individual role of different types of alcoholic beverages and their effects on colon cancer and to assess changes in drinking patterns on colon cancer risk. **Source of funding:** None specified	**Population:** *Source:* Study population derived from representative national survey (National Health Epidemiologic Follow-up Study) 14,407 participants eligible for follow-up, 13,291 (92.2%) were successfully traced through 1992 *Exclusion criteria:*previous history of cancer; subjects who were pregnant during the interview period were also excluded because drinking behaviours very likely were changed as a result of health recommendations *Study pop*: = 10,418 aged 25-74 (3,887 men and 6,531 women) **Observation time:** 10-yr follow-up (1982–84 to 1993), 111 colon cases	**Exposure:** *Questionnaire:* quantity frequency measure of drinking *Repeated during follow-up*: baseline only *Reference period:*over past 12 months *Drink type:* yes **Measure:**drinks per day, **Reference group**: non drinker **Results:** <1 1.08 0.65-1.79 ≥1 1.69 1.03-2.79 *ptrend 0.04* *Beer* *Wine* *Spirits* 1 drink/day 27 1.04 0.65-1.66 31 1.04 0.67-1.61 33 1.48 0.95-2.31 ≥1 drink/day 8 1.09 0.51-2.34 3 0.78 0.24-2.49 15 2.48 1.66-4.53

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Thygesen 2008 **Country:**USA **Study aims:** to investigate the effect of long-term alcohol intake on risk of breast cancer **Source of funding:** National Institutes of Health	**Population:**HEALTH PROFESSIONALS FOLLOW-UP STUDY FOR FURTHER DETAILS OF STUDY SAMPLE AND CHARACTERISTICS SEE SECTION 2.2, BOX 2.1 **Observation time:** 868 colorectal cancer cases were identified between 1986 and 31 January 2002; 583 were classified as colon cancer and 175 as rectal cancer.	**Exposure:** *Questionnaire:* FFQ *Repeated during follow-up*: Baseline alcohol intake used as first approach, (1986 FFQ). Updated information on alcohol intake was included (most recent intake at any time point), for which each 4-year interval between FFQs was treated as a mini-follow-up study and only the most recent alcohol intake was included *Reference period:*within the previous year, *Drink type:*beer, wine and spirits **Measure:** grams per day, **Reference group**: Non-drinkers =67 **Results:** *Baseline* *Updated* *Cumulative average* 0.1-5 g 167 1.05 (0.79-1.40) 124 1.14 (0.83–1.56) 202 1.02 (0.75-1.37) 5.1-10 g 120 1.30 (0.96-1.76) 98 1.15 (0.83–1.60) 130 1.16 (0.85-1.59) 10.1-20 g 192 1.38 (1.04-1.83) 186 1.34 (0.99–1.81) 188 1.31 (0.97-1.78) 20.1-30 g 52 1.43 (0.99-2.07) 46 1.21 (0.81–1.79) 58 1.08 (0.74-1.57) 30.1-45 g 86 1.44 (1.04-2.00) 77 1.36 (0.95–1.93) 88 1.56 (1.10-2.20) ≥45 g 59 1.75 (1.21-2.52) 24 1.62 (1.08–2.41) 46 1.59 (1.06-2.38) Past drinkers 125 1.31 (0.97-1.77) 232 1.05 (0.78–1.40) 99 1.15 (0.83-1.60) P for trend 0.0006 0.020 0.0006 HR (per 10 g/d) 1.07 (1.02-1.11) 1.07 (1.02–1.12) 1.08 (1.03–1.13)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Tsong 2007 **Country:**Singapore **Study aims:** To investigate the possible roles of tobacco and alcohol in colorectal cancer in non-white populations **Source of funding:** National Cancer Institute	**Population:**Singapore Chinese Health Study *Source:* permanent residents of Singapore who lived in government-built housing estates (86% of population lived in such facilities during enrolment period. Between April 1993 & December 1998, 63,257 subjects (85% of eligible subjects approached) recruited *Exclusion criteria:*baseline history of invasive cancer (except non-melanoma skin cancer) or superficial, papillary bladder cancer from the *Study pop*: 61,321 **Observation time:** 1993-1998 to 31 December 2004; average 8.9 yrs of follow-up; LFU: 0.7%; 852 colorectal cancer cases	**Exposure:** *Questionnaire:* in-person interview, 165-item food frequency questionnaire *Repeated during follow-up*: baseline only *Reference period:* n/s *Drink type:* (beer, wine, western hard liquor and Chinese hard liquor **Measure:***drinks per week,* **Reference group**: nondrinker (colorectal=658, colon -416, rectal = 242) **Results:** *Colorectal* *Colon* *Rectal* <7 117 0.96 (0.72–1.25) 60 0.96 (0.72–1.25) 57 1.22 (1.07–2.35) 7+ 70 1.84 (1.31–2.58) 40 1.84 (1.31–2.35) 30 1.59 (1.07–2.35) *p* trend 0.0004 0.01 0.01

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Wei 2004 **Country:** USA **Study aims:** To examine established risk factors to determine whether they were differentially associated with colon and rectal cancer **Source of funding:** National Institutes of Health	**Population:** NURSES' HEALTH STUDY (NHS)AND HEALTH PROFESSIONALS FOLLOW UP STUDY (HPFS). See Chapter 2.2 Box 2.1 - *Study pop*: 134,365 **Observation time:** 2,302,712 person years, 1,139 cases of colon cancer and 339 cases of rectal cancer	**Exposure:** NURSES' HEALTH STUDY (NHS) AND HEALTH PROFESSIONALS FOLLOW UP STUDY (HPFS). See Chapter 2.2 Box 2.1 **Measure:** grams per day, **Reference group:** 0 grams per day **Results:** Colon Rectal <10 0.97 0.82-1.14 1.04 0.77-1.40 10-19 1.04 0.85-1.26 1.07 0.75-1.55 ≥20 1.27 1.03-1.56 1.26 0.85-1.87 past 1.02 0.79-1.32 0.93 0.56-1.54 *p*trend *0.003* *p=0.20*

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Ye 2003 **Country:** Sweden **Study aims:** to quantify the risk of colorectal cancer among patients hospitalised at least once with a diagnosis of alcoholism. **Source of funding:** Swedish Cancer Society.	**Population:** record-linkage study based on the Swedish Inpatient Register created by the National Board of Health and Welfare. identified 193040 discharge records in the Inpatient Register with a diagnosis of alcoholism (ICD-8=291, 303; ICD-9=291, 303, 305A) during 1970–1994 *Exclusion criteria:*prevalent cancers; erroneous or incompletenational registration number, patients who died during the hospitalisation for alcoholism *Study pop:* 179398 patients, 36568 women and 142830 men **Observation time:**average follow up of 9 yrs, 1627902 person-years at risk; 929 incident cancers of the colon or rectum	**Exposure:** consumption defined by specified ICD-7,8,9 codes (ICD-7=307, 322; ICD-8=291, 303; ICD-9=291, 303, 305A), into category 'alcoholism' **Method:** drinking status (alcoholism), Standardised incidence ratio **Results:** *Colorectal* All 1.0 0.93-1.06 Male 1.02 0.95-1.09 Female 1.6 0.74-1.06

Descriptive Tables for colorectal cancer: case control studies

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Ho 2004 **Country:** Hong Kong **Study aims:** To investigate any association of colorectal cancer with smoking cigarettes and drinking. **Source of funding:** Health Services Research Committee of Hong Kong	**Population:** *Cases:* ethnic Chinese recruited from the surgical departments of 3 public hospitals, representing approx. 30% of population in Hong Kong. N=822 consecutive new patients, 452 colon cancer and 357 rectal cancer *Controls:* from same hospitals as cases N=926 **Exclusion criteria:** too ill for interview or had past history of malignancy; controls who required a special diet due to underlying medical conditions **Observation time:** April 1998 to March 2000 Response rate: Cases (82.2%) Controls (95.5%)	**Exposure:** *Questionnaire:* Structured interviews trained interviewers *Interviewers blinded*: n/s *Reference period:* Drinking habits' immediately prior to cancer diagnosis *Drink type:* n/s **Measure:** units per day, **Reference group**: never drinkers **Results:** Current > 4 units CRC 1.42 1.09-1.85 1.29 0.81-2.06 Colon 1.49 1.08-2.04 1.18 0.67-2.08 Rectal 1.34 0.95-1.88 1.38 0.77-2.47

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Hong 2005 **Country:** South Korea **Study aims:** To evaluate contribution of polymorphisms of the XRCC1 gene to the risk of colorectal cancer **Source of funding:** Inha University	**Population:** *Cases:* all newly diagnosed at outpatient clinics of general surgery at the Inha University Hospital, Incheon, South Korea, N=209 (rectal 145, colon 64) *Controls:* selected by random sampling of subjects who voluntarily visited the health-screening clinic at same hospital, N=209 **Exclusion criteria:** None specified **Observation time:** 2001–2003; Response rate n/s	**Exposure:** *Questionnaire:* Self administered questionnaire *Interviewers blinded*: n/s *Reference period:* n/s *Drink type:* yes **Measure:** grams per week, **Reference group**: <80 g/wk **Results:** *ca/co* ≥80g/w 64/52 2.60 1.46 -4.62

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Ji (2002) **Country:** China **Study aims:** To examine the association between colorectal cancer risk and alcohol and tobacco **Source of funding:** None specified	**Population:** *Cases:* permanent Shanghai residents newly diagnosed with cancers of the colon or rectum at ages 30–74 year N=931 with colon 874 with rectal cancer *Controls:* randomly selected from the general Shanghai population from Shanghai Resident Registry N=1552 **Exclusion criteria:** None specified **Observation time:** Between October 1990 and July 1992 Response rate n/s	**Exposure:** *Questionnaire:* standardized questionnaire *Interviewers blinded*: n/s *Reference period:*n/s *Drink type:* n/s **Measure:** grams per week, **Reference group:**non drinker **Results:** *g/w* *Colon* *Rectal* Ex drinker 2.3 1.4-3.7 1.1 0.9-1.4 Current 1.0 0.8-1.3 0.6 0.4-1.0 ≤159 0.8 0.5-1.2 0.6 0.4-0.9 >159-≤329 0.8 0.5-1.2 0.9 0.6-1.3 >329-<560 0.9 0.6-1.4 1.0 0.6-1.5 ≥560 1.5 1.1-2.2*ptrend 0.16* 1.2 0.8-1.7 *ptrend 0.60* *Years of drinking* <15 0.7 (0.5–1.1) 0.7 (0.4–1.0) 15–30 0.8 (0.5–1.2) 0.8 (0.5–1.2) 30–44 1.3 (0.9-1.8) 1.0 (0.7–1.5) 45+ 1.4 (0.9–2.2)*ptrend* 0.10 1.3 (0.7–2.1)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Kim 2004 **Country:** Canada **Study aims:** to assess the effects of alcohol consumption on the risk of colorectal cancer according to anatomical sub-site by examining separately the proximal colon, the distal colon, and the rectum	**Population:** *Cases:* All cases of colorectal cancer at 21 sites occurring in men aged 35-70 years diagnosed at all the large hospitals in Montreal area N=585 (176 proximal and 179 distal colon cancers, and 230 rectal cancers). *Controls:* selected using as sampling frames either electoral lists or random-digit dialling. N=533 **Exclusion criteria:** inadequate histories of alcohol consumption **Observation time:** Between 1979 and 1985 Response rates: Cases (85.8%) Controls (72.0%)	**Exposure:** *Questionnaire:* face-to face interview *Interviewers blinded*: *Reference period:*lifetime consumption *Drink type:* yes **Measure:** grams per week, **Reference group:**non drinker **Results:** for non weekly drinkers proximal distal rectum 1-2g/w 0.8 0.4-1.4 1.8 1.0-3.2 1.3 0.7-2.3 3-4g/w 0.8 0.4-1.7 2.3 1.2-4.4 1.7 1.0-3.1 ≥5g/w 1.6 0.9-2.9 3.0 1.6-5.6 2.0 1.1-3.6

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Murata 1999 **Country:** Japan **Study aims:** To explore a possible etiologic role of alcohol-drinking habit in the incidence of colorectal cancer with special reference to the *ALDH2* genotypes. **Source of funding:** Ministry of Education, Science, Sports and Culture of Japan	**Population:** *Cases:* cancer patients who underwent surgery in Chiba Cancer Centre Hospital N=265 colon 164 rectum *Controls:* selected from outpatients at same hospital as cases N=794 **Exclusion criteria:**history of cancer **Observation time:** from 1989 through 1997. Response rate n/s	**Exposure:** *Questionnaire:* Self-administered questionnaire. *Interviewers blinded*: n/s *Reference period:*n/s *Drink type:* Japanese sake, shochu, beer, whisky or wine **Measure:** cups of sake, **Reference group:**non drinker **Results:** men only Colon Rectal <1.0 0.53 0.29-0.99 0.48 0.22-1.02 1.0-1.9 0.81 0.48-1.4 0.84 0.45-1.6 2.0-2.9 1.66 0.88-3.1 2.04 0.97-4.3 3.0+ 2.19 1.10-4.5 2.10 0.91-4.9

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Murtagh 2004 **Country:** USA **Study aims:** To investigate how fluid intake from beverages and sources of fluid intake influence risk of rectal cancer. **Source of funding:** National Institute of Health	**Population:** from Kaiser Permanente Medical Care Program of Northern California and the state of Utah *Cases:*all eligible incident rectal cancer cases within these populations between 30-79 yr identified using a rapid-reporting system N=952 *Controls:* randomly selected from membership lists, and, in Utah, controls ≥65 yr randomly selected from social security lists and controls <65 yr, randomly selected from driver's license lists N=1,205 **Exclusion criteria:**previous colorectal tumour known familial adenomatous polyposis, ulcerative colitis, or Crohn's disease **Observation time:** May 1997 to May 2001 Response rates; 65.2% cases, 65.3% controls	**Exposure:** *Questionnaire:* trained and certified interviewers using laptop computers *Interviewers blinded*: n/s *Reference period:* per week 10 and 20 yr ago. *Drink type:* n/s **Measure:** grams per week, **Reference group:**non drinker **Results:** *Rectal* *Men* *Women* ≤114 1.0 0.75-1.32 1.03 0.73-1.47 >114 1.0 0.78-1.38 1.07 0.76-1.50

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Sharpe 2002 **Country:** Canada **Study aims:** to assess the effects of alcohol consumption on the risk of colorectal cancer according to anatomical sub-site by examining separately the proximal colon, the distal colon, and the rectum	**Population:** *Cases:* All cases of colorectal cancer at 21 sites occurring in men aged 35-70 years diagnosed at all the large hospitals in Montreal area N=585 (176 proximal and 179 distal colon cancers, and 230 rectal cancers). *Controls:* selected using as sampling frames either electoral lists or random-digit dialling. N=533 **Exclusion criteria:** inadequate histories of alcohol consumption **Observation time:** 1979 to 1985 Response rates: Cases (85.8%) Controls (72.0%)	**Exposure:** *Questionnaire:* face-to face interview *Interviewers blinded*: *Reference period:*lifetime consumption *Drink type:* yes **Measure:** grams per week, **Reference group:**non drinker **Results: non weekly drinkers** proximal distal rectum 1-2p/w 0.8 0.4-1.4 1.8 1.0-3.2 1.3 0.7-2.3 3-4p/w 0.8 0.4-1.7 2.3 1.2-4.4 1.7 1.0-3.1 ≥5p/w 1.6 0.9-2.9 3.0 1.6-5.6 2.0 1.1-3.6

Descriptive tables for endometrial cancer: cohort studies

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Friberg 2009 **Country:** Sweden **Study aims:** to examine the association between alcohol and endometrial cancer incidence **Source of funding:** WCRF, Swedish Cancer Foundation, The Swedish Research Council for Infrastructure.	**Population:** *Source:* population-based Swedish Mammography Cohort includes women from central Sweden who were 40 to 76 years of age at enrolment between 1987 and 1990. *Exclusion criteria:*n/s *Study pop*: 61,226 after exclusions **Observation time:** From December 31, 2005 to December 31, 2007; mean follow-up of 17.6 yrs loss to follow up: n/s, 687 incident endometrial (adenocarcinoma) cancer cases.	**Exposure:** *Questionnaire:* self-administered FFQ *Repeated during follow-up*: baseline and in 1997, used updated information on alcohol from 2nd quest, and by using average alcohol consumption for Jan. 1, 1998 to Dec. 31, 2007 from two questionnaires. *Reference period:* n/s *Drink type:* n/s **Measure:** grams per day, **Reference group**: Non-drinkers (n=268) **Results:** *ca* *Baseline* *ca* *Long-term* <3.4 273 1.01 (0.85-1.20) 300 1.01 (0.84-1.22) 3.4-9.9 122 0.95 (0.75-1.19) 141 1.01 (0.80-1.27) ≥10.0 24 1.12 (0.73-1.71) 25 1.09 (0.71-1.67)

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Loerbroks 2007 **Country:** Netherlands **Study aims:** To examine the association between alcohol consumption, cigarette smoking, and endometrial cancer. **Source of funding:** n/a	**Population:** *Source:* Netherlands Cohort Study (NLCS) started in September 1986 when 62,573 women aged 55-69 years were enrolled in cohort. Sub-cohort of 2,589 women sampled after the baseline exposure measurement. *Exclusion criteria:* diagnosed with non-epithelial tumours; information on either alcohol consumption or cigarette smoking was incomplete; undergone hysterectomy. *Study pop*: 1,901 (after exclusions) **Observation time:** 11.3-year follow-up period from September 1986 to December 1997 and no loss to follow-up; 280 cases	**Exposure:** *Questionnaire:* self-administered questionnaire *Repeated during follow-up*: baseline only *Reference period:* during year preceding baseline interview *Drink type:* beer, red wine, white wine, sherry, other fortified wine, liqueur, and liquor **Measure:** grams per day, **Reference group**: less than once per month (n= 82) **Results:** 0.1–4 105 1.09 (0.78–1.52) 5–14 39 0.95 (0.62–1.45) 15–29 17 0.94 (0.52–1.69) ≥30 11 1.78 (0.88–3.60) *p* trend 0.62

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Setiawan 2008 **Country:**USA **Study aims:** To examine the impact of alcohol intake on endometrial cancer risk among postmenopausal African-American, Japanese-American, Latina, Native-Hawaiian and White women **Source of funding:** National Cancer Institute.	**Population:** *Source:* Multiethnic Cohort Study: participants identified via US state driver's license files, voter registration lists and Health Care Financing Administration data files. Cohort consisted of >215,000 men and women (45-75 yrs at baseline) and comprised mainly 5 self-reported racial/ethnic populations: African Americans, Japanese Americans, Latinos, Native Hawaiians and Whites living in Hawaii and California. *Exclusion criteria:*had cancer other than nonmelanoma skin cancer; reported a hysterectomy or a bilateral oophorectomy; missing data on any of the key lifestyle variables *Study pop*: 41,574 postmenopausal women (15.7% African Americans, 31.5% Japanese Americans, 21.5% Latinas, 6.7% Native Hawaiians, 24.5% whites **Observation time:** 1993-1996 to December 31, 2002, average follow-up 8.3 yrs, 324 incident cases	**Exposure:** *Questionnaire:* self-administered FFQ, nine intake categories ranged from "never" to "4 or more times per day" and information on usual serving size also requested *Repeated during follow-up*: baseline only *Reference period:* during the year preceding the baseline questionnaire *Drink type:* regular beer, light beer, red wine, white/pink wine (including champagne and sake) and hard liquor **Measure:**grams per day (12grams =1 'standard' drink), **Reference group**: non-drinkers [0 g/d or <1 drink/day] (n=196) **Results:** *g/d* *ca* *Total alcohol* *ca* *Beer* >0 to <12 85 1.01 (0.77-1.33) 42 1.04 (0.73-1.49) 12 to <24 14 1.09 (0.62-1.93) 5 1.68 (0.67-4.21) ≥ 24 29 2.01 (1.30-3.11) 4 1.46 (0.52-4.12) *p* trend 0.1910.327 *g/d* *ca* *Wine* *ca* *Spirits* >0 to <12 81 1.14 (0.85-1.52) 44 1.18 (0.82-1.69) 12 to <24 9 1.37 (0.68-2.78) 8 2.25 (1.06-4.77) ≥ 24 11 3.15 (1.63-6.09) 10 1.96 (0.98-3.90) *p* trend 0.0070.015

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Terry 1999 **Country:** Sweden **Study aims:** examine associations of physical activity, weight, fruit, vegetable, and alcohol consumption, SES, parity and presence of diabetes mellitus with risk of endometrial cancer **Source of funding:** Swedish Cancer Society	**Population:** *Source:* Swedish Twin Registry cohort, of male and female same sexed twin pairs, born 1886–1925 and living in Sweden in 1961, In 1961, 12,186 women, approx. 85% of females in Registry, replied to initial questionnaires. *Exclusion criteria:*incomplete lifestyle information *Study pop*: 11,659 women **Observation time:** 1961 to December 31, 1992. Mean follow-up period of 20.4 years, No loss to follow up, 133 incident cases,	**Exposure:** *Questionnaire:* Mailed self completed questionnaire *Repeated during follow-up*: baseline only *Reference period:*n/s *Drink type:*n/s **Measure:** drinks per week, **Reference group:** non-drinkers **Results:** < 2 22 1.7 (1.0-2.8) ≥2-< 4 10 1.2 (0.6-2.4) ≥4 7 1.3 (0.6-2.8)

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Weiderpass 2001 **Country:** Sweden **Study aims:** To investigate whether alcohol intake in general and alcohol abuse in particular increases risk for endometrial cancer **Source of funding:** Swedish Cancer Society	**Population:** *Source:* women who were hospitalized at least once with a diagnosis of alcoholism between 1965 and 1994, identified from National Inpatient Registrar *Exclusion criteria:*records with erroneous national registration numbers; patients with prevalent cancer inconsistencies uncovered during record linkage *Study pop*: n= 36856 **Observation time:** between 1964 and 1994, followed for an average of 9.6 years, LFU: n/s 69 primary endometrial cancer cases	**Exposure:** Diagnosis of alcoholism (undefined) *Questionnaire:* n/a *Repeated during follow-up*: n/a *Reference period :*n/a *Drink type:* n/a **Measure:** standardised incidence ratio, **Reference group**: n/a **Results:** *Total intake* 69 0.76 (0.59–0.96) *Age at follow-up (yr)* <50 17 1.7 1.0–2.7 50–59 21 0.6 0.4–1.0 ≥60 31 0.6 0.4–0.9 *Calendar year at entry* 1965–1974 19 0.9 0.5–1.4 1975–1984 38 0.7 0.5–1.0 1985–1994 12 0.8 0.4–1.4 *Duration of follow-up (yr)* 1–9 42 0.8 0.6–1.0 ≥10 27 0.8 0.5–1.1

Descriptive tables for endometrial cancer: case control studies

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Hosono 2008 **Country:** Japan **Study aims:** To examine the association between alcohol consumption and endometrial cancer risk **Source of funding:** the Ministry of Education, Science, Sports, Culture, and Technology of Japan, Ministry of Health, Labour, and Welfare of Japan	**Population:** *Cases:* all incident cases from Hospital-based Epidemiologic Research Program at Aichi Cancer Centre N= 148 *Controls:* randomly selected from the Hospital-based Epidemiologic Research Program at Aichi Cancer Centre N= 11 814 **Exclusion criteria:**cancer-free **Observation time:** January 2001 to June 2005 Response rate: 90% for cases and controls	**Exposure:** *Questionnaire:* self-administered questionnaire *Interviewers blinded*: n/a *Reference period:* during the 1-year period before onset of the present disease or before being interviewed *Drink type:* Japanese sake, beer, shochu, whiskey and wine **Measure:** frequency and amount (grams per week), **Reference group**: non drinking in last week (108/929) **Results:** *Frequency* *Amount* <1/week 14/166 0.71 (0.39–1.29) <25 g/w 23/246 0.79 (0.49–1.28) 1–2/week 11/119 0.77 (0.40–1.50) 25–175 g/w 12/232 0.42 (0.23–0.79) 3–4/week 8/99 0.67 (0.31–1.43) >175 g/w 3/47 0.47 (0.14–1.58) *p*trend 0.005 ≥5-/week 7/154 0.37 (0.17–0.82) *p*trend 0.009

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
McCann 2000 **Country:** USA **Study aims:** to investigate the effect of diet on risk of endometrial cancer accounting for known risk factors. **Source of funding:** None specified	**Population:** *Cases:* from series of case-control studies of diet and cancer of the breast, endometrium, ovary, and prostate in western New York N= 523 *Controls:* randomly selected from driver's license lists for women <65 years of age and from Health Care Finance Administration lists for women ≥ 65 years of age N=865 **Exclusion criteria:** None specified **Observation time:** Between November 1986 and April 1991 Response rate: 51% for cases and controls	**Exposure:** *Questionnaire:* trained nurse interviewers with interview schedule *Interviewers blinded*: n/s *Reference period:* up to 2 years prior to the interview, 10 years, and 20 years before the interview and at age 16. *Drink type:*n/s **Measure:** grams per month, **Reference group**: 0.5 grams per month **Results:** 0.6-2.1 62/168 1.0 (0.6-1.6) 2.2-9.0 42/173 0.8 (0.5-1.3) >9.0 39/159 1.0 (0.5-1.8) *p*trend=0.58 .

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Weiderpass and Baron 2001 **Country:** Sweden **Study aims:** To assess effects of cigarette smoking and alcohol consumption on risk of endometrial cancer among postmenopausal women. **Source of funding:** American Cancer Society, Swedish Cancer Society, US National Institutes of Health	**Population:** *Cases:* identified from six regional cancer registries in Sweden N=1055 *Controls:* randomly selected from continuously updated population register, N=4216 **Exclusion criteria:** premenopausal women; previous diagnosis of breast cancer **Observation time:** 1 January 1994 and 31 December 1995 Response rate: cases 75% and controls 79.9%	**Exposure:** *Questionnaire:* mailed questionnaires supplemented by telephone interviews for 14% of controls *Interviewers blinded*: n/a *Reference period:* one year before interview *Drink type:*beer (light, strong), wine, fortified wine, spirits **Measure:** grams per day, **Reference group**: non drinkers **Results:** *g/d* *ca/co* >0-<1.59 132/491 1.16 (0.90-1.49) 1.6-3.99 104/506 0.92 (0.70-1.92) ≥ 4 107/250 0.92 (0.70-1.92) ptrend 0.44

Descriptive Tables for gastric cancer: cohort studies

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Barstad 2005 **Country:** Denmark **Study aims:** to assess the effects of types of alcoholic beverage on the risk of developing gastric cancer **Source of funding:** None specified	**Population:** *Source:* Copenhagen Centre for Prospective Population Studies, consisting of 3 longitudinal population studies in Copenhagen area randomly selected from age-stratified population, and from 14 large workplaces in Copenhagen *Exclusion criteria:* previously diagnosed gastric cancer. *Study pop*: 15 236 men and 13 227 women Mean participation rate was 80% **Observation time:** 389 051 person-years , LFU: <1%; 122 incident cases of gastric cancer	**Exposure:** *Questionnaire:* self-administered questionnaire *Repeated during follow-up*: baseline only *Reference period:* n/s *Drink type:* beer, wine and spirits **Measure:**drink per week, **Reference group**: <1 drink per week **Results:** 1-6 1.47 (0.93-2.02) 7-13 0.95 (0.32-1.58) 14-27 1.04 (0.40-1.68) 28- 1.13 (0.41-1.86) *trend test in drinks per day* Beer 1.02 (0.88-1.17) *p*trend0.81 Wine 0.60 (0.39-0.93) *p*trend0.02 Spirits 1.22 (0.95-1.56) *p*trend0.12

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Freedman 2007 **Country:** USA **Study aims:** To investigate associations between alcohol and tobacco with oesophageal adenocarcinoma and gastric cardia adenocarcinoma risk and compared them with those for ESCC and gastric noncardia adenocarcinoma **Source of funding:** Intramural Research Program of the National Cancer Institute, NIH	**Population:** *Source:* risk factor questionnaire mailed to 3.5m members of American Association of Retired Persons- open to those >50 yrs, residing in 6 US states and two metropolitan areas, Of 617,119 persons who returned questionnaire (17.6%), 566,407 completed survey *Exclusion criteria:* cancer at baseline; energy intake >two interquartile ranges from median; died or diagnosed with cancer on 1st day of follow-up; no information on alcohol use *Study pop*: =474,606, 282,856 men and 191,750 women. **Observation time:** 1995/1996 to 2000 (2,121,797 pys follow-up), LFU: n/s, 188 with gastric cardia, and 187 gastric noncardia adenocarcinoma cases	**Exposure:** *Questionnaire:* Self administered questionnaire *Repeated during follow-up*: baseline only *Reference period:* over the past 12 months *Drink type:* wine beer liquor **Measure:** drinks/day, **Reference group**: >0–1 drinks per day **Results:** *ca* *Gastric cardia* *ca* *Gastric noncardia* 0 46 1.19 0.83-1.70 59 1.30 0.93-1.82 >1–3 29 0.99 0.65-1.52 31 1.17 0.77-1.77 >3 27 1.57 0.98-2.52 *p*trend0.12 9 0.62 0.30-1.27 *p*trend 0.15

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Huang 2000 **Country:** Japan **Study aims:** to evaluate whether lifestyle before diagnosis is related to survival of gastric cancer patients **Source of funding:** the Ministry of Health and Welfare	**Design:** retrospective cohort **Population:** *Source:* Patients who underwent operations in the Department of Gastrointestinal Surgery of a major cancer hospital in Aichi, Japan *Exclusion criteria:*none specified *Study pop*: 877 study subjects (578 men and 299 women) between 40 and 79 years **Observation time:** From January 1988 to December1994, LFU: n/s 636 gastric cancer cases	**Exposure:** *Questionnaire:* Self completed questionnaire *Repeated during follow-up*: n/s *Reference period:* n/s *Drink type:* sake **Measure:** Drinking Status*&*'go' per day, **Reference group**: Never(0 go/day, 1 go = 180 ml Japanese wine) **Results:** *Drinking status* *go per day* *Quantity* Ever 1.40 (0.95-2.06) 0.1-1.0 1.53 (0.98-2.39) Current 1.36 (0.91-2.02) 1.1-1.9 1.08 (0.70-1.66) Former 1.66(0.89-3.08) ≥2 1.08 (0.70-1.66)

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Kasum 2002 **Country:** USA **Study aims:** to study whether, whole-grain intake is related to reduced risk of upper aerodigestive tract cancers **Source of funding:** N/s	**Population:** *Source:* Random sample of women aged 55–69 years from state of Iowa driver's license list. *Exclusion criteria:*if left 30 or more items blank on the FFQ or reported implausibly high or low energy intake; premenopausal women; women at baseline reporting cancer of any site other than skin *Study pop*: A total of 41,836 women responded to mail survey (42.7% response rate). After exclusions, cohort = 34,651 **Observation time:** 1986–1999, approx 400 ,000 person years, LFU <1%; 56 women with gastric cancer	**Exposure:** *Questionnaire:* Self-administered 127-item FFQ *Repeated during follow-up*: baseline *Reference period:* n/s *Drink type:* n/s **Measure:**drinks per day, **Reference group:** 0 drinks per day **Results:** d/d ca HR >0-1.9 8 0.63 ≥2 16 1.15 no confidence intervals presented in study text

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Larsson2007 **Country:** Sweden **Study aims:** Investigated the association between total alcohol (ethanol) intake as well as specific alcoholic beverages and risk of gastric cancer in **Source of funding:** n/s	**Population:** Swedish Mammography Cohort *Source:* women from central Sweden 40 to 76 yrs at enrolment between 1987 and 1990. 66,651 women, (74%) returned questionnaire *Study pop*: After exclusions, 61,433 women. *Exclusion criteria:*implausible values for total energy intake; incorrect or missing national registration number; previous diagnosis of cancer other than non-melanoma skin cancer **Observation time:** 1987–1990 to June 30, 2005, (966,807pys follow-up), LFU: n/s; 160 incident cases of gastric cancer	**Exposure:** *Questionnaire:* 96-item FFQ *Repeated during follow-up*: baseline only *Reference period:* over the past year *Drink type:* light beer, medium-strong beer, strong beer, wine, and hard liquor. **Measure:** grams per week, **Reference group**: Non-drinkers (n=61) **Results:** *g/w* *ca* 0.1–19.9 50 0.85 (0.58-1.25) 20.0–39.9 27 1.18 (0.73-1.91) ≥40.0 22 1.33 (0.79-2.25) *p*-trend0.14

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Sasazuki 2002 **Country:** Japan **Study aims:** evaluated the role of smoking or alcohol use as a risk factor in gastric cancer, but few have considered anatomic and histo-pathologic subdivisions **Source of funding:** Ministry of Health and Welfare of Japan; Grant sponsor: Foundation for the Promotion of Cancer Research in Japan.	**Population:** *Source:* men living in 14 catchment areas administered by 4 Public Health Centres in Japan who returned baseline questionnaire, n=20,665 men (76%), aged 40-59yrs *Exclusion criteria:*self-reported serious illness (cancer, ischemic heart disease; cerebrovascular disease, chronic liver disease) at baseline; subjects who were not Japanese *Study pop*: After exclusions, cohort =19,657 men. **Observation time:** 1 January 1990 to 31 December 1999, LFU: n/s; identified 253 gastric cancer cases	**Exposure:** *Questionnaire:* Mailed lifestyle questionnaire *Repeated during follow-up*: baseline *Reference period:* consumption at least once per week *Drink type:* sake, shochu/awamori, beer and whiskey **Measure:** grams per week**, Reference group:** 0–3 days/month **Results:** *All sites* 0-161.0 0.8 (0.6-1.2) 162.0-322.0 1.1 (0.8-1.5) 325.5+ 1.1 (0.8-1.6) *p*trend=0.66 *Histologic type* *Cardia* *Distal Diff* *Distal Undiff* 0-161.0 8 2.5 (0.7-9.5) 27 0.9 (0.5–1.5) 11 0.7 (0.3–1.4) 162.0-322.0 13 3.3 (0.9-11.6) 38 1.1 (0.7–1.8) 15 0.9 (0.5–1.9) 325.5+ 11 3.0 (0-8-11.1) 27 0.9 (0.5-1.5) 20 1.3 (0.7-2.6) *p*trend= 0.66 1.00 0.07

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Sjödahl 2006 **Country:** Norway **Study aims:** to provide valid evidence for the role of smoking and alcohol drinking in relation to gastric adenocarcinoma **Source of funding:** Swedish Cancer Society, Swedish Research Council	**Population:** *Source:* health survey in the county of Nord-Trondelag in Norway between the years 1984 and 2002. Written invitations to participate in the survey were mailed to 85,100 adults living in the county 75,043 (88.2%) who attended the survey were eligible for subsequent follow-up *Exclusion criteria:* attending persons whose follow-up time after participation in the health survey was 3 years or less to avoid selection bias *Study pop*: 69,962 **Observation time:** (between 1984 and 1986) through December 31, 2002, (1,117,648 pys) , LFU: n/s 251 cases of gastric cancer, of which 224 (89%) were non-cardia gastric cancer and 27 were gastric cardia cancer	**Exposure:** *Questionnaire:* writtenquestionnaires *Repeated during follow-up*: baseline only *Reference period:* during the last 14 days *Drink type:* n/s **Measure:** Frequency of alcohol drinking, **Reference group**: Never drinking alcohol (n=27 gastric & n=226 non cardia gastric cancer **Results:** *Gastric cancer (including cardia)* — *Non cardia gastric cancer* Drinking occasionally 109 1.24 (0.80-1.91) 1.16 (0.74–1.82) 1–4 times 58 1.30 (0.78-2.16) 1.29 (0.76–2.18) ≥5 times 17 1.49 (0.78-2.83) 1.66 (0.87–3.20) *Feeling of intoxication when drinking* No 70 1.10 (0.67-1.77) 1.12 (0.69–1.82) Yes 26 1.47 (0.81-2.69) 1.50 (0.80–2.83) *Drinking excessively, or at least a bit to much* No 113 1.15 (0.73-1.80) 1.13 (0.71–1.79) Possibly or maybe 31 1.56 (0.88-2.76) 1.49 (0.82–2.72) Yes 15 1.13 (0.57-2.24) 1.30 (0.65–2.60)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Sung 2007 **Country:** Korea **Study aims:** investigated the effects of smoking and alcohol consumption on the risk of gastric cancer by sub-site in the National Health Insurance Corporation Study **Source of funding:** Korean National Cancer Center	**Population:** *Source:* government employees, teachers and their dependents who were insured by the Korea National Health Insurance Program in 1996, had at least one medical examination, n= 692 108 men aged ≥30yrs *Exclusion criteria:*- cancer at enrolment; missing information on questionnaire *Study pop*: n=669 634 **Observation time:** 1996 to 2002, (4,353,317 pys); LFU: n/s; 3452 cases of gastric cancer, (127 (4%) cardia and upper-third cancers, 2409 (70%) distal gastric cancer and 1007 (26% unclassified)	**Exposure:** *Questionnaire:* no details *Repeated during follow-up*: baseline only *Reference period:* n/s *Drink type:* Soju **Measure:**grams per day, **Reference group**: 0 grams per day (*Gastric* n=946, *Distal* 633, *Cardia and upper third* 36 **Results:** *ca Gastric cancer ca Distal ca Cardia and upper third* 1 –14.9 946 1.0 (0.9-1.1) 633 1.0 (0.9-1.2) 36 1.3 (0.8-2.1) 15.0-24.9 644 1.1 (1.0-1.3) 430 1.2 (1.0-1.3) 31 1.7 (1.0-2.8) ≥25 863 1.2 (1.1-1.4) 594 1.3 (1.2-1.5) 31 1.3 (0.8-2.2) *p*trend 0.0001 0.0002 0.5914

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Tran et al 2005 **Country:** China **Study aims:** 'We examined risk factors for oesophageal squamous cell carcinoma, gastric cardia cancer, and gastric non-cardia cancer' **Source of funding:** n/s	**Population:** *Source:* General Population Trial from the general population of Linxian. *Exclusion criteria:* no history of cancer or debilitating disease *Study pop*: 29,584 individuals,40–69 yrs **Observation time:** March 1986 until May 2001, 15 years of follow-up, LFU<1%; 1,089 gastric cardia cancer and 363 gastric non-cardia cancer	**Exposure:** *Questionnaire:* Interview and self-complete questionnaire *Repeated during follow-up*: baseline *Reference period:* in the past 12 months *Drink type:* n/s **Measure:** frequency, **Reference group** not drank in last 12 months **Results:** *cardia* use in last 12 months 0.84 (0.72-0.97) *non cardia* use in last 12 months 0.79 (0.61-1.02)

Descriptive tables for gastric cancer: case control studies

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Chow 1999 **Country:** Poland **Study aims:** To evaluate risk factors for stomach cancer in Poland **Source of funding:** U.S. National Cancer Institute	**Population:** Cases: identified by collaborating physicians in each of 22 hospitals serving the Warsaw area N=324 Controls: randomly selected among Warsaw residents from a computerized registry of all legal residents in Poland N=480 **Exclusion criteria:** None specified **Observation time:** between March 1, 1994, and April 30, 1996 *Response rate*: Cases (82.1%) Controls (87.4%)	**Exposure:** *Questionnaire:* interviewed by trained interviewers *Interviewers blinded*: n/s *Reference period:* prior to 2 years before *Drink type:* beer, wine, liquor **Measure:** drinks/week, **Reference group:** no alcohol on a monthly basis for at least 6 months **Results:** Current Former <1 41/52 0.7 (0.4-1.2) 0.6 (0.3-1.1) 1-<3 42/76 0.5 (0.3-0.9) 1.2 (0.5-2.6) 3-<7 32/66 0.4 (0.2-0.7) 1.0 (0.4-2.3) ≥7 79/54 1.2 (0.7-2.0) 0.5 (0.2-1.3)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Kikuchi 2002 **Country:** Japan **Study aims:** to evaluate relationship between smoking or drinking doses and risk for stomach cancer, and to clarify whether the relationship is dose-dependent or U-shaped**.** **Source of funding:** Japanese Ministry of Education, Culture, Sports, Science and Technology	**Population:** *Cases:* stomach cancer patients newly hospitalized in one of nine hospitals in Tokyo N=787 *Controls*: recruited from several health check programs in a hospital in same area N=1007 **Exclusion criteria:** aged over 70 years; prior therapy for stomach cancer; information incomplete on smoking or drinking habits **Observation time:** Between June 1993 and July 1995. *Response rate*: n/s	**Exposure:** *Questionnaire:* self completed questionnaire *Interviewers blinded*: n/s *Reference period:*' lifetime' *Drink type:* n/s **Measure:***l*ifetime alcohol years, **Reference group:**never drinker **Results:** *alcohol years* *Males* *Females* 0.1-134.9 0.57 (0.33-1.00) 0.54 (0.35-0.82) 135.0-1349.9 1.23 (0.73-2.06) 0.75 (0.43-1.30) 1350.0+ 1.40 (0.85-2.31*)* *p*trend<*0.001* *p*trend<*0.001*

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Lagergren 2000 **Country:** Sweden **Study aims:** to test the association between tobacco, snuff and alcohol use and the risk of oesophageal and cardia cancer **Source of funding:** Swedish Cancer Society	**Population:** *Cases*: patients with new diagnosis of adenocarcinoma of the gastric cardia in Swedish population N=262 *Controls:* randomly selected from age and sex strata in study base to resemble age and sex distributions among the oesophageal adenocarcinoma cases N=820 **Exclusion criteria:** persons aged 80 years or older and individuals born abroad **Observation time:** 1995 through 1997 *Response rate:* Cases (83%) Controls (73%)	**Exposure:** *Questionnaire:* face-to-face interviews *Interviewers blinded*: not blinded to case/control status of the interviewees, but unaware of study hypotheses *Reference period:* 20 years before the interview *Drink type:* beer, wine and liquor **Measure:** units per week, **Reference group:**never drank **Results:**, *gastric cardia* u/w Any alcohol 1-15 0.9 (0.5-1.5) 16-70 0.6 (0.4-1.1) >70 0.9 (0.5-1.5)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Lindblad 2005 **Country:** United Kingdom **Study aims:** Toprospectively assess influence of BMI, tobacco, and alcohol on the occurrence of oesophageal, gastric cardia, and non-cardia gastric adenocarcinoma, and to detect any sex differences that could explain the male predominance of these tumours **Source of funding:** AstraZeneca R&D and Swedish Cancer Society	**Population:** *Cases*: For details see Lindblad et al in Descriptive tables for Oesophageal cancer N=1023 gastric cancers (195 gastric cardia, 327 distal, 501 unknown) *Controls:* For details see Lindblad et al in Descriptive tables for Oesophageal cancer N= 10,000 **Exclusion criteria:**patients with any cancer recorded in database before start of study period **Observation time:** January 1, 1994 to December 31, 2001 *Response rate*: n/s	**Exposure:** For details see Lindblad et al in descriptive tables for oesophageal cancer **Measure:** units per day, **Reference group:** 0-2 units per day **Results:** u/d *ca/co* *Total gastric adenocarcinoma* 3-15 166/1662 0.92 0.75-1.12 16-34 58/563 0.91 0.67-1.22 >34 16/183 0.75 0.44-1.27 Unknown 432/4219 0.99 0.80-1.24 *Cardia* *Non-cardia* *Unknown subsite* 3-15 1662/33 1.08 0.70-1.69 1662/61 0.99 0.72-1.36 1662/72 0.82 0.61-1.09 16-34 563/14 1.22 0.67-2.24 563/19 0.91 0.55-1.51 563/25 0.79 0.51-1.22 >34 183/4 1.04 0.37-2.93 83/2 0.29 0.07-1.18 183/10 0.96 0.49-1.87 Unknown 89/4219 1.38 0.84-2.26 89/121 0.57 0.38-0.87

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Munoz 2001 **Country:** Venezuela **Study aims:** To investigate behavioural and environmental risk factors for gastric cancer **Source of funding:** None specified	**Population:** *Cases*: identified in the general hospital at San Cristobal, capital of Tachira State, Venezuela N= 302 *Controls:* drawn from neighbourhoods around hospital, had to be resident in Tachira for at least 5 years N=485 *Exclusion criteria:*previous gastric surgery; non-epithelial tumours of the stomach **Observation time:** Between January 1991 and January 1997 Response rate: n/s	**Exposure:** *Questionnaire:* Social workers, who were specially trained for the study, interviewed with a structured questionnaire that had been *Interviewers blinded:* n/s *Reference period:* during the year preceding the interview *Drink type:*n/s **Measure:**Drinking Status, grams per week, years since quitting, **Reference group:** never and 1-150g/w **Results:** *Drinking Status* Current 2.9 (1.9-4.3) Ex 3.5 (2.0-6.0) *Years since quitting (referent group 6–10yrs)* *Quantity* 11–15 9/8 0.8 (0.2, 2.8) 151+ 32/27 1.0 (0.5-2.1) 16–20 9/5 1.3 (0.3, 5.3) 20+ 7/4 1.1 (0.3, 4.8)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Rao 2002 **Country:** India **Study aims:** to identify association of tobacco use, alcohol drinking, non-vegetarian dietary items, consumption of tea and coffee and living environment with stomach cancer in India **Source of funding:** n/s	**Population:** Cases: were patients attending cancer centre for diagnosis and treatment in Mumbai, N=170 Controls: were cancer free patients attending same hospital as cases, N=2,184 *Exclusion criteria:*infectious disease or benign lesion **Observation time:** 1988–1992, Response rate: n/s	**Exposure:** *Questionnaire:* Interviewed by trained social workers *Interviewers blinded:* n/s *Reference period:* n/s *Drink type:*n/s **Measure:** habitual drinking, **Reference group:**non drinkers **Results:** alcohol drinkers 0.8 (0.4-1.3) p =0.2

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Suwanrungruang 2008 **Country:** Thailand **Study aims:** To investigate various aspects of dietary factors, smoking, and alcohol drinking in determining risk of stomach cancer **Source of funding:** n/s	**Population:** *Cases:* recruited from Srinagarind Hospital and KhonKaen Regional Hospital in KhonKaen Province, Thailand, N= 101 *Controls:* from same hospitals as cases, N= 202 **Exclusion criteria:** none specified **Observation time:** 2002-2006, Response rate*:* n/s	**Exposure:** *Questionnaire:* interviewed by trained interviewer using a structured questionnaire *Interviewers blinded*: n/s *Reference period:* n/s *Drink type:* n/s **Measure:** drinking status, **Reference group**: non-drinkers **Results:** Ever drinker 35/62 1.4 0.68-2.66

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Wu 2001 **Country:** USA **Study aims:** ' to determine role of smoking, alcohol use, and body size in the etiology of esophageal, gastric cardia, and distal gastric adenocarcinomas' **Source of funding:** National Cancer Institute	**Population:** *Cases:* men and women aged 30-74 years identified by Cancer Registry, Los Angeles, N = 500 gastric cardia/787 distal gastric cancers *Controls*: selected from same cancer registry N=1289 **Exclusion criteria:** none specified **Observation time:** 1992-1997 Response rate: n/s	**Exposure:** *Questionnaire:* structured questionnaire administered by interviewer *Interviewers blinded:* not blind to case or control status, but were not aware of study hypotheses *Reference period:* lifetime use *Drink type:*beer, wine, hard liquor **Measure:** drinks per week, **Reference group:**never drinkers **Results:** *Cardia* *Distal* Former 0.91 (0.6-1.4) 0.85 (0.6-1.2) Current 0.98 (0.7-1.5) 0.96 (0.7-1.3) 1-7 1.00 (0.7-1.5) 0.83 (0.6-1.2) 8-21 0.70 (0.4-1.1) 0.68 (0.5-1.0) 22-35 1.09 (0.7-1.8) 1.10 (0.7-1.7 36+ 1.35 (0.8-2.3) *p*trend 0.42 1.35 (0.8-2.2) *p*trend 0.29

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Ye 1999 **Country:** Sweden **Study aims:** To analyse the effects of smoking, use of smokeless tobacco, alcohol intake and the risk of gastric cancer by sub-site and histology **Source of funding:** Swedish Cancer Society	**Population:** *Cases:* individuals with newly confirmed gastric cancer, identified by all departments of surgery and pathology, supplemented by linkages to regional and national cancer registries, born in Sweden, and living in one of 5 counties in northern and central Sweden N=567 *Controls* randomly sampled from general population N=1165 **Exclusion criteria:** none specified **Observation time:** February 1989 through January 1995. Response rate: cases 62%, controls 76%	**Exposure:** *Questionnaire:* Face-to-face interviews were carried out by specially trained professionals *Interviewers blinded*: not blinded to case/control status, but unaware of study hypotheses *Reference period:* 20 years before interview *Drink type:* light beer, medium-strong beer, strong beer, wine and hard-liquor c **Measure:** lifetimes (ml), **Reference group:** non drinkers **Results:** *Cardia* / *Distal diffuse* / *Distal Intestinal* 1-35 0.9 (0.4-1.9) 1.3 (0.8-2.1) 1.2 (0.8-1.9) 36-160 0.8 (0.4-1.7) 1.0 (0.6-1.7) 1.2 (0.8-1.9) >160 0.7 (0.3-1.5) 1.0 (0.5-1.8) 1.2 (0.7-1.9) *p*trend= 0.30 0.73 0.56

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Zaridze 2000 **Country:** Russia **Study aims:** To examine the risk of gastric cancer associated with alcohol consumption and smoking in men and women in Moscow, Russia. **Source of funding:** American Institute for Cancer Research	**Population:** *Cases*: patients, who lived in Moscow, with newly diagnosed stomach cancer in two main cancer-treatment hospitals in Moscow. N= 248 men & 200 women *Controls:* selected among patients of the same hospitals as cases and living in Moscow N=292 men & 318 women **Exclusion criteria:** patients who had cancer and/or gastrointestinal diseases **Observation time:** February 1996-March 1997 Response rate: cases 98.3% controls 96.5%	**Exposure:** *Questionnaire:* self-administered structured questionnaire *Interviewers blinded*: n/s *Reference period:* preceding year *Drink type:* vodka sweet wine **Measure:** litres per year, **Reference group:**never drinkers **Results:** *ca/co* *Males* *ca/co* *Females* Ever 224/251 1.9 1.1-3.4 125/194 1.2 0.8-1.8

Descriptive Tables for kidney cancer: cohort studies

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Lee 2006 **Country:** USA **Study aims:** examined total fluid intake and intakes of specific beverages in relation to risk of renal cell cancer in two large cohorts, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS) **Source of funding:** NIH	**Population:** *Source:* see box 2 section 2.4 (p28) *Study pop*: 88,759 women in the NHS and 47,828 men in the HPFS (after exclusions) **Exclusion criteria:** previously diagnosed with cancer (except non-melanoma skin cancer); left extensive items blank on the baseline FFQ for each analysis **Observation time:** 1986 to May 31, 2000, for women; January 31, 2000, for men, Loss to follow up: <10% 132 incident cases of renal cell cancer during 1,708,260 person-years of follow-up in the NHS and 116 cases during 608,265 person-years of follow-up in the HPFS	**Exposure:** *Questionnaire:* semi quantitative FFQ *Repeated during follow-up*: every four years *Reference period:* during past year *Drink type:* beer wine spirits **Measure:** grams per day, **Reference group**: 0 g/drams per day (n=58) **Results:** 0.1-4.9 88 0.96 (0.68-1.34) 5.0-14.9 61 0.87 (0.46-1.64) ≥15.0 41 0.66 (0.43-1.00), *p* trend 0.07 *Wine (servings per week, month)* 1/mo to <2/wk 96 1.16 (0.86-1.55) >2/wk 59 1.12 (0.70-1.79) *Beer drinkers* 0.68 (0.38-1.23) *Spirits (servings per week, month)* 58 0.90 (0.65-1.23) 60 0.87 (0.62-1.21)

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Mahabir 2005 **Country:** Finland **Study aims:** To examine the relationship between alcohol consumption and risk of RCC in a large prospective cohort of middle-aged Finnish male smokers with detailed information on body mass index (BMI), diet, and lifestyle factors **Source of funding:** National Cancer Institute	**Population:** *Source:* randomized, double-blind, placebo-controlled, two-by-two factorial design, primary prevention trial, n= 29,133 males, 50- 69 yrs, who smoked five or more cigarettes p/day *Exclusion criteria:* diagnosed with prior cancer or serious disease limiting long term participation; those taking supplements or vitamins E, A, or h-carotene in excess of defined amounts *Study pop*: = 27,111 (93%) **Observation time:** 1985 to 1999, median 12.2yrs follow-up , LFU n/s, 195 incident cases of RCC	**Exposure:** *Questionnaire:* self-administered food frequency questionnaire *Repeated during follow-up*: baseline only *Reference period:* over previous 12 months *Drink type:* beer, wine spirits **Measure:** grams per day, **Reference group**: 0-2.5 grams per day (n=56) **Results:** *g/d* *Total alcohol* *Beer* *Spirits* 2.6-11.0 52 0.91 (0.62-1.33) 1.22 (0.85-1.76) 0.93 (0.63-1.39) 11.1-24.0 53 0.94 (0.64-1.38) 0.83 (0.57-1.22) 0.84 (0.58-1.20) 24.1-278.5 34 0.53 (0.34-0.83) 0.55 (0.36-0.85) 0.55 (0.36-0.85) *p* trend 0.005

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Nicodemus 2003 **Country:** USA **Study aims:** To investigate risk factors for renal cancer **Source of funding:** National Cancer Institute	**Population:** *Source:* Women aged 55 to 69 randomly chosen from Iowa Department of Transportation's driver's license list. Of the 99,826 women mailed a questionnaire, 41,836 women (42%) responded *Exclusion criteria:* implausible energy intakes (> 5,000 calories or < 500 calories per day); prevalent cancer at the time of the baseline questionnaire; - pre- or peri-menopausal status. *Study pop*: n= 34,637 after exclusions **Observation time:** 1986 to 31 December 1999 466,398 person-years of follow-up,, loss to follow up <1%, 124 incident kidney cancer cases	**Exposure:** *Questionnaire:* self administered postal FFQ *Repeated during follow-up*: baseline only *Reference period:* within last year *Drink type:* beer wine spirits **Measure:** grams per week, **Reference group**: 0 g/w (n=79) **Results:** 0.1–2.9 31 1.02 (0.67–1.55) ≥3.0 14 0.43 (0.24–0.76) *Red wine* *Beer* Current drinker 0.47 (0.27-0.83) 0.61 (0.35–1.07 *White wine* *Spirits* Current drinker 0.63 (0.38-1.04) 0.67 (0.43–1.06)

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Rashidkhani 2005 **Country:** Sweden **Study aims:** to examine the relation between major dietary patterns and RCC in a large prospective population-based cohort study of Swedish women. **Source of funding:** World Cancer Research Fund International, SwedishCancer Foundation, Swedish Research Council	**Population:** *Source:* Swedish women, aged 40-76 yrs (n=66,651) who responded to baseline questionnaire in national survey *Exclusion criteria:*those with extreme energy intake estimates; previous diagnosis of cancer other than non-melanoma skin cancer; missing information on alcoholic beverages *Study pop*: 59, 237 women after exclusions **Observation time:** (1987–1990) to June 30, 2004, 665,981 person-yrs, LFU 0%; 93 incident cases of RCC	**Exposure:** *Questionnaire:* self-administered food frequency questionnaire *Repeated during follow-up*: baseline only *Reference period:*how often, on average, per week or per day during the last 6 months *Drink type:*wine, liquor, beer **Measure:** grams per day, **Reference group**: <2.5 g/day (n=94) **Results:** *Total Alcohol>55yrs* *g/d* *caca* 2-5-4.3 19 0.66 0.40-1.09 10 0.78 0.40-1.53 >4.3 19 0.71 0.42-1.19 3 0.33 0.10-1.05 *p*trend 0.12 0.04

Descriptive tables for kidney cancer: case control studies

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Greving 2007 **Country:** Sweden **Study aims:** To investigate the association of different types of alcoholic beverages and of total alcohol (ethanol) consumption with the risk of renal cell cancer **Source of funding:** Swedish Cancer Foundation	**Population:** *Cases:* through regional cancer registers, identified all incident cases of renal cell cancer in five of Sweden's six hospital regions N= 877/1,275 *Controls:* randomly selected from the Swedish population registry N=1,508/2,046 **Exclusion criteria:**- n/s **Observation time:** between 1 January 1996 and 30 June 1998 Response rate: cases 69%, controls 74%	**Exposure:** *Questionnaire:* self-administered questionnaire *Interviewers blinded*: n/a *Reference period:*5 years before study, disregarding recent changes *Drink type:* beer (medium, strong) wine, spirits *Quest validated:* n/s **Measure:** grams per month, **Reference group**: Non-users alcohol (136 cases, 179 controls **Results:** <54.8 202/258 1.0 (0.7 –1.4) 54.9-148.9 171/255 0.9 (0.7 –1.3) 149.0-313.6 185/256 0.9 (0.7 –1.2) 313.6-620 115/163 0.9 (0.6 –1.3) >620 g 46/93 0.6 (0.4 –0.9)*p*trend 0.03

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Hsu 2007 **Country:** Russia, Romania, Poland and Czech Republic **Study aims:** To examine the role of total dairy, meat, vegetable, and alcohol consumption, as well as specific dietary components, in relation to risk of kidney cancer. **Source of funding:** International Agency for Research on Cancer.	**Population:** *Cases:* no details provided N=1,065 *Controls:* patients admitted to the same hospital as cases for conditions unrelated to smoking or genitourinary disorders (except for benign prostatic hyperplasia) N=1,509 **Exclusion criteria:**- information missing on diet or alcohol consumption; those with missing covariates (age, sex, tobacco use, hypertension medication use, body mass index, or education) **Observation time:** between August 1999 and January 2003, Response rate ranged from 90 to 98.6% for cases and from 90.3% to 96.1% for controls	**Exposure:** *Questionnaire:* standardized questionnaire *Interviewers blinded*: n/s *Reference period:*usual weekly consumption during different periods of adult life (i.e., ages ≤25, 26–40, 41–50, 51–60, and >60 years) *Drink type:* beer wine spirits **Measure:** grams per week, **Reference group**: no weekly consumption **Results:** *g/w* *Total alcohol* *Spirits* <36.5 310/378 1.18 (0.93-1.49) <30.0 1.20 (0.71-2.02) 36.5–137.5 290/378 1.15 (0.88-1.48) 30.0–157.0 1.08 (0.69-1.72) >137.5 191/391 0.83 (0.61-1.12) ≥157.0 0.51 (0.27-0.97) *Beer* *Wine* <15.0 1.20 (0.73-1.97) <9.5 1.50 (0.93-2.44) 15.0–49.0 1.03 (0.58-1.83) 9.5–23.0 0.73 (0.40-1.30) ≥49.0 0.77 (0.42-1.43) ≥23. 0.05 (0.51-2.18)

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Parker 2002 **Country:** USA **Study aims:** to address the potential for a gender-specific association of alcohol consumption and RCC development after adjustment for accepted and newly identified confounding factors **Source of funding:** National Cancer Institute	**Population:** *Cases:* residents of Iowa who were aged 40-85 years and with newly diagnosed RCC N =406 (261 men and 145 women) *Controls:* Controls aged <65yrs, randomly selected from computerized state driver's license records. Controls aged ≥65 yrs selected randomly from listings provided by US Health Care Financing Administration N = 2,429 (1,598 men and 831 women) **Exclusion criteria:** previous diagnosis of malignant neoplasm, except basal and squamous cell carcinomas of the skin **Observation time:** 1985-1987, Response rate: cases 88%, controls 80%	**Exposure:** *Questionnaire:* mailed FFQ supplemented by a telephone interview *Interviewers blinded*: yes (see above) *Reference period:* over all adult years. Participants specifically instructed to ignore recent changes in alcohol consumption. *Drink type:* beer, wine and spirits. **Measure:**grams per week, **Reference group**: never drinkers (n=98/376) **Results:** *Total Alcohol* *g/w* *ca/co* *Men* *ca/co* *Women* ≤35 77/362 1.3 (0.9-1.9) 41/217 1.0 (0.6-1.5) >35 86/500 0.9 (0.6-1.3) 11/101 0.4 (0.2-0.9 *p*trend = 0.5 = 0.04 *can p/w* *Beer* *shot p/w* *Spirits* ≤1 1.4 (0.9-2.0) 1 1.4 (1.0-2.1) >1 1.0 (0.7-1.4) >1 1.1 (0.7-1.6)

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Pelucchi 2008 **Country:** Italy **Study aims:** analysed the association of alcohol with RCC in Italy, using data from two case–control studies of RCC conducted from 1985 to 2004 **Source of funding:** Italian Association for Cancer Research; the Italian League against Cancer; the Italian Ministry of Education Italian Foundation for Cancer Research	**Population:** *Cases:* first study, data collected from major teaching and general hospitals in the greater Milan area and the province of Pordenone, in northern Italy, and in second study from 4 Italian areas, including greater Milan area and provinces of Udine and Pordenone in northern Italy, province of Latina in central Italy and urban area of Naples in southern Italy, N=1,115 *Controls:* Controls were admitted to the same hospitals as cases for a wide spectrum of acute, non-neoplastic conditions, unrelated to known risk factors for RCC, N=2,582 **Exclusion criteria:** n/s **Observation time:** Between 1985 and 1992 and 1992 to 2004 Response rate: >95% for cases and controls	**Exposure:** *Questionnaire:* structured questionnaire administered by trained interviewer *Interviewers blinded*: n/s *Reference period:* up to 1 year before diagnosis for cases or hospital admission for control *Drink type:* wine, beer and spirits **Measure:** drinks p/day, drinking duration, age started, **Reference group**: Non-drinkers (258/495) **Results:** Drinks per day ≤4 617/1371 0.87 (0.73–1.04) >4 to ≤8 170/477 0.76 (0.59–0.99) >8 70/238 0.70 (0.50–0.97) *p*trend 0.01 Continuous OR 0.97 (0.95–1.00) *Duration of drinking, years* *Age at starting, years* ≤34 288/797 0.73 (0.58–0.91) 17–19 92/198 0.94 (0.67–1.32) 35–44 288/655 0.91 (0.73–1.14) 20–22 162/331 0.99 (0.74–1.33) ≥45 233/532 0.97 (0.76–1.24) ≥23 145/292 1.02 (0.75–1.39) *p*trend 0.94 0.81

Descriptive tables for laryngeal cancer: case control studies

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Bosetti 2002 **Country:** Italy and Switzerland **Study aims:** to study the separate effect of alcohol and tobacco on laryngeal cancer risk' **Source of funding:** Italian Association for Cancer Research and Swiss Foundation for Research against Cancer	**Population:** *Cases:* Pooled from two hospital case control studies conducted in Italy (cases = 162) and in Switzerland (cases = 527), N=40 non-smoking cases *Controls:* non smoking controls selected from the same network of hospitals N=160 **Exclusion criteria:**patients admitted with acute non-neoplastic conditions related to alcohol consumption and smoking **Observation time:** 1986-1992 (Italy) & 1992-2000 (Switzerland) Response rate: n/s	**Exposure:** *Questionnaire:* structured questionnaire by trained interviewer *Interviewers blinded*: n/s *Reference period:* within last year *Drink type:* no **Measure:**drinks per day, **Reference group**: 3 TO <5 drinks per day **Results:** OR for alcohol drinking non smokers 5->8 *no odds ratio presented* ≥8 2.46 0.98-6.20

Study and Aims	Study and sample characteristics	Exposure measurement and main results
De Stefani 2004 **Country:** Uruguay **Study aims:** to compare the risks for smoking and drinking by tumour site in the high-risk population of Uruguay **Source of funding:** International Agency for Research on Cancer	**Population:** *Cases:* All cases of carcinomas of the hypopharynx and larynx which occurred in men from four major hospitals in Montevideo N=300 *Controls:* selected from the same hospitals N=640 **Exclusion criteria:** diseases related with tobacco smoking, alcohol drinking with recent changes in their diets **Observation time:** 1997-2003 Response rate: case-97.5% control 97.2 %	**Exposure:** *Questionnaire:* Interviewed in the hospitals by two trained social workers with questionnaire a complete history of alcohol drinking (age at star, age ofquit, number of glasses drunk per day *Interviewers blinded*: n/s *Reference period:*lifetime *Drink type:* beer wine spirits **Measure:** status, lifetime intake (milligrams per day) and drinking years, **Reference group**: Never drinkers' (occasional or less than monthly) **Results:** *Status co/ca Hypopharynxca ca Larynx* Former 88/15 5.8 1.7-19.3 44 1.8 1.0-3.3 Current 361/66 6.0 2.0-18.0 159 1.6 0.9-2.5 Ever 449/81 6.0 2.0-17.7 203 1.6 1.0-2.6 *Lifetime total alcohol* *(mg) co/ca Hypopharynx ptrend ca Larynx ptrend* 1-60 175/10 2.3 0.7-8.1 31 0.8 0.4-1.5 61-120 116/23 7.6 2.3-24.4 45 1.5 0.8-2.8 121-240 88/17 5.6 1.7-18.6 68 2.4 1.4-4.2 241+ 70/31 12.8 4.0-41.2 <0.001 59 2.5 1.4-4.5 <0.0001 *Years of drinking* *yrs co/caHypopharynx caLarynx* 1-29 107/17 5.1 1.5-17.4 36 1.5 0.8-2.9

Study and Aims	Study and sample characteristics	Exposure measurement and main results
		30-39 131/19 3.9 1.2-12.9 51 1.4 0.8-2.5 40-49 127/27 8.2 2.5-26.5 66 1.9 1.1-3.4 50+ 84/18 7.9 2.3-27.8 0.0005 50 1.6 0.9-3.0 0.06 *(*mg)*Wine* *Spirits* *Beer* 1-60 0.9 0.5-1.6 0.9 0.5-1.4 1-60 0.6 0.3-1.2 61-120 2.8 1.7-4.7 1.5 0.8-2.8 61+ 0.8 0.4-1.6 121+ 2.3 1.4-3. 9.5 10.8-2.6

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Gallus 2003 **Country:** Italy and Switzerland **Study aims:** To obtain additional information about laryngeal cancer risk in women **Source of funding:** Italian Association for Cancer Research, Italian Ministry of Health, Leagues against Cancer of Italy and Vaud, and Swiss Foundation for Research against Cancer	**Population:** *Cases:* All female cases from hospitals in (1) in the provinces of Milan and Pordenone and (2) in the provinces of Pordenone and Padua, the greater Milan area, northern Italy, and the Swiss Canton of Vaud N= 68 women *Controls:* randomly selected from same network of hospitals as cases N=340 women **Exclusion criteria:**patients admitted with acute non-neoplastic conditions related to alcohol consumption and smoking **Observation time:** 1986 and 1992 and 1992 and 2000 Response rate: 95% for cases and controls	**Exposure:** *Questionnaire:* Trained interviewers using structured questionnaires *Interviewers blinded*: n/s *Reference period:*No information provided on alcohol questions *Drink type:* no **Measure:** drinks per day, **Reference group**: < 3 drinks per day **Results:**Total intake *d/d* *ca/co* 3-4 16/28 1.9 0.6-5.8 ≥ 5 12/6 4.3 0.8-24.1 (*p*trend=0.062)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Garavello 2006 **Country:** Italy **Study aims:** To investigate whether the risk of laryngeal cancer depends on the types of alcoholic beverage consumed, **Source of funding:** Italian Association for Cancer Research, Italian League against Cancer, Italian Ministry of Education and European Research Advisory Board	**Population:** *Cases:* All cases admitted to major teaching and general hospitals in Milan and in province of Pordenone, in northern Italy N=672 *Controls:* selected from those residing in the same geographical areas and admitted to the same network of hospitals N=3,454 **Exclusion criteria:** patients admitted with acute non-neoplastic conditions related to alcohol consumption and smoking **Observation time:** 1986-2000 Response rate: 95% for cases and controls	**Exposure:** *Questionnaire:* structured questionnaire, by trained interviewer *Interviewers blinded*: n/s *Reference period:*within last year *Drink type:* wine, beer and spirits, including amari, grappa, whisky, cognac, brandy **Measure:**drinks per day and duration, **Reference group**: For beer and spirits, non-drinkers were chosen as the reference category; for total alcohol and wine, non-drinkers and drinkers of up to two drinks per day were taken as reference category **Results:** *d/d* *ca/co* *Total Alcohol* *Wine* 3-4 111/809 1.12 0.83-1.50 1.12 0.83-1.50 5-7 149/510 2.43 1.79-3.28 2.45 1.79-3.28 8-11 180/389 3.65 2.68-4.98 3.29 2.68-4.98 ≥12 84/174 4.83 3.18-7.33 5.91 3.18-7.33 *Beer* *Spirits* 1-2 1.65 1.31-2.10 0.88 0.70-1.11 ≥3 1.36 0.86-2.15 1.15 0.67-1.96

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Hashibe 2007 **Country:** Central and Eastern Europe **Study aims:** to assess whether differences exist in risk factors for supraglottic and glottic tumours **Source of funding:** European Commission	**Population:** *Cases:* from five hospital or cancer clinic in Central and Eastern Europe: Bucharest (Romania), Budapest (Hungary), Lodz (Poland), Moscow (Russia), and BanksaBystrika (Slovakia). N=384 *Controls:* inpatients or outpatients in the same hospital as the cases N=823 **Exclusion criteria:** - histologic type was missing, was not squamous cell carcinoma, or was an in situ carcinoma diseases related to tobacco and alcohol (no details) **Observation time:** from 2000 to 2002, Response rate: n/s	**Exposure:** *Questionnaire:* structured questionnaire by the same team of interviewers in each centre. *Interviewers blinded*: n/s *Reference period:*in last year *Drink type:* beer wine spirits **Measure:** grams per week, years of drinking, Cumulative consumption, **Reference group**: light drinkers (1–139 grams per week, 431 controls, 106 cases), (1-19yrs 127 controls, 21 cases **Results:** *Grams per week* *Years of drinking* No drinking 58/ 6 0.60 0.22-1.65 No drinking 58/6 0.85 0.28-2.59 140–279 144/94 1.57 1.05-2.33 20–39 463/23 1.56 0.94-2.59 280–419 71/29 1.13 0.64-1.99 ≥40 203/97 1.85 0.88-3.91 ≥420 147/80 1.45 0.92-2.26 Beer drinker 0.58 0.23-1.47 Wine drinker 1.92 0.76-4.83 Spirit drinker 0.85 0.55-1.30

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Menvielle 2004 **Country:** France **Study aims:** to study the effects of alcohol and tobacco consumption on laryngeal and hypopharyngeal cancer and to compare these across subsites (glottis, supraglottis, epilarynx, hypopharynx). **Source of funding:** Foundation de France	**Population:** *Cases:* all male cases of cancer of the larynx or hypopharynx. in 15 French hospitals in 6 cities N=528 *Controls:* same hospitals as the cases, N=242 **Exclusion criteria:** non-respiratory cancers; patients with bladder, liver and pancreatic cancer. **Observation time:** Response rate: cases 80%, controls 86%	**Exposure:** *Questionnaire:* Personal interviews conducted by trained interviewers, *Interviewers blinded*: n/s *Reference period:*n/s *Drink type:* wine, beer, cider, aniseed spirit or pastis, whisky, calvados, fortified wines **Measure:** grams per day, **Reference group**: occasional drinkers (less than 1 g/d) **Results:** *ca/co* *Larynx* 1-2 56/62 1.4 1.2-1.6 3-4 80/49 2.0 1.5-2.7 5-8 156/64 2.9 1.9-4.4 9-12 109/17 4.1 2.4-7.2 >13 81/13 5.9 2.9-11.8 *By tumour type* *g/d* *Glottis* *Supraglottis* *Hypopharynx.* 1-2 1.2 1.0-1.5 1.3 1.1-1.6 1.6 1.4-1.9 3-4 1.5 1.1-2.2 1.7 1.1-2.7 2.7 1.9-3.7 5-8 1.9 1.1-3.2 1.3 1.2-4.3 4.4 2.6-7.2 9-12 2.3 1.1-4.8 3.1 1.3-7.0 7.2 3.7-14.0 >13 2.9 1.1-7.1 4.1 1.4-11.5 11.7 5.1-27.2

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Pacella-Norman 2002 **Country:** South Africa **Study aims:** to estimate the importance of tobacco and alcohol consumption and other suspected risk factors with respect to cancer of the oesophagus, lung, oral cavity and larynx **Source of funding:** South African Medical Research Council, Cancer Association of South Africa, & Cancer Research UK.	**Population:** *Cases:* recruited from three main public referral hospitals of greater Johannesburg, N=51 *Controls:* selected from the same network of hospitals N=1,370 female patients and 804 male **Exclusion criteria:** patients, who had cancers associated with effects of tobacco and/or alcohol, were excluded i.e. cancers of the stomach, bladder, liver, pancreas, naso-pharynx, and uterine cervix plus cancer of the larynx in women **Observation time:** 1995-1999, Response rate:n/s	**Exposure:** *Questionnaire:* questionnaire by trained nurse interview was conducted in the preferred language of the patient (usually Zulu or Sesotho), *Interviewers blinded*: n/s *Reference period:*n/s *Drink type:* maize, from sorghum, and, commercial beer, wine, commercial and home-distilled spirits, **Measure:** drinks per week/day, **Reference group**: Non drinkers' (not defined) **Results:** < 1 drink per week 3/84 1.1 0.2-4.8 1-3 drinks per week 8/121 1.0 0.3-3.3 ≥1drink on most days 34/333 1.8 0.7-4.8

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Ramroth 2004 **Country:** Germany **Study aims:** To assess the joint effect of smoking and alcohol consumption on laryngeal risk on tumour sub-sites. **Source of funding:** Federal Ministry for, Education, Science, Research and Technology	**Population:** *Cases:* recruited from laryngeal treatment clinics in the Rhein-Neckar-Odenwald region of South-West Germany N=257 *Controls:* selected randomly from the population registries of the study areas, N=769 **Exclusion criteria:** restricted to Germans aged up to 80 who were registered as citizens in the study region. **Observation time:** 1998-2000; response rate: cases89%, controls 62.4%	**Exposure:** *Questionnaire:* interviews conducted by trained interviewers, under standardized conditions *Interviewers blinded*: n/s *Reference period:*10 years before interview *Drink type:* yes but no details provided **Measure:** grams per day, **Reference group**: ≤25g/day **Results:** Grams/d Combined Glottis & Sub glottis Supraglottis >25-50 1.3 0.8-2.1 1.4 0.8-2.5 1.3 0.4-3.8 >50-75 1.6 1.2-2.7 1.3 0.7-2.5 1.6 0.5-5.3 >75-100 1.6 0.9-2.9 2.0 1.0-3.9 1.6 0.4-6.2 >100-150 2.2 1.1-4.3 1.8 0.7-4.2 2.0 0.5-7.6 >150 3.0 1.6-5.9 1.9 0.8-4.4 4.3 1.4-13.2

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Sapkota 2007 **Country:** India **Study aims:** To investigate risks of hypopharyngeal and laryngeal cancers associated with smoking, snuffing and chewing different tobacco products used in India. **Source of funding:** International Agency for Research on Cancer	**Population:** *Cases:* all cases from four participating cancer treatment centres N=1,024 *Controls:* 19% of the controls were hospital-based and 81% were visitors to patients at the hospital. N=718 **Exclusion criteria:** patients with disease not related to alcohol or tobacco consumption **Observation time:** between 2001 and 2004. Response rate: n/s	**Exposure:** *Questionnaire:* standardized questionnaire was administered to all study participants by trained staffmembers *Interviewers blinded*: n/s *Reference period:* n/s *Drink type:* no **Results:** *co/ca* *Hypopharynx* *ca* *Glottis* *ca* *Supraglottis* <Once a week 60/23 0.47 (0.26–0.87) 18 1.02 (0.53–1.95) 7 0.91 (0.33–2.54) <Daily 51/49 0.97 (0.59–1.59) 13 0.66 (0.32–1.35) 12 1.63 (0.71–3.74) Daily 17/42 2.22 (1.11–4.45) 10 1.46 (0.56–3.82) 11 3.76 (1.25–11.30)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Schlecht 2001 **Country:** Brazil **Study aims:** To investigate the effects of alcohol consumption on the risk of cancers of the upper aero-digestive tract **Source of funding:** Ludwig Institute for Cancer Research, and Cancer Research Society of Canada	**Population:** *Cases:* selected from hospitals in three metropolitan areas of Brazil, N=194 *Controls:* recruited from the same or nearby hospitals N=388 **Exclusion criteria:**patients with mental disorders (ICD-9, 290-319) or neoplastic diseases (140-239) **Observation time:** 1986-1989 Response rate: <1% in cases and controls	**Exposure:** *Questionnaire:* Standardised questionnaire by trained nurses *Interviewers blinded*: Subjects and interviewers blinded to study aims *Reference period:*Lifetime consumption(volume X frequency) *Drink type:* beer, wine, hard liquor, cachaça. **Measure:**kilograms of alcohol, **Reference group**: non-drinkers (not defined) **Results:** *kg Cachaca* — *Wine* — *Beer* — *Liquor* 1-10: 1.3 0.1-13.1 — 1.5 0.7-3.3 — 1.1 0.5-2.4 — 4.2 0.9-20.4 11-100: 0.95 0.4-2.5 — 3.7 1.3-10.7 — 2.1 0.9-4.9 — 2.1 0.9-5.1 100-500: 4.0 1.7-9.3 — 1.5 0.6-4.0 — 1.8 0.6-5.7 — 1.8 0.6-5.4 501-1000: 4.4 1.8-10.4 1001-2000: 4.3 1.9-10.0 >2000: 9.9 3.0-33.0

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Talamini 2002 **Country:** Italy andSwitzerland **Study aims:** To provide information on the effects of alcohol and tobacco on laryngeal cancer and its subsites **Source of funding:** Italian Association for Cancer Research, Italian Ministry of Health, and Swiss Foundation for Research against Cancer	**Population:** *Cases:* identified from major teaching and general hospitals in Milan, and in the province of Pordenone, in northern Italy and in the Swiss Canton of Vaud N=527= (478 men and 49 women) *Controls:* selected from those residing in the same geographical areas and admitted to the same network of hospitals N=1,297 (1027 men and 245 women) **Exclusion criteria:** patients admitted with acute non-neoplastic conditions related to alcohol consumption and smoking **Observation time:** 1992-2000 Response rate: cases 97% controls 95%	**Exposure:** *Questionnaire:* interviewed by nurses, using validated food frequency questionnaire *Interviewers blinded*: n/s *Reference period:* up to 1 year prior to cancer diagnosis or hospital admission *Drink type:* wine, beer, herb liquors, grappa and whisky/brandy) **Measure:** drinks per day, **Reference group**: abstainers (i.e. never drunk in lifetime) **Results:** Ex-drinkers 2.8 1.4-2.5 — Current drinkers 1.8 1.0-3.3 *Total Alcohol Intake* — *Duration of drinking* >0-13 0.9 0.5-1.8 — <35 years 2.3 1.2-4.3 14-27 1.2 0.6-2.2 — 35-44 years 1.8 0.9-3.3 28-55 2.6 1.4-4.7 — ≥45 1.6 0.8-3.0 ≥56 5.9 3.1-11.3 x^2 trend 0.08 (p=0.78)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Zvrko 2008 **Country:** Serbia **Study aims:** to identify possible aetiological agents of laryngeal cancer . **Source of funding:** n/s	**Population:** *Cases:*All laryngeal cancer patients diagnosed and treated at the Clinic for Otorhinolaryngology and Maxillofacial Surgery, Montenegro in Podgorica N=108 *Controls:* patients admitted to different centre clinics N=108 **Exclusion criteria:**acute, non-malignant conditions, related to smoking and alcohol consumption **Observation time:** January 2001 and June 2003. Response rate: 94% for cases and controls	**Exposure:** *Questionnaire:* structured questionnaire administered by one study doctor *Interviewers blinded*: no *Reference period:* n/s *Drink type:* wine, beer, spirits **Measure:** drinks per day, **Reference group**: Never drinkers(abstained from any alcoholbeverage lifelong) **Results:** *ca/co* >2 d/d n/s 4.96 2.04-12.04

Descriptive tables for liver cancer: cohort studies

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Mori 2000 **Country:** Japan **Study aims:** To examine the effect of viral infections and lifestyle habits, after adjustment for potential confounding variables, on the risk of HCC **Source of funding:** n/s	**Population:** *Source:* study group consisted all inhabitants (4,904) aged ≥30 yrs resident in K. Town, Japan, invited to a national health insurance screening programme for liver disorders *Exclusion criteria:*those on in screening programs supported financially by different health insurance agencies; liver disorders *Study pop*: 3,059 (62.4%) **Observation time:** June 1992 until March 1997, median 4.65yrs, 13,983 person-years, LFU = 2.6%; 51 incident cases of HCC	**Exposure:** *Questionnaire:* structured questionnaire *Repeated during follow-up*: baseline only *Reference period:* lifetime *Drink type:* sake, beer, whiskey, wine, and sochu converted into equivalent of glasses of Japanese sake **Measure:** drink-years, **Reference group**: non-habitual drinkers (n=10) **Results:** *drinks years* *ca* 1-19 3 2.05 0.48-8.79 ≥20 9 1.14 0.40-3.26 *p*trend = 0.873

Descriptive tables for liver cancer: case control studies

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Donato 2002 **Country:** Italy **Study aims:** To investigate the relation between alcohol habits and HCC in men and women taking account of hepatitis B and hepatitis C virus infections **Source of funding:** Italian Ministero della Ricerca Scientifica e Universitaria (MURST) and the Ente Universitario Lombardia Orientale (EULO)	**Population:** *Cases:* first diagnosis of HCC admitted to the two main hospitals in province of Brescia, N=464 *Controls:* admitted to departments of ophthalmology, dermatology, urology, surgery, cardiology, and internal medicine of same hospitals as cases, N=824 **Exclusion criteria:** hospitalized for liver disease or malignant neoplasms; hospitalized for injuries **Observation time:** between January 1995 and April 2000 Response rate: cases (93.5%), controls (96.1%)	**Exposure:** *Questionnaire:* standardized questionnaire *Interviewers blinded*: n/s *Reference period:* lifetime *Drink type:*wine, beer, spirits **Measure:**grams per day, **Reference group**: 0 grams per day **Results:** *"peak" exposure* *Men* *Women* 1-20 24/56 2.3 0.7-7.2 22/49 0.6 0.2-1.7 21-40 27/101 0.9 0.3-2.7 15/19 1.4 0.4-5.4 41-60 44/130 1.6 0.5-4.6 11/10 1.9 0.4-8.1 61-80 33/89 2.4 0.8-7.1 4/3 3.1 0.3-29.7 81-100 62/112 4.2 1.5-11.0 8/3 16.5 3.0-90.1 101-120 47/50 7.7 2.7-22.7 121-140 48/38 9.8 3.3-29.1 >140 87/68 11.0 3.9-31.0

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Hassan 2008 **Country:** USA **Study aims:** to evaluate the independent effects of different types of smoking exposure along with multiple risk factors for HCC and determined whether the magnitude of smoking was modified by other risk factors in men and women. **Source of funding:** National Institutes of Health/ Texas Tobacco Settlement	**Population:** *Cases:* recruited from population of patients with newly diagnosed HCC at cancer centre in Texas, N=319 *Controls:* were healthy nonblood relatives, particularly spouses, of patients with cancers other than liver, gastrointestinal, lung or head and neck (smoking-related cancers) who were undergoing treatment at same cancer centre, N=1,061 **Exclusion criteria:** not have ever had cancer; non U.S. residency, inability to communicate in English **Observation time:** January 2000 through December 2006, Response rate: cases and controls 82%	**Exposure:** *Questionnaire:* personally interviewed by well-trained interviewers, using a structured questionnaire *Interviewers blinded*: n/s *Reference period:* lifetime (consumed at least 4 alcoholic drinks of beer, wine or hard liquor each month for 6 months during their lifetimes *Drink type:* wine, beer, spirits **Measure:** lifetime intake, mL/day, **Reference group:** not defined , n= cases114/ controls463 **Results:** *All* *Men* *Women* <60 134/530 1.1 (0.7–1.5) 106/405 0.7 (0.4–1.2) 28/125 1.5 (0.8–2.9) ≥60 69/65 2.7 (1.5–4.7) 59/57 1.8 (1.1–3.4) 10/8 7.7 (2.3–25.1)

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Kuper 2000 **Country:** Greece **Study aims:** To examine tobacco smoking, alcohol consumption and their interaction in the causation of hepatocellular carcinoma **Source of funding:** Europe Against Cancer Program of the European Union.	**Population:** *Cases:* admitted to 3 teaching hospitals in Athens N=333 *Controls:* patients hospitalized for injuries or for eye, ear, nose or throat conditions, admitted to same hospitals as cases N=360 **Exclusion criteria:**conditions related to smoking, alcohol intake or coffee consumption **Observation time:** Between January 1995 and December 1998 Response rate: cases (89%) controls (94%) who	**Exposure:** *Questionnaire:* Interviewed in hospital *Interviewers blinded*: n/s *Reference period:* within last year *Drink type:*n/s **Measure:** glasses per week, **Reference group**: Non-drinkers **Results:** <20 0.8 (0.4–1.4) 20–39 0.7 (0.3–1.5) ≥40 1.9 (0.9–3.9) *p* for trend 0.13 *with HBsAgand/or anti-HCV* *without both HBsAg and anti-HCV* <20 1.0 (0.2–4.1) 0.7 (0.3–1.3) 20–39 1.4 (0.3–7.9) 0.6 (0.2–1.4) ≥40 5.4 (0.6–50.3) *p* trend 0.14 1.6 (0.8–3.4)*p*trend 0.33

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Marerro 2005 **Country:**USA **Study aims:** To test the hypothesis that tobacco, alcohol, and obesity independently increase the risk of HCC among Americans with cirrhosis **Source of funding:** National Institute of Health	**Population:** *Cases:* subjects enrolled from the Liver or General Medicine Clinics at in one hospital in Michigan N=210 *Controls:* For each case enrolled, 2 controls matched for age and gender were recruited (1 matched control with cirrhosis and 1 matched control with no liver disease) randomly selected for each case from patients admitted to same hospital. N=420 **Exclusion criteria:** None specified **Observation time:** between June 2002 and August 2003 Response rate: n/s	**Exposure:** *Questionnaire:* Skinner Alcohol Use Inventory by a single trained interviewer *Interviewers blinded*: n/s *Reference period:* lifetime *Drink type:* beer, wine or hard liquor **Measure:**gram-years (average daily consumption (grams) times total duration of alcohol exposure (years), **Reference group**: none (not defined) **Results:** HCC versus cirrhotics / HCC versus no liver disease <1500: 0.5 (0.1-0.7) / 1.4 (0.8-1.9) ≥1500: 5.7 (2.4-13.7) / 23.8 (7.3-79)

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Munaka 2003 **Country:** Japan **Study aims:** To test hypothesis that alcohol abuse and/or tobacco smoking is a risk factor for the development of HCC, and to examine effects of the GSTs, CYP2E1 and ALDH2 polymorphism on the susceptibility of HCC in relation to alcohol-drinking **Source of funding:** Ministry of Education, Science & Culture of Japan	**Population:** *Cases:* patients seen in the University of Occupational and Environmental Health (UOEH) Hospital in Japan N=78 *Controls:* selected from same hospital N=138 **Exclusion criteria:**no evidence of cancer in any organ **Observation time:** from June 1997 to April 1998 Response rate: n/s	**Exposure:** *Questionnaire:* questionnaire administrated by a trained interviewer *Interviewers blinded*: n/s *Reference period:* lifetime *Drink type:* n/s **Measure:** Lifetime ml, **Reference group**: non drinker **Results:** 1–<200,000: 0.31 (0.15–0.62) ≥200,000–<600,000 ml: 0.79 (0.40–1.57) ≥600,000 ml: 4.52 (2.39–8.55)

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Ohishi 2008 **Country:** Japan **Study aims:** To determine whether HBV or HCV infections, alcohol consumption, smoking, coffee drinking, BMI, and diabetes mellitus are independent risk factors for hepatocellular carcinoma, and how the effects of these factors might change after adjusting for severity of liver fibrosis **Source of funding:** Japanese Ministry of Health, Labor and Welfare	**Population:** Adult Health Study established in 1958, 20,000, age, gender, and city-matched proximal and distal atomic bomb survivors not present in the cities at the time of bombings examined biennially in outpatient clinics in Hiroshima and Nagasaki. *Cases:* identified through Hiroshima Tumour and Tissue Registry and Nagasaki Cancer Registry, supplemented by additional cases detected via pathologic review of related diseases, N= 224 *Controls:* Nested control selection was random among those who matched the case on gender, age, city, time of serum storage, and method of serum storage, and counter-matched on radiation exposure N= 644 **Exclusion criteria:**- inadequate stored serum **Observation time:** between 1970 and 2002; Response rate: n/s	**Exposure:** *Questionnaire:* Self-administered questionnaire *Interviewers blinded*: n/s *Reference period:* lifetime *Drink type:* n/s **Measure:** gram per day. **Reference group**: Never drinker **Results:** >0 and <20 1.27 (0.56-2.87) >20 and <40 1.02 (0.34-3.05) ≥40 4.36 (1.48-13.0) Continuous (per 20-g ethanol per day) 1.73 (1.19-2.52)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Sakamoto 2006 **Country:** Japan **Study aims:** (i) toevaluate the dose-response pattern between alcohol intake and HCC risk, and (ii) to examine whether ALDH2 and ADH2 polymorphisms modify the HCC risk, depending on the amount of alcohol intake **Source of funding:** n/s	**Population:** *Cases:* identified among those who were admitted or outpatients of two hospitals in Saga province, Japan N=209 *Controls:* First control group recruited from among first time visitors at the general outpatient clinic to one of the above hospitals Second control group were patients with CLD but without HCC who were out- or inpatients of the above 2 hospitals N=275 & 381 **Exclusion criteria:**<40 yrs old; non-Japanese residents; Patients with special types of CLD (primary and secondary biliary cirrhosis, autoimmune hepatitis and liver disease because of parasitosis, congestive heart failure or metabolic disorders) **Observation time:** between January 2001 and March 2004 Response rate: Cases (92%) Controls (73%) & (96%)	**Exposure:** *Questionnaire:* Questionnaire from research nurses *Interviewers blinded*: *Reference period:* during last 1-2 years and at 10 years prior to interview *Drink type:* n/s **Measure:** go's/day, **Reference group**: **Results:** during last 1-2 years *HCC cases vs. hospital controls* *HCC cases vs. CLD patients* >0-0.9 33/33 3.4 1.1-10.1 33/56 1.2 0.7-2.2 1.0-1.9 20/33 0.8 0.2-2.9 20/30 1.0 0.5-2.1 2.0-2.9 15/25 0.6 0.2-2.4 15/19 1.8 0.8-4.4 3.0-3.9 8/7 10.2 1.7-60.5 8/5 5 0 1.3-19.2 >4.0 9/4 18.0 3.0-107.9 p < 0.01 9/7 9.4 2.5-35.4 p < 0.01 *During 10 years before* *HCC cases vs. hospital controls* *HCC cases vs. CLD patients* >0-0.9 22/24 4.1 1.1–15.2 22/43 1.2 0.6-2.3 1.0-1.9 25/26 1.6 0.5–5.8 25/42 1.3 0.7-2.6 2.0-2.9 20/33 0.8 0.2–2.8 20/33 1.1 0.5-2.3 3.0-3.9 19/13 8.7 2.2–34.4 19/13 2.8 1.1-6.8 >4.0 25/8 19.5 4.7–81.7 25/24 3.3 1.5-7.1

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Takeshita 2000 **Country:** Japan **Study aims:** to examine associations between ADH2 and ALDH2 polymorphisms, alcohol drinking and HCC **Source of funding:** Ministry of Health and Welfare of Japan	**Population:** *Cases:* recruited from 20 major hospitals in Hyogo prefecture in Japan ,N=102 *Controls:* enrolled from outpatients or inpatients in the same hospitals so that age, sex, and living areas were the same or similar to the cases, N=125 **Exclusion criteria:** patients with liver diseases with HBs antigen positives and with HCV antibody positives **Observation time:** 1995-1996 Response rate: 100% cases and controls	**Exposure:** *Questionnaire:* self-administered questionnaire *Interviewers blinded*: n/s *Reference period:* lifetime *Drink type:* beer, whisky, `Sake', spirits **Measure:** drink-years:cumulative amounts of alcohol intake during last 30 years, **Reference group**: 0-20 drink years **Results:** 20-40 23/23 1.7 (0.8-3.5) ≥40 32/21 2.7 (1.3-5.5) *p* trend 0.007

Descriptive tables for lung cancer: cohort studies

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Allen 2009 **Country:**United Kingdom **Study aims:** describe the relationship of low to moderate levels of alcohol intake, with subsequent risk of cancer, overall and at particular sites, in a large cohort of women in the **Source of funding:** Cancer Research UK, UK MRC, UK National Health Service breast screening program	**Population:** *Source:* middle-aged women who attended breast cancer screening clinics in the United Kingdom completed between 1996 and 2001 *Exclusion criteria*:none specified *Study pop*: 1,280,296 women, average age of 55 yrs **Observation time:** From 1996-2001 to 31 December 2006, followed up for cancer incidence over 9.2 millionperson-years, for an average of 7.2 years per woman; 5023 incident cases of lung cancer	**Exposure:** *Questionnaire:* no details provided *Repeated during follow-up:* Yes, three years after baseline interview *Reference period:* n/s *Drink type:* wine, beer, and spirits **Measure:** drinks per week **Reference group**: <2 drinks per week **Results:** Non-drinkers 1735 1.17 (1.12 - 1.23) ≤ 2 1210 1.00 (0.94 - 1.06) 3-6 886 0.91 (0.85 - 0.97) 7-14 1040 1.06 (1.00 - 1.13) ≥15 332 1.01 (0.90 - 1.12) *p*trend =0.2

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Chao 2008 **Country:** USA **Study aims:** To investigate the effect of alcoholic beverage consumption on the risk of lung cancer **Source of funding:** None specified	**Population:** (California Men's Health Study) *Source:* all males from, a managed care organization, in California, 45 to 69 yrs in January 2000, and members of the health plan for at least 1 year at recruitment, *Exclusion criteria:* Any previous cancer diagnosis (except non-melanoma skin) and lung cancer cases diagnosed within 6 months after study baseline *Study pop*: 84,170 men (40% response rate to questionnaire). Between study baseline and December 2006, 11,144 men in the cohort terminated their health plan leaving 78,168 men for analysis **Observation time:** 2002 to 2006, 300,516 person-years, LFU 13%. 210 incident cases of lung cancer	**Exposure:** *Questionnaire:* semi-quantitative food frequency questionnaire adapted from the Women's Health Initiative and other studies and modified for men's health *Repeated during follow-up:* NO *Reference period:* n/s *Drink type:* beer, red wine, white or rose´ wine, and liquor **Measure:** drinks per day or per week, **Reference group**: non-drinker (n=94) **Results:** Beer Liquor <1 d/w 64 1.48 (1.00-2.19) 43 0.92 (0.60-1.42) ≥1 d/w, <1 d/d 34 1.04 (0.65-1.65) 26 1.05 (0.64-1.71) ≥1 d/d 18 0.78 (0.45-1.35) 18 0.93 (0.54-1.58) *Linear for 1 d/m increase 1.00 (0.99-1.00) 1.00 (1.00-1.01)* *p* for trend 0.42 0.75 Red wine White wine <1 d/w 55 1.15 (0.73-1.81) 49 0.86 (0.54-1.37) ≥1 d/w, <1 d/d 21 0.65 (0.37-1.15) 20 1.09 (0.62-1.92) ≥1 d/d 7 0.55 (0.23-1.29) 4 0.87 (0.31-2.40) *Linear for 1 d/m increase 0.98 (0.97-1.00) 1.00 (0.98-1.01)* *p* for trend 0.06 0.71

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Djoussé 2002 **Country:** USA **Study aims:** To evaluate association between total alcohol consumption and the risk of lung cancer among men and women participating in the Framingham Study **Source of funding:** National Heart, Lung, and Blood Institute's Framingham Heart Study, National Institutes of Health	**Population:** *Source:* Cohort started in 1948 in Framingham, Massachusetts. Original cohort included 5209 participants. In 1971, children of original cohort and their spouses formed the Offspring study (n=5,124) *Exclusion criteria*: incomplete smoking and alcohol data *Study pop*: 4,265 participants from the original cohort and 4,973 subjects from the offspring cohort. **Observation time:** original cohort: mean follow-up of 32.8 yrs,194 lung cancer cases, LFU: n/s offspring cohort: mean follow-up of 16.2 yrs, 75 lung cancer cases, LFU: n/s	**Exposure:** *Questionnaire:* standardized questionnaires administered by the examining physician. *Repeated during follow-up:* every four years *Reference period:* in previous month *Drink type:* cocktails, beer, wine **Measure:** grams per day, **Reference group**: 0 grams per day (n=44) **Results:** *g/d* *ca* *Both cohorts* *ca* *Original cohort* *ca* *Offspring cohort* 0.1–12 100 1.2 (0.7-2.1) 77 1.0 (0.5-2.1) 23 1.4 (0.5-3.6) 12.1–24 39 1.1 (0.6-2.1) 24 1.0 (0.5-2.3) 15 1.1 (0.3-3.6) >24 86 1.3 (0.7-2.4) 60 1.1 (0.5-2.3) 12 2.0 (0.7-5.7)

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Prescott 1999 **Country:** Denmark **Study aims:** whether alcohol intake is an independent risk factor for the development of lung cancer and whether any such effect depends on the type of alcoholic beverage consumed **Source of funding:** Italian Association for Cancer Research, the Italian League against Cancer, the Italian Ministry of Education and the European Research Advisory Board	**Population:** *Source:* Copenhagen City Heart Study, the Centre of Preventive Medicine (formerly the Glostrup Population Studies), and the Copenhagen Male Study conducted in 1964-1992 in Copenhagen, Denmark (see section 2.4) *Exclusion criteria:* n/s *Study pop*: 15,107 men and 13,053 women **Observation time:** sample was followed until January 1, 1994, 382,612 person-years, 674 cases of lung cancer (480 men and 194 women)	**Exposure:** *Questionnaire:* self-administered questionnaires *Repeated during follow-up:* NO *Reference period:* n/s *Drink type:* wine, beers, spirits **Measure:**drinks per week, **Reference group**: <1 drink per week (men= 52, women=63) **Results:** *ca* *men* *ca* *women* 1-6 85 0.85 0.60-1.22 82 0.89 0.64-1.25 7-13 106 1.01 0.72-1.42 30 1.00 0.64-1.56 14-20 65 0.86 0.59-1.26 11 0.97 0.50-1.85 21-41 114 1.23 0.88-1.74 **7** 0.99 0.45-2.18 >41 58 1.57 1.06-2.33 1 0.80 0.11-5.79 Beer *men* *women* 1-13 1.09 0.83-1.43 0.91 0.62-1.32 >13 1.36 1.02-1.82 1.49 0.70-3.13 Spirits 1-13 1.21 0.97-1.50 0.83 0.58-1.19 >13 1.46 0.99-2.14 0.67 0.21-2.18 Wine 1-13 0.78 0.63-0.97 0.89 0.59-1.33 >13 0.44 0.22-0.86 0.18 0.03-1.33

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Rohrmann 2006 **Country:** 10 European countries **Study aims:** to separately determine effects of past and current ethanol intake on lung cancer and to examine whether lung cancer risk differs between never drinkers and former drinkers **Source of funding:** Europe Against Cancer Program of the European Commission	**Population:** *Source:* European Prospective Investigation into Cancer and Nutrition; conducted in 23 centers in 10 European countries. The majority of the 521,457 participants were recruited from the general population (see box 2 Section 2.4 for further details). *Exclusion criteria*: prevalent cancer cases; subjects with incomplete follow-up information; or with a ratio of energy intake to energy expenditure in the top ort bottom one per cent *Study pop*: =478,590 **Observation time:** Start date n/s, end point varied from 1999-2003, 2,980,381 person-years of observation ; median follow-up 6.4 yrs, LFU: n/s 1,119 lung cancer cases (606 in men, 513 in women)	**Exposure:** *Questionnaire:* assessed using dietary assessment instruments (FFQs) that had been specifically developed for each participating country *Repeated during follow-up:* no *Reference period:* previous 12 months (lifelong intake determined as a weighted average of intakes at different ages, with weights equal to total subject-specific time under investigation *Drink type:* beer and/or cider, wine, sweet liquor, distilled spirits, and fortified wine **Measure:** grams per day for both current intake and mean lifelong intake **Reference group**: 0-1-4.9 grams per day (current, n=310) **Results:**

g/d	*ca*	*Intake at recruitment*		*ca*	*Mean lifelong intake*	
non-drinker	146	1.22	0.99-1.50	30	1.01	0.67-1.50
5–14.9	232	0.76	0.63-0.90	229	0.80	0.66-0.97
15–29.9	169	0.83	0.68-1.01	201	0.99	0.80-1.22
30–59.9	184	0.95	0.78-1.16	117	0.87	0.67-1.13
≥60	78	0.86	0.66-1.14	82	1.29	0.93-1.74
p-trend		0.31			0.12	

Baseline intake – tumour type

g/d	*Adenocarcinoma*			*Squamous-cell carcinoma*			*Small-cell carcinoma*		
Non-drinker	40	1.14	0.77-1.67	40	1.85	1.20-2.87	18	0.90	0.51-1.57
5–14.9	82	0.90	0.67-1.22	49	0.83	0.56-1.24	42	0.81	0.53-1.22
15–29.9	58	1.06	0.75-1.50	31	0.78	0.49-1.25	26	0.69	0.42-1.12
30–59.9	62	1.27	0.89-1.80	40	0.96	0.61-1.50	33	0.87	0.54-1.40
≥60	24	1.22	0.74-2.01	21	0.93	0.53-1.63	16	0.92	0.50-1.71
*p*trend		0.19			0.30			0.85	

Mean lifelong intake – tumour type

Non-drinker	9	1.03	0.50-2.15	6	1.15	0.47-2.83	2	0.60	0.14-2.56
5–14.9	72	0.86	0.61-1.21	43	0.59	0.38-0.91	43	0.99	0.62-1.59
15–29.9	69	1.30	0.89-1.89	42	0.73	0.46-1.17	32	0.94	0.55-1.61
30–59.9	35	1.09	0.68-1.75	29	0.70	0.41-1.20	23	1.00	0.54-1.85
≥60	19	1.41	0.76-2.63	19	0.94	0.49-1.82	16	1.38	0.66-2.83
*p*trend		0.16			0.87			0.38	

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Shimazu 2008 **Country:** Japan **Study aims:** to investigate the association between alcohol drinking and lung cancer among the Japanese population **Source of funding:** Ministry of Health, Labour and Welfare of Japan	**Population:** *Source:* all registered Japanese inhabitants (n= 133,323) in 10 public health centre areas, aged 40–59 years in cohort I, launched in 1990, and 40–69 years in cohort II, launched in 1993, at the start of the respective baseline survey *Exclusion criteria:*non-Japanese nationality, late report of emigration before the start of the follow-up period and history of previous cancer *Study pop*: 106,206 (80% response rate to questionnaire). Analysis limited men, n= 46,347 since prevalence of regular drinkers among women in study cohort was low **Observation time:** until 31 December 2004, LFU 9.1% 651 incident cases of lung cancer	**Exposure:** *Questionnaire:* self-administered, covering frequency and amount of alcohol consumption *Repeated during follow-up:* NO *Reference period:* N/S *Drink type:* sake (rice wine), shochu or awamori (white spirits), beer, whiskey, wine **Measure:**grams per week, **Reference group**: Occasional drinkers (1–3 days/month) **Results:** All lung cases / Adenocarcinoma Non-drinkers 211 1.47 (1.04-2.09) 76 1.96 (1.04–3.72) 1-149 105 1.10 (0.76-1.61) 35 1.30 (0.66–2.57) 150-299 117 1.07 (0.74-1.55) 44 1.49 (0.76–2.90) 300-449 99 1.34 (0.92-1.95) 38 1.87 (0.95–3.68) ≥450 81 1.31 (0.89-1.94) 21 1.23 (0.59–2.57) *p* for trend 0.07 0.31 Squamous cell carcinomas / Small cell carcinoma Non-drinkers 57 1.51 (0.76–2.98) 26 1.06 (0.43–2.61) 1-149 30 1.25 (0.61–2.58) 12 0.78 (0.29–2.10) 150-299 31 1.07 (0.52–2.20) 13 0.68 (0.26–1.81) 300-449 20 1.03 (0.48–2.22) 13 1.00 (0.38–2.66) ≥450 26 1.56 (0.74–3.26) 13 1.20 (0.45–3.21) *p* for trend 0.38 0.38

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Toriola 2009 **Country:** Finland **Study aims:** to examine the association between binge drinking and lung cancer **Source of funding:** Academy of Finland	**Population:** *Source:* part of the Findrink study, population based sample of middle-aged men from Eastern Finland, originally participants part of a prospective cohort originally designed to investigate risk factors for cardiovascular diseases, and other health related outcomes. Of 3235 men, 2682 (83%) participation *Exclusion criteria*: death or serious disease and history of previous cancer *Study pop*: 2267 men aged 42, 48, 54, and 60 years at the time of baseline examination **Observation time:** (March 1984 to December 1989) and December 2005, average follow-up 16.7 years, LFU: n/s, 65 incident cases of lung cancer	**Exposure:** *Questionnaire:* assessed with a structured quantity and frequency method using the Nordic alcohol consumption inventory *Repeated during follow-up:* NO *Reference period:* N/S *Drink type:* beer, wine, strong wine, spirits **Measure:** binge drinkers (classified as the consumption of more than 70 g of ethanol at one drinking session), **Reference group**: non binge drinkers **Results:** In whole cohort Model 1 1.89 1.10–3.20 P-value 0.02 Among smokers alone Model 2 1.79 1.03–3.12 P-value 0.04

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Woodson 1999 **Country:** Finland **Study aims:** studied the independent role of alcohol consump-tion in lung carcinogenesis among participants in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study **Source of funding:** National Cancer Institute, National Institutes of Health	**Population:** *Source:* 29 133 white male smokers aged 50-69 yrs participating in the ATBC Study in Finland, a randomized, placebo-controlled trial designed to determine whether α -tocopherol (50 mg/day), β-carotene (20 mg/day), or both substances would reduce incidence of lung and other cancers. *Exclusion criteria*:men who were alcoholics, who had liver cirrhosis, severe angina with exertion, diagnosed with chronic renal insufficiency, previously diagnosed with cancer, or taking vitamin A or E or β-carotene beyond specified doses *Study pop*: 26,052menaged 50-69 yrs **Observation time:** 1985 to 1988, followed during active trial period until death or 30/4/1993 (median follow-up, 7.7 yrs), LFU: n/s; 1059 incident cases of lung cancer	**Exposure:** *Questionnaire:* self-administered food-use questionnaire *Repeated during follow-up:* no *Reference period:* over the previous year *Drink type:* beer, wine and spirits **Measure:** grams per day, **Reference group**: 0.04-5,2 grams per day (n=233) **Results:** *ca* Non-drinkers 154 1.2 (0.9-1.4) 5.3-13.3 234 1.0 (0.8-1.2) 3.4-27.6 208 0.9 (0.8-1.1) 27.7-278.5 230 1.0 (0.8-1.2)

Descriptive tables for lung cancer: case control studies

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Benedetti 2006 **Country:** Canada **Study aims:** to investigate role that different types of alcohol might play, to assess the effect of alcohol on the different histological types of lung cancer and to identify possible interactions between gender, smoking, selected dietary factors, and alcohol **Source of funding:** Health Canada, National Cancer Institute of Canada, Canadian Institutes of Health Research.	**Population:** Two large population-based case-control studies The first, in early 1980s, designed to explore associations between occupational substances and multiple cancer sites in men. The second, in mid-1990s, focussed on same occupational exposures and lung cancer in men and women. *Cases:* all newly diagnosed lung cancer cases at any Montreal-area hospital, and living in the Montreal area. N= Study I 699 (64.6% response rate) N= Study II 699 (76.4% response rate) *Controls:* population controls were randomly selected from the electoral lists N= Study I 1,094 (68.5% response rate) N= Study II 1,468 (66.5% response rate) **Exclusion criteria:** non-completion of interview and incomplete alcohol information **Observation time:** Study I: n/s; Study II: n/s	**Exposure:** *Questionnaire:* subjects asked, separately for beer, wine and spirits, if there had ever been a period when they had consumed the alcoholic beverage the equivalent of at least once a week, or nearly every day. *Interviewers blinded*: n/s *Reference period:* n/s *Drink type:* beer, wine and spirits **Measure:** drinks per week (d/w), **Reference group**: never drank weekly **Results:** Study I Men d/w Total Alcohol Beer Wine Spirits 1-6 172 1.2 (0.8-1.8) 182 1.2 (0.9-1.7) 208 1.4 (1.0-1.9) 276 1.4 (1.0-1.9) ≥7 413 1.3 (0.9-1.9) 339 1.5 (1.1-2.1) 82 0.7 (0.4-1.1) 138 1.2 (0.8-1.7) Study II Men 1–6 162 1.0 (0.7-1.4) 197 1.0 (0.7-1.4) 142 0.6 (0.4-0.8) 150 0.9 (0.7-1.2) ≥7 363 1.2 (0.9-1.8) 259 1.0 (0.7-1.4) 98 0.8 (0.5-1.1) 90 0.9 (0.7-1.3) Study II Women 1–6 105 0.4 (0.2–0.5) 63 0.3 (0.2–0.5) 75 0.3 (0.2–0.4) 55 0.4 (0.3–0.6) ≥7 116 0.7 (0.5–1.1) 58 0.9 (0.5–1.6) 55 0.7 (0.4–1.2) 39 1.7 (0.8–3.5)

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
De Stefani 2002 **Country:** Uruguay **Study aims:** to examine relationship between alcohol drinking and risk of adenocarcinoma of the lung **Source of funding:** Comisión Honoraria de Lucha contra el Cáncer, IARC	**Population:** *Cases:* all cases of incident adenocarcinoma of the lung admitted to the four major hospitals in Montevideo N= 160 (response rate 96.9%) *Controls:* identified through the log book of admissions at the same hospital. N= 160 (response rate 93.3%) **Exclusion criteria:** permanent residents in Uruguay of <15 yrs; condition related with tobacco smoking and alcohol drinking and with recent changes in the diet **Observation time:** January 1998 to July 2000	**Exposure:** *Questionnaire:* FFQ was administered two social workers *Interviewers blinded*: n/s *Reference period:* lifetime *Drink type:* beer, wine hard liquor **Measure:** millilitres per day (lifetime consumption). **Reference group**: non-drinkers including those who drank less than 1 day per week regularly (n25/123) **Results:** All Wine Beer Hard liquor 1-60 36/171 0.8 0.4-1.5 50/205 0.6 0.3-1.2 10/29 1.1 0.5-2.5 32/83 1.5 0.8-2.6 61-120 34/95 1.1 0.6-2.1 37/89 0.6 0.3-1.2 9/32 0.6 0.3-1.6 22/28 2.9 1.4-6.2 ≥121 65/131 1.2 0.6-2.1 29/66 0.4 0.2-1.1 n/a 22/47 1.4 0.7-3.0 *p*trend 0.34 0.31 0.09

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Freudenheim 2003 **Country:** USA **Study aims:** to investigate association between lung cancer and lifetime alcohol consumption and interactions with ADH_3 genotype **Source of funding:** National Institute on Alcohol Abuse and Alcoholism (partial)	**Population:** *Cases:* all individuals with newly diagnosed lung cancer identified at all the major hospitals in Erie and Niagara Counties who were between 35 and 79 y old N=111 *Controls* between 35 and 65 y were randomly selected from a list of those holding a New York State driver's license and residing in Erie and Niagara Counties; those _65 y were randomly selected from the rolls of the Health Care Finance Administration N=1546 **Exclusion criteria:** previous cancer diagnosis (other than non-melanoma skin cancer), **Observation time:** February 1996 to November 1998 Response rate: cases 48% and controls 65%	**Exposure:** *Questionnaire:* structured questionnaire and computer assisted interviews. Used the Cognitive Lifetime Drinking History to obtain information on lifetime alcohol intake; participants reported how old they were when they started drinking alcohol at least once a month for 6 mo and at what ages their drinking patterns changed. *Interviewers blinded*: n/s *Reference period:* within 12 months for cases, and 12-24 months for controls *Drink type:* beer wine spirits **Measure:** recent (drinks per week) and lifetime consumption, **Reference group**: non-drinkers (n=7 cases/314controls) **Results:** *Total alcohol intake* ca/co Lifetime *ptrend* d/w ca/co Over last 12-24 months *ptrend* ≤82 4/1517 1.10 (0.46-2.63) ≤2.5 30/988 0.96 (0.38-2.44) >82 113/1520 1.13 (0.47-2.72) 0.44 >2.5 66/998 1.35 (0.54-3.41) 0.41 *Beer(ref group = 37/1265)* ≤62 41/1041 1.17 (0.70-1.94) ≤1.6 18/576 0.75 (0.39-1.44) >62 90/1045 1.36 (0.82-2.27 0.30 >1.6 50/597 1.67 (0.96-2.92) 0.05 *Wine (ref group = 111/1624)* ≤19 23/863 0.87 (0.53-1.44) ≤1.0 14/569 0.67 (0.36-1.28) >19 34/864 0.80 (0.51-1.25) 0.06 >1.0 18/573 0.72 (0.40-1.29) 0.10 *Hard liquor (ref group = 60/1355)* ≤28 41/998 1.21 (0.77-1.91) ≤1.0 14/431 0.63 (0.33-1.22) >28 67/998 0.79 (0.52-1.20) 0.44 >1.0 27/434 0.87 (0.51-1.48) 0.47

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Kubik 2004 **Country:** Czech Republic **Study aims:** to examine the relationship between dietary factors and the risk of lung carcinoma in non-smoking and smoking women **Source of funding:** Ministry of Health of the Czech Republic	**Population:** *Cases:* all women with microscopically confirmed diagnosis of primary lung cancer identified at Prague University hospital N= 435 (90% response rate) *Controls:* were all women and were spouses, relatives or friends of other patients in the same hospital N= 1,710 (79% response rate) **Exclusion criteria:** conditions unrelated to smoking; **Observation time:** April 1998 and November 2002	**Exposure:** *Questionnaire:* structured questionnaire administered by trained interviewer, *Interviewers blinded*: n/s *Reference period:* usual consumption in most years within the past 10-year period *Drink type:* beer, wine and spirits **Measure:**drinking frequency, **Reference group**: never **Results:** Beer ref 271/1033 Wine ref 318/1059 Monthly 47/224 1.81 0.55-1.18 Monthly 72/408 0.66 0.48-0.91 Weekly 59/257 0.98 0.69-1.39 Weekly or daily 45/243 0.62 0.42-0.92 Daily 58/196 1.01 0.70-1.46 *p*trend =0.940 *p*trend =0.002

Study and Aims	Study and sample characteristics	Exposure measurement and Main results
Ruano-Ravina 2004 **Country:** Spain **Study aims:** to ascertain the effect of wine-both overall and by type (red and white)-on the development of lung cancer **Source of funding:** Spanish Ministry of Education and Culture	**Population:** *Cases:* all, recruited from one hospital in north west Spain serving population of approx. 500 000 N=132 *Controls:* selected from those attending the Santiago University Teaching Hospital Preoperative Unit for non-tobacco related minor surgery N=187 **Exclusion criteria:** Prevalent cases, those aged less than 30 years, those with a clinical history of any type of cancer, and those scheduled to undergo major surgery **Observation time:** 1999-2000 Response rate: cases and controls 99%	**Exposure:** *Questionnaire:* Personal interviews conducted by trained interviewers, *Interviewers blinded*: n/s *Reference period:*n/s *Drink type:* wine (white, red, rose), beer, and spirits (whisky, rum, gin, brandy, and aguardiente (a clear schnapps-like drink distilled from fermented fruit juice). **Measure:**drinking status i.e. current drinkers, **Reference group**: non-drinkers **Results:** Type of wine *(ref group* = 33/41) *ca/co* White 26/9 1.47 (0.49 to 4.38) Red 47/101 0.43 (0.19 to 0.96) Rose´ 7/11 0.35 (0.09 to 1.38) All types 18/25 0.48 (0.16 to 1.40) Beer *(ref group* = 76/111) Spirits *(ref group* = 85/147) Drinkers 56/76 1.10 (0.59 to 2.08) 47/40 1.64 (0.79 to 3.40)

Descriptive Tables for oesophageal cancer: cohort studies

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Fan 2008 **Country:** Shanghai **Study aims:** to identify risk factors for oesophageal cancer in a high-risk population **Source of funding:** National Institutes of Health	**Population:** Shanghai Cohort Study *Source:* all eligible male residents of four small, geographically defined communities from a wide area of Shanghai City *Exclusion criteria:*previous history of cancer; <45 and >64 years of age *Study pop*: 18,244 men (80% of eligible subjects) **Observation time:** 1986–1989,to 2006, 100 cases, LFU: n/s	**Exposure:** *Questionnaire:* face-to-face interview by a trained nurse. A structured questionnaire used to collect information *Repeated during follow-up*: no *Reference period:* ever drunk alcoholic beverages at least once a week continuously for six months or longer *Drink type:* beer, rice wine, spirit. **Measure:** grams per day, **Reference group**: non-drinkers **Results:** *Current* *Lifetime* <20 19 1.42 (0.81, 2.52) <300 32 1.69 (1.03, 2.77) 20 - <40 14 1.67 (0.88, 3.18) 300-<800 20 2.00 (1.11, 3.59) 40 - <80 24 2.88 (1.64, 5.06) 800+ 17 4.26 (2.26, 8.01) 80+ 12 4.65 (2.31, 9.36) *p* for trend <0.0001 *p* for trend <0.0001

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Freedman 2008 **SEE GASTRIC DESCRIPTIVE TABLEs**	**Population:** **SEE GASTRIC DESCRIPTIVE TABLES** *Study pop*: = **Observation time:** 302 cases (97 SCC, 305 adenocarcinoma)	**Exposure: SEE GASTRIC DESCRIPTIVE TABLES** **Measure:** drinks per day, **Reference group**: >0–1 drinks per day (n=24-SCC, 101=adeno) **Results:** squamous cell adenocarcinoma 023 2.06 1.16-3.68 42 0.96 0.66-1.38 >1–3 20 2.33 1.28-4.24 35 0.95 0.64-1.40 > 30 4.93 2.69-9.03 27 1.10 0.69-1.74 *P* trend <0.0001 0.68

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Kasum 2002 **Country:** USA **Study aims:** To study whether, whole-grain intake is related to reduced risk of upper aero-digestive tract cancers **Source of funding:** N/s	**Population:** *Source:* random sample of women aged 55-69 yrs from Iowa state driver's license list. A total of 41,836 women responded to a mail survey in Jan. 1986 (42.7% response rate) *Exclusion criteria:*if left ≥30 items blank on the FFQ or reported implausibly high or low energy intake pre-menopausal women; women who at baseline reported cancer of any site other than skin *Study pop*: = 34,651 **Observation time:** 1986-1999, approx 400,000 person years, LFU <1%, 51 oesophageal, cancers,	**Exposure:** *Questionnaire:* Self-administered 127-item FFQ *Repeated during follow-up*: baseline only *Reference period:* n/s *Drink type:* no **Measure:**drinks per day, **Reference group**: 0 drinks per day **Results:** *d/d* *HR* >0-1.9 0.80 ≥2 1.90 *no confidence intervals presented in study text*

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Sakata 2005 **Country:** Japan **Study aims:** to elucidate which characteristics of smoking and alcohol intake contribute to oesophageal cancer mortality **Source of funding:** Ministry of Education, Culture, Sports and Technology of Japan	**Population:** *Source:* Baseline survey carried out in 45 areas of Japan from 1988 to 1990 *Exclusion criteria:*history of cancer; did not give information about their smoking or drinking status *Study pop*: 42 578 men **Observation time:** 1988-1990 through to end of 1999, LFU n/s 100 deaths identified,	**Exposure:** *Questionnaire:* self administered *Repeated during follow-up*: baseline only *Reference period:* usual yearly intake *Drink type:* sake (rice wine), shochu (spirit), beer, whisky and wine **Measure:**units per day, years of drinking, **Reference group**: never drinkers **Results:** *d/w* *current* *years of alcohol drinking* <1 1.47 0.28-7.68 <25.0 1.71 0.64-4.60 1.0-1.9 1.58 0.65-3.86 25.1-35.0 3.23 1.32-7.92 2.0-2.9 3.74 1.62-8.66 35.1-45.0 3.74 1.33-7.81 3.0+ 6.39 2.54-16.12 45.1+ 6.39 0.85-9.03, *p*trend = 0.028 0.100

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Tran et al 2005 **Country:** China **Study aims:** 'We examined risk factors for oesophageal squamous cell carcinoma, gastric cardia cancer, and gastric non-cardia cancer…" **Source of funding:** n/s	**Population:** *Source:* General Population Trial from the general population of Linxian *Exclusion criteria:*no history of cancer or debilitating disease *Study pop*: 29,584 individuals, 40–69 yrs at baseline **Observation time:** March 1986 until May 2001, 15 years follow-up, LFU <1%; 1,958 ESCC, incident cancer cases	**Exposure:** *Questionnaire:* interviewed to complete baseline questionnaire *Repeated during follow-up*: baseline only *Reference period:*past 12 months *Drink type:* no **Measure:**drink status, **Reference group**: not drank in last 12 months **Results:**'drank in the previous 12 months' *ca* RR 23 0.92 0.82-1.03

Descriptive Tables for oesophageal cancer: case-control studies

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Boonyaphiphat 2002 **Country:** Thailand **Study aims:** to determine the risk factors of oesophageal cancer in the Thai population **Source of funding:** Prince of Songkla University	**Population:** *Cases:* patients at university hospital in south Thailand N=202 *Controls:* selected from same hospital N=261 **Exclusion criteria:** alcohol or tobacco related diseases **Observation time:** August 1997 to May 2000; Response rate: n/s	**Exposure:** *Questionnaire:* face to face interview using structured questionnaire *Interviewers blinded*: n/s *Reference period:*n/s *Drink type:* no **Measure:**grams per day, **Reference group**: non drinkers **Results:** *g/d* ≤60 50/78 2.13 (1.15-3.93) >60 99/50 5.84 (3.15-10.83)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Bosetti 2000 **Country:** Italy **Study aims:** To investigate the separate and combined effect of wine-drinking and other alcoholic beverages on oesophageal cancer, in a high wine-consuming population **Source of funding:** Italian Association for Cancer Research	**Population:** *Cases:* selected from hospitals in greater Milan area and Pordenone N=714 (618 males, 96 females) *Controls:* selected from those admitted to same network of hospitals N=3,137 (2,400 males, 737 females), **Exclusion criteria:** non-neoplastic conditions related to alcohol or tobacco consumption. **Observation time:** Between 1984 and 1998, Response rate:n/s	**Exposure:** *Questionnaire:* Trained interviewer structured questionnaires *Interviewers blinded*: n/s *Reference period:*n/s *Drink type:* wine, beer and spirits **Measure:** drinks per day, **Reference group**: <3 drinks p/d **Results:** *ca/co* *All alcohol* 3-4 114/701 1.98 (1.46-2.67) 5-7 149/480 4.22 (3.10-5.75) 8-11 190/346 7.60 (5.51-10.48) ≥12 120/175 12.35 (8.37-18.21)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Brown 2001 **Country:** USA **Study aims:** To evaluate relation between social class factors and squamous cell oesophageal cancer and the extent to which alcohol, tobacco, diet, and low income contribute to higher incidence among Black men than White men in USA **Source of funding:** National Cancer Institute	**Population:** *Cases:* male residents of Atlanta, Georgia, Detroit, Michigan, and the state of New Jersey aged 30–79 years N=347 (119 White, 228 Black) *Controls:* aged 30-64 yrs were selected using a random digit dialling technique whereas controls aged 65-79 yrs randomly chosen from computerized listings of Medicare registrants N=1,354(743 White, 611 Black) **Exclusion criteria:**not having a telephone **Observation time:** between August 1, 1986 and April 30, 1989 Response rate: 68% (cases) 74% (controls)	**Exposure:** *Questionnaire:* In-person interviews by trained interviewers *Interviewers blinded*: n/s *Reference period:*n/s *Drink type:*n/s **Measure:**drinks per week, **Reference group**: <8 drinks p/w **Results:** *White and Black men combined* 8-14 3.2 1.8-5.8 15-35 6.2 3.7-10.3 ≥36 16.9 10.1-28.1

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Castellsague 1999 **Country:** South America **Study aims:** To explore the effectiveness of alcohol drinking and tobacco smoking cessation in reducing oesophageal cancer risk, taking into account the key characteristics of each habit and the simultaneous exposure to both habits **Source of funding:** IARC	**Design:** pooled analysis of five case control studies **Population:** *Cases:* selected from hospitals included in the five studies N=830 *Controls:* selected from hospitals included in the five studies N=1,779 **Exclusion criteria:** none specified **Observation time:** from 1986 through 1992 Response rate: >98% in cases and controls	**Exposure:** *Questionnaire:* interviewed at the hospitals according to pre-tested standardized questionnaire *Interviewers blinded*: *Reference period:* throughout life. *Drink type:* beer, wine, spirits **Measure:** grams per day, **Reference group**: never drinker **Results:** *Males* *Females* Ex-drinker 3.4 (2.3-5.0) 1.9 (0.9-3.8) Current (< 1year) 4.4 (3.1-6.2) 2.2 (1.3-3.9) 1-24 1.8 (1.2-2.6) 25-49 3.0 (2.1-4.4) 50-149 4.1 (3.0-5.8) 150-249 6.9 (4.5-10.6) 250+ 11.5 (7.4-17.6)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Cheng 2000 **Country:** England/Scotland **Study aims:** To investigate the incidence of adenocarcinoma of the oesophagus in British women **Source of funding:** Scottish Office; the LORS in East Anglia; Special Trustees to the Nottingham University Hospitals; and Medical Research Council	**Population:** *Cases:* all women aged <75yrs in study areas of East Anglia and Oxford, part of Trent RHA and Eastern Scotland covering Health Boards of Highland, Grampian, Tayside, Fife, Lothian and Forth Valley diagnosed with oesophageal cancer. N=74 *Controls:* randomly selected using Family Health Service Authority or Health Board primary care registers. N=74 **Exclusion criteria:** none specified **Observation time:** Between 1993 and 1996; Response rate: 65%	**Exposure:** *Questionnaire:* Trained interviewers used a standard form to conduct interviews, either in hospital or at home *Interviewers blinded*: n/s *Reference period:*n/s *Drink type:*n/s **Measure:**units per week and total lifetime consumption, **Reference group**: non-drinker (n=14/22) **Results:** *u/w* — *over lifetime* — *units* — *total lifetime (units* <2 25/26 0.44 (0.15-1.29) ≤2850 20/18 0.42 (0.14-1.24) 2-13.99 2/22 0.28 (0.09-0.90) 2881-8312.4 21/17 0.32 (0.09-1.11) ≥14 2/3 0.66 (0.08-4.96) ≥8212.5 18/16 0.37 (0.11-1.25) *p* trend 0.074 0.154

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Engel 2003 **Country:** USA **Study aims:** to comprehensively examine PARs separately for adenocarcinoma and squamous cell carcinoma of the oesophagus, as well as for cardia and non-cardia sub-sites of gastric adenocarcinoma. **Source of funding:** National Cancer Institute,	**Population:** *Cases:* newly diagnosed with oesophageal adenocarcinoma, gastric cardia adenocarcinoma, oesophageal squamous cell carcinoma, or non-cardia gastric adenocarcinoma, identified via rapid reporting systems. N= esophageal adenocarcinoma(293), gastric cardia adenocarcinoma(261), oesophageal squamous cell carcinoma(221), gastric adenocarcinoma(368), *Controls:* selected via random-digit dialling (for ages 30–64 yrs) or via Health Care Administration records (for ages 65–79 years). N=695 **Exclusion criteria:** - None specified **Observation time:** from 1993 through 1995 Response rate: 77% cases and 80% controls	**Exposure:** *Questionnaire:* Trained interviewers administered structured, in-person interviews *Interviewers blinded*: n/s *Reference period:* 1 year before the interview *Drink type:* beer, wine, and liquor **Measure:**drinks per week, **Reference group**: never drinker (includes < 1 drink per month) **Results:** <5 1.3 0.6-3.0 5-11 2.5 1.1-5.6 12-30 4.7 2.2-9.7 >30 9.4 4.6-19.2

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Gallus 2001 **Country:** Italy and Switzerland **Study aims:** to investigate risk of squamous cell oesophageal cancer in women	**Population:SEE BOSETTI 2000 ABOVE** *Cases:* N=114 *Controls:* N=425 **Exclusion criteria:** **Observation time:**	**Exposure: SEE BOSETTI 2000 ABOVE** **Measure:**drink per day, **Reference group**: <1 drink per day **Results:** 1-2 50/181. 1.99 1.15-3.44 ≥3 35/40 5.40 2.70-10.80 p<0.001

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Hashibe 2007 **Country:** Central and Eastern Europe: Bucharest (Romania), Lodz (Poland), Moscow (Russia), Olomouc and Prague (Czech Republic) **Study aims:** To evaluate the role of risk factors for oesophageal cancer **Source of funding:** World Cancer Research Fund;EuropeanCommission	**Population:** *Cases:* hospitals and cancer centres from participating countries, *no further details provided* N=227 *Controls:* selected from same hospitals etc. as cases no further details provided N=1,114 **Exclusion criteria:** none specified **Observation time:** August 2000 to 2002, Response rate: 96% for cases and 97%, for controls.	**Exposure:** *Questionnaire:* face to face interview using structured questionnaire *Interviewers blinded*: n/s *Reference period:* drinking of beer, wine and spirits in atypical week during specific age periods (at age 25, 40, 50 and60). *Drink type:* as above **Measure:** grams per week, **Reference group**: No drinking (SCC cases = 5, Adeno =3) **Results:** *co/ca SCC ca Adenocarcinoma* 1–139 540/69 3.08 1.11-8.60 13 1.06 0.25-458 140–279 159/34 4.51 1.46-13.9 46 2.22 0.40-12.39 280–419 71/20 8.14 2.45-27.04 4 5.39 0.73-39.93. 420 142/55 9.78 3.08-31.04 6 2.31 0.30-17.58 *p* for trend <0.01 0.20 *Years of drinking* 1–19 129/12 2.25 0.63-8.04 1 0.38 0.02-6.09 20–39 554/131 4.80 1.68-13.72 17 1.08 0.24-4.94 40+ 229/35 2.39 0.83-6.90 11 1.44 0.31-6.66 p for trend 0.08 0.55

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Ibiebele 2008 **Country:**Australia **Study aims:** to measure the association between carbonated beverage intake and risk of adenocarcinomas and squamous cell carcinoma (SCC) of the esophagus **Source of funding:** not specified	**Population:** *Cases:* patients at university hospital in south Thailand N=202 *Controls:* selected from same hospital N=1,484 **Exclusion criteria:**alcohol or tobacco related diseases **Observation time:** August 1997 to May 2000 Response rate: not specified	**Exposure:** *Questionnaire:* FFQ *Interviewers blinded*: n/s *Reference period:*within the last year *Drink type:* beer only **Measure:** grams per day, **Reference group**: non drinkers **Results:** *g/d ca/co* ≤60 50/78 2.13 (1.15-3.93) >60 99/50 5.84 (3.15-10.83)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Lagergren 2000 **Country:** Sweden **Study aims:** to test the association between tobacco, snuff and alcohol use and the risk of oesophageal and cardia cancer **Source of funding:** Swedish Cancer Society	**Population:** *Cases:* all patients in Sweden with a new diagnosis of adenocarcinoma of the oesophagus or gastric cardia and half of the patients with oesophageal squamous-cell carcinoma: N= adenocarcinoma (189), Squamous-cell carcinoma cases (167), gastric cardia adenocarcinoma (262) *Controls:* selected from age and sex strata in study base to resemble age and sex distributions among the oesophageal cases, N=820 **Exclusion criteria:** persons aged 80 years or older and individuals born abroad **Observation time:** 1995 through 1997 Response rate: cases 73 to 87%, controls 73%	**Exposure:** *Questionnaire:* face-to-face interviews *Interviewers blinded*: not blinded to case/control status of interviewees, but unaware of study hypotheses *Reference period:* 20 years before interview *Drink type:* beer, wine and liquor **Measure:**units per week, **Reference group**: never drank **Results:** *Any alcohol* u/w adenoscc 1-15 0.6 0.4-1.1 0.9 0.4-1.8 16-70 0.4 0.2-0.7 0.8 0.4-1.8 >70 0.6 0.3-1.1 3.1 1.4-6.7

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Lee 2005 **Country:**Taiwan **Study aims:** To investigate the independent and combined effects of alcohol intake, tobacco smoking and betel quid chewing on the development of oesophageal cancer **Source of funding:** Taiwan National Science Council, Taiwan National Health Research Institute	**Population:** *Cases:*all incident oesophagus cancers occurring in 3 hospitals intropical southern Taiwan N=513 *Controls:*derived from same geographic areas as cases and chosen from healthy community residents who attended same network of hospitals N=818 **Exclusion criteria:**patients who were not mentally alert and coherent; refused to be interviewed; lacked blood specimens **Observation time:** July, 1996 to December, 2003 Response rate: Cases (64.5%), Controls (95%)	**Exposure:** *Questionnaire:* face to face interviews using pre-designed and pre-tested questionnaire developed specifically for study *Interviewers blinded*: *Reference period:*a minimum of 6 months prior to study *Drink type:*beer, wine or distilled spirits **Measure:** grams per day, years of alcohol drinking, **Reference group**: never drinkerincluding former and current drinkers **Results:** *g/d Average over lifetime Years of alcohol drinking* 1-20 3.6 2.4-5.4 1–15 45/43 5.5 3.1-9.9 21-40 6.1 3.6-10.3 16–35 203/131 6.1 4.1-9.2 >40 19.5 12.1-31.2 >35 155/60 8.6 5.5-13.5 *P*trend <0.0001 =0.0001 SD unit change 2.29 (1.69–3.08) SD unit change; 1.84 (1.55–2.18

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Lindblad 2005 **Country:** United Kingdom **Study aims:** Toprospectively assess the influence of BMI, tobacco, and alcohol on the occurrence of oesophageal, gastric cardia, and non-cardia gastric adenocarcinoma **Source of funding:** AstraZeneca R&D and Swedish CancerSociety	**Population:** *Cases:*All patients aged between 40-84yrs during study period became members of study cohort when enrolled in a General practitioners research database for at least two years. During follow-up of the study cohort 2128 patients with a diagnosis code indicating oesophageal or gastric cancer were found N=1950 (1315 males and 635 females) *Controls:*randomly selected from same GP database N=10,000 **Exclusion criteria:**any cancer recorded in the database before start of the study period were not eligible for the study cohort **Observation time:** January 1, 1994 through December 31, 2001 Response rate: n/s	**Exposure:** *Questionnaire:* Computerised records from General practitioners research database *Interviewers blinded*: n/a *Reference period:* n/s *Drink type:* no **Measure:**units per day, **Reference group**: 0-2: units per day **Results:** *u/d co/ca Squamousco/caAdenoco/caunknown histology* 3-15 1662/20 1.01 0.59-1.72 1662/59 1.06 0.76-1.49 1662/77 1.05 0.78–1.39 16-34 563/13 2.44 1.26-4.71 563/15 0.69 0.39-1.20 563/26 1.02 0.66–1.58 >34 183/5 3.39 1.28-8.99 183/ 9 1.25 0.61-2.55 183/16 1.83 1.05–3.17

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Pacella-Norman 2002 **Country:** South Africa **Study aims:** to estimate the importance of tobacco and alcohol consumption and other suspected risk factors with respect to cancer of the oesophagus, lung, oral cavity and larynx **Source of funding:** University of Witwatersrand, the South African Medical Research Council, Cancer Association of South Africa, and Cancer Research UK.	**Population:** *Cases:* recruited from three main public referral hospitals of greater Johannesburg N=51 *Controls:* selected from same network of hospitals, N=1,370 female patients and 804 male **Exclusion criteria:** cancers associated with the effects of tobacco and/or alcohol, i.e. cancers of the stomach, bladder, liver, pancreas, nasopharynx, and uterine cervix plus cancer of the larynx in women **Observation time:** 1995-1999 Response rate: n/s	**Exposure:** *Questionnaire:* questionnaire by trained nurse, interview conducted in preferred language of patient (usually Zulu or Sesotho), *Interviewers blinded*: n/s *Reference period:* n/s *Drink type:* maize, sorghum, and, commercial beer, wine, commercial and home-distilled spirits **Measure:** drinking frequency, **Reference group**: 'Non drinkers' **Results:** *co/ca Men ca Women* Occasional 84/13 0.7 0.3-1. 5 234/13 0.7 0.4-1.4 Weekly 121/29 0.7 0.4-1. 3 102/27 2.2 1.3-4.0 Frequent 333/187 1.8 1.2-2. 8 189/38 1.7 1.0-2.9

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Sharp 2001 **Country:** England/Scotland **Study aims:** To investigate the incidence of squamous cell carcinoma of the oesophagus in British women **Source of funding:** Chief Scientist Office, Scottish Office; the LORS in East Anglia; and the Medical Research Council in Oxford	**Population:** *Cases:* all women aged <75 years in study areas of East Anglia and Oxford, and Eastern Scotland covering six Health Boards. N=159 *Controls:* randomly selected using Family Health Service Authority or Health Board primary care registers. N=159 **Exclusion criteria:**none specified **Observation time:** between 1993 and 1996. Response rate:n/s	**Exposure:** *Questionnaire:* Trained interviewers used a standard form *Interviewers blinded*: n/s *Reference period:*n/s *Drink type:*n/s **Measure:**Average weekly alcohol consumption over lifetime;units p/w, **Reference group**: non drinker **Results:** *ca/co* <2 47/52 0.81 0.42-1.56 2-13.99 41/47 0.72 0.34-1.53 ≥14 11/8 0.86 0.25-2.95 ptrend 0.454)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Takezaki 2000 **Country:** Japan **Study aims:** To clarify the sub-sitespecific risk factors for hypopharyngeal cancer (HC) and oesophageal cancer by anatomical subsite, **Source of funding:** Ministry of Health and Welfare, Japan	**Population:** *Cases:* recruited from male first visit outpatients who visited a Cancer Centre hospital in Nagoya, Japan. N=284 oesophageal, 62 hypopharnygeal *Controls:* selected from all first-visit male outpatients to same hospital N=11,936 **Exclusion criteria:**cancer-free **Observation time:** between 1988 and 1997 Response rate: 100%	**Exposure:** *Questionnaire:* self administered questionnaire *Interviewers blinded*:none specified *Reference period:*at least 1 year previously *Drink type:* Japanese sake, beer, shochu and whiskey **Measure:** drinks per day, **Reference group**: 'almost never' **Results:** <1-5 1.8 1.1-2.9 ≥5 8.5 5.6-13.1

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Vioque 2008 **Country:** Spain **Study aims:** To estimate the independent effect of different alcoholic beverages and type of tobacco smoking on the risk of EC and its main histological cell type (squamous cell carcinoma) **Source of funding:** Spanish Ministry of Health	**Population:** *Cases:* Spanish-speaking men and women 30-80 yrs, and hospitalized in any of 9 participant hospitals in provinces of Alicante and Valencia, N=202 *Controls:* selected from same hospital and matched on sex, age and province, N=457 **Exclusion criteria:** diseases not related a priori to the main exposures of interest (tobacco, alcohol and diet). **Observation time:** August January 1995 and March 1999 Response rate: >99.5% in cases and controls	**Exposure:** *Questionnaire:* face to face interview using structured questionnaire *Interviewers blinded*: not blinded to case/control status, but unaware of main study hypothesis and trained to administer structured questionnaires in equal manner to cases and controls *Reference period:*n/s *Drink type:* beer wine and spirits **Measure:** grams per day, **Reference group**: never-drinkers (n=171) **Results***: ca/co Average intake ca/co Years of drinking* Former drinker 49/38 5.40 (2.43 –12.00) 1–19 88/50 1.94 (0.88 – 4.27) 1–24 147/27 1.16 (0.54 – 2.49) 20–39 59/34 1.04 (0.53 – 2.02) 25–74 62/45 2.89 (1.29 – 6.48) ≥ 40 72/52 1.71 (0.86 – 3.40) ≥ 75 26/75 7.65 (3.16 – 18.49) p for trend<0.00001

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Wang 2008 **Country:** China **Study aims:** to investigate the risk of oesophageal squamous cell carcinoma in relation to exogenous factors in a rural area of China with a high incidence of oesophageal squamous cell carcinoma. **Source of funding:** National NatureScience Foundation of China	**Population:** *Cases:* recruited from Yangzhong Cancer Research Institute and Yangzhong People's Hospital N=355 *Controls:* randomly selected from the local community population living in the same county N=408 **Exclusion criteria:**≤ 30 years old **Observation time:** 1 January 2004 and 28 February 2006 Response rate: n/s	**Exposure:** *Questionnaire:* face to face interview using structured questionnaire *Interviewers blinded*: n/s *Reference period:* drinking alcoholat least once aweek and lasting for more than 6 months. *Drink type:*n/s **Measure:** drink frequency and years of drinking, **Reference group**: never drinkers (n=79/137) **Results:** *drink frequency* *ca/co men pvalue ca/co women pvalue* Some 144/115 2.197 1.510–3.195 < 0.001 4/6 0.826 0.221–3.087 0.776 Occasional 50/45 1.990 1.212–3.267 0.007 3/3 1.476 0.279–7.798 0.647 Everyday 94/70 2.325 1.529–3.533 < 0.00 1/13 0.326 0.033–3.261 0.340 *Alcohol-drinking duration (years)* < 30 47/47 1.802 1.082–3.001 0.024 2/4 0.663 0.114–3.843 0.647 ≥30 97/68 2.436 1.605–3.697 < 0.001 2/2 1.107 0.152–8.083 0.920

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Wu 2001 **Country:** USA **Study aims:** to determine the role of smoking, alcohol use, and body size characteristics in the aetiology of oesophageal, gastric cardia, and distal gastric adenocarcinoma. **Source of funding:** National Cancer Institute	**Population:** *Cases:* men and women aged 30-74 years identified by Cancer Registry, Los Angeles N=222 *Controls:* selected from same cancer registry, N=1289 **Exclusion criteria:** - none specified **Observation time:** 1992-1997 Response rate: Cases 77%, Controls >50%	**Exposure:** *Questionnaire:* structured questionnaire administered by interviewer *Interviewers blinded*: interviewers not blind to case or control status, but were not aware of study hypotheses *Reference period:*n/s *Drink type:* beer, wine, hard liquor **Measure:** Drinks/week, **Reference group**:never drinkers **Results:** 1-7 0.72 (0.5-1.2) 8-21 0.57 (0.3-0.9) 22-35 0.77 (0.4-1.4) 36+ 0.93 (0.5-1.6) ptrend 0.79

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Zambon 2000 **Country:** Italy **Study aims:** the role of alcohol drinking and tobacco smoking in cancer of the oesophagus in men from 3 areas of northern Italy,	**Population:SEE BOSETTI 2000 ABOVE** *Cases:* N=275 *Controls:* N=593 **Exclusion criteria:** **Observation time:**	**Exposure: SEE BOSETTI 2000 ABOVE** **Measure:**drinks/week, years of drinking, age started drinking **Reference group**: drinks/week 1-20 drinks per week; Years of drinking (<45 yrs); Age started drinking (≥21 years) **Results:** Abstainers 1/22 0.63 0.08–5.19 21–34 47/163 4.13 (2.11–8.08) 35–55 57/120 6.21 (3.16–12.20) 56–83 84/70 14.48 (7.29–28.77) ≥ 84 72/36 24.47 (11.74–51.01) (p < 0.001) *Years of drinking* *Age started drinking* 45–54 51/131 0.99 (0.51–1.92) 17–20 137/247 1.12 (0.75–1.67) 55–64 86/191 0.93 (0.47–1.84) <17 70/194 0.68 (0.44–1.05) *p*trend0.06 ≥ 65 74/154 1.86 (0.72–4.78) (*p*trend0.31)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Znaor 2003 **Country:** India **Study aims:** To investigate patterns of tobacco smoking, chewing and alcohol drinking in the development of oral, pharyngeal and oesophageal cancers in Southern India **Source of funding:** not stated	**Population:** *Cases:* male patients at a Cancer Institute and Regional Cancer Centre, Kerala, India N=566 *Controls:* male patients from the same centres. N=3,638 **Exclusion criteria:** - tobacco-related cancers **Observation time:** during 1993 and 1999 Response rate: n/s	**Exposure:** *Questionnaire:* Interviewed by trained social investigators *Interviewers blinded*: n/s *Reference period:*No details *Drink type:*No details **Measure:** ml/day, **Reference group**: never drinkers **Results:** *Average daily amount* <20 70 / 371 1.13 0.83–1.55 20–50 80/ 178 1.83 1.31–2.55 >50 110 /167 2.53 1.85–3.46

Descriptive Tables for oral cancer: case control studies

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Altieri 2004 **Country:** Italy/Switzerland **Study aims:** In order to clarify and better quantify the separate and combined effect of wine and other alcoholic beverages on oral cancer, **Source of funding:** Italian Association for Cancer Research, Italian and Swiss Leagues against Cancer, Swiss Foundation for Research Against Cancer	**Population:** *Cases:* admitted to major teaching and general hospitals in two areas of Italy (Pordenone and Rome) and in Swiss Canton of Vaud N=749 *Controls:* admitted to same network of hospitals N=1,772 **Exclusion criteria**: non-neoplastic conditions associated with smoking or alcohol consumption. **Observation time:** between January 1992 and November 1997 Response rate: 95% in cases or controls	**Exposure:** *Questionnaire:* trained interviewer using structured questionnaire *Interviewers blinded*: n/s *Reference period:* in year before onset of symptoms which led to hospital admission *Drink type:* wine, beer and spirits **Measure:** drinks per day (d/d), **Reference group**: non-drinkers and 1-2 d/d **Results:** d/d Total alcohol 3–4 95/365 2.1 1.5–2.9 5–7 132/208 5.0 3.5–7.1 8–11 199/118 12.2 8.4–17.6 ≥12 196/60 21.1 14.0–31.8 (*p*trend <0.0001)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Balarm2000 **Country:** India **Study aims:** to evaluate the relative importance of smoking, alcohol drinking and paan chewing, with or without tobacco, on cancer of the oral cavity in men and women and the modifying effect, if any, of various indicators of oral hygiene **Source of funding:** n/s	**Population:** *Cases:* identified by interview and oral examination from hospitals in Bangalore, Madras and Trivandrum, in Southern India. N=309 *Controls:* identified from same hospitals where cases were found either from relatives and friends who were attending patients admitted for cancer other than oral cancer in Bangalore and Madras. In Trivandrum, controls chosen among outpatients N=292 **Exclusion criteria:**none specified **Observation time:** Between July 1996 and May 1999 Response rate: >90% for cases and controls	Exposure: *Questionnaire:* interviewed by social workers *Interviewers blinded*: n/s *Reference period:*n/s *Drink type:* arrack, toddy, beer and wine **Measure:** drinks per week, **Reference group**: Abstainers **Results**: *analyses restricted to men only* *Former drinkers* 65/34 1.78 (0.97–3.28) *Current drinkers* <3 29/18 2.17 (1.00–4.69) 3–13 22/13 2.14 (0.89–5.19) ≥14/ 29/12 1.97 (0.85–4.57), *p*trend 0.01 Age at start drinking (yr) *(ref group ≥31 yrs)* 23-30 29/12 2.11 (0.69–6.48) ≤23 25/18 0.67 (0.20–2.26) *p*trend 0.78 Years since quit drinking <10 49/27 0.94 (0.43–2.09) ≥10 16/7 0.62 (0.19–2.05), *p*trend 0.55

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Bosetti 2000 **Country**: Italy/Switzerland **Study aims:** to better quantify the role of smoking and alcohol in oral and pharyngeal cancer among women **Source of funding**: See Altieri (2004)	**Population:SEE ALTIERI 2OO4 ABOVE** *Cases:* N=195 cases, women *Controls:* N=1113 controls, women **Exclusion criteria:** **Observation time:**	Exposure: **SEE ALTIERI 2OO4 ABOVE** **Measure:** drinks per day, **Reference group**: non-drinkers **Results:**Referent group, d/d ca/co <2 42/339 1.45 (0.86–2.43) ≥2 121/392 2.74 (1.71–4.38) *p*trend <0.0001

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Castellsague 2004 **Country:**Spain **Study aims**: To explore the role and impact of tobacco type and beverage type in oral carcinogenesis, **Source of funding:** n/s	**Population:** *Cases:* histologically diagnosed cases recruited from 4 hospitals: in Granada, Sevilla and Barcelona N=375 *Controls:* from same hospitals as cases N=395 **Exclusion criteria:**diagnosis related to alcohol or tobacco consumption **Observation time:** between November 1996 and July 1999 Response rate: cases (76.5%), controls (91%)	**Exposure:** *Questionnaire:* pretested standardized questionnaire administered by trained interviewers *Interviewers blinded*: n/s *Reference period:* lifetime *Drink type:* beer, wine and spirits **Measure:**drinks per day, Years of alcohol drinking, **Reference group**: never drinkers **Results**: Total alcohol intake Years of alcohol drinking 1 59/114 2.00 (1.06–3.77) 1–20 27/42 1.37 (0.65–2.91) 2 27/41 3.74 (1.62–8.63) 21–30 69/67 2.49 (1.22–5.09) 3–4 49/44 6.22 (2.82–13.71) 31–40 96/84 3.18 (1.61–6.29) 5–6 55/28 10.58 (4.57–24.46) 41–50 88/69 4.00 (1.99–8.02) 7–10 68/37 10.29 (4.57–23.17) ≥51 60/37 5.13 (2.45–10.72) ≥11 82/35 13.66 (6.02–30.96) *p*trend <0.0001 *p*trend < 0.0001

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Fioretti 1999 **Country:** Italy **Study aims:** we considered risk factors for oral and pharyngeal cancer in lifelong non-smokers	**Population:SEE ALTIERI 2OO4 ABOVE** *Cases:* N=42 *Controls:* N=864 **Exclusion criteria: SEE ALTIERI 2OO4 ABOVE** **Observation time: SEE ALTIERI 2OO4 ABOVE**	**Exposure: SEE ALTIERI 2OO4 ABOVE** **Measure:**drinks/day, **Reference group**: non drinkers **Results:** *Total alcohol intake* *Duration of alcohol intake (years)* >0-<3 25 327 3.4 (1.1-10.1) <35 16/382 2.9 (0.9-9.2) ≥3 13 333 2.6 (0.7-9.3) ≥35 22/278 3.6 (1.2-11.2) *p*trend. 0:03)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Franceschi 1999 **Country:** Italy/ Switzerland **Study aims:** to compare the separate and combined effect of alcohol and tobacco between oral cancer and pharyngeal cancer.	**Population:SEE ALTIERI 2OO4 ABOVE** *Cases:* N=274 oral cancer cases, 364 pharyngeal cancer cases *Controls:* N= 1254 **Exclusion criteria:** **Observation time:**	**Exposure: SEE ALTIERI 2OO4 ABOVE** **Measure:** **Reference group**: **Results:** See main text, Chapter 2.13

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Garrote 1999 **Country:** Cuba **Study aims:** examine contribution of oral hygiene, dentition, sexual habits, sexually transmitted diseases, smoking, alcohol drinking, and dietary habits to cancer of the oral cavity and oro-pharynx in Cuba **Source of funding:** Pan American Health Organization	**Population:** *Cases:* identified in oncology hospital in Havana (Cuba) N=200 (153 mouth, 19 oropharynx, 28 both sites) *Controls:* admitted to oncology and 3 other major hospitals in Havana N=200 **Exclusion criteria:** - diseases related to smoking or drinking habits **Observation time:** Between April 1996 and July 1999 Response rate: n/s	**Exposure:** *Questionnaire:* interviewed during their hospital stay by one trained dentist *Interviewers blinded*: n/s *Reference period:* n/s *Drink type:* n/s **Measure:**drinks/wk, duration of drinking, **Reference group**: never drinkers, <33yrs **Results:** *Drinking habit* *Duration of drinking (years)* <7 15/21 1.09 (0.46–2.57) 33–44 31/21 1.98 (0.93–4.22) 7–20 25/19 1.60 (0.70–3.67) ≥45 30/17 1.81 (0.85–3.87) *p*trend. 0.46 21–69 21/ 14 2.20 (0.89–5.45) ≥70 20/ 6 5.73 (1.77–18.52) *p*trend.< 0.01

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Hayes 1999 **Country:** Puerto Rico **Study aims:** To evaluate the role of tobacco and alcohol in the aetiology of nonsalivary gland cancers of the mouth and pharynx and cancers of the major and minor salivary **Source of funding:** n/s	**Population:** *Cases:* all men 21-79 yrs newly diagnosed, with cancer of oral cavity or pharynx identified through l cancer registry and histologically confirmed, N=519 *Controls:* selected from among all male Puerto Ricans by probability sampling of households. N=629 **Exclusion criteria:**none specified **Observation time:** December 1992 and February 1995, Response rate: cases (73%), controls (83%).	**Exposure:** *Questionnaire:* interviewed using structured pre-tested questionnaire *Interviewers blinded*: n/s *Reference period:* lifetime *Drink type:* wine, beer, spirits **Measure:**Lifetime consumption, drinks per week, **Reference group**: non-drinker **Results:** 1-7 19/117 0.8 (0.3-2.1) 8-21 28/87 1.4 (0.6-3.4) 22-42 49/55 3.3 (1.4-8.0) >42 164/58 7.7 (3.3-17.9), *p* trend <0.0001

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Huang 2003 **Country:** Puerto Rico **Study aims:** to evaluate the effects of alcohol concentration and the intake of homemade rum as potential explanations for the high rates of oral cancer reported in Puerto Rico	**Population:SEE HAYES 1999 ABOVE** *Cases:* N=286 *Controls:* N=417 **Exclusion criteria:** **Observation time:**	**Exposure: SEE HAYES 1999 ABOVE** **Measure:**Drinks per week **Reference group**: Non-drinkers **Results:**

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Lissowska 2003 **Country:** Poland **Study aims:** The effect of smoking, drinking, diet, dental care and sexual habits on the risk of oral and pharyngeal cancer was investigated **Source of funding:** The Polish State Committee for Scientific Research and IARC	**Population:** *Cases:* aged 23-80yrs, with cancer of the oral cavity and pharynx in large maxillofacial surgery clinics in the province of Warsaw, histologically confirmed N=122 *Controls:* admitted for acute illnesses to major hospitals serving the same areas where cases lived were eligible control N=124 **Exclusion criteria:** Tobacco and alcohol-related diseases (e.g. chronic bronchitis, cardiovascular diseases, liver cirrhosis and pancreatitis). **Observation time:** between March 1997 and June 2000 Response rate: cases (96%) controls (93%)	**Exposure:** *Questionnaire:* interviewed by trained interviewers *Interviewers blinded*: n/s *Reference period:* n/s *Drink type:*n/s **Measure:**drinks per week/Age start drinking, **Reference group**: abstainers/<20 yrs **Results:** *Total alcohol intake* Former drinker 10/8 1.47 (0.40–5.34) Current drinker <5 20/28 1.57 (0.57–4.31) 5–21 28/26 1.74 (0.58–5.24) >21 21/7 4.25 (1.07–16.93),) *p*trend.0.02 *Age start drinking* 20–24 22/25 0.55 (0.22–1.41) **≥24** 19/13 1.49 (0.50–4.43)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Llewellyn 2004 **Country:** United Kingdom **Study aims:** to evaluate the major risk factors for oral cancer in young adults in the United Kingdom. **Source of funding:** NHS Executive London Research & Development, Responsive Funding Programme	**Population:** *Cases:* age 45 years or younger in south east of England, identified through Thames Cancer Registry database, pathologically confirmed, N=116 *Controls:* conducted by contacting cases' general medical practitioner and identifying from Practice Register two controls who had never had cancer. N=207 **Exclusion criteria:**- None specified **Observation time:** between 1990 and 1997 Response rate: cases controls (59% response rate)	**Exposure:** *Questionnaire:* Mailed structured questionnaire *Interviewers blinded:* not applicable, postal questionnaire *Reference period:*in last year *Drink type:* wine, beer, spirits **Measure:**units per week/Age started drinking, **Reference group**: ≤14 units per week for females and ≤21 units per week for males/ ≥18yrs **Results:** Total alcohol intake *Age started drinking* Men ≥ 21 1.6 (0.8-3.1) ≤18yrs 67/107 1.1 (0.5-2.0) Women ≥14 1.6 (0.6-4.2)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Llewllyn 2004 **Country:** United Kingdom **Study aims:** to evaluate the major risk factors for oral cancer in young adults in the United Kingdom. **Source of funding:** NHS Executive London Research & Development, Responsive Funding Programme	**Population:** *Cases:* age 45 years or younger in south east of England, identified through Thames Cancer Registry database, pathologically confirmed N=116 *Controls:* conducted by contacting cases' general medical practitioner and identifying from Practice Register two controls who had never had cancer. N=207 **Exclusion criteria:**- None specified **Observation time:** between 1990 and 1997 Response rate: cases controls (59% response rate)	**Exposure:** *Questionnaire:* Mailed structured questionnaire *Interviewers blinded*: *Reference period:* *Drink type:* **Measure:** units per week/Age started drinking, **Reference group**: ≤14 units per week for females and ≤21 units per week for males/ ≥18yrs **Results:** Total alcohol intake *Age started drinking* Men ≥ 21 37/46 1.6 (0.8-3.1) ≤18yrs 67/107 1.1 (0.5-2.0) Women ≥14 XXX 1.6 (0.6-4.2)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Maso 2002 **Country:** Italy and Switzerland	**Population:SEE ALTIERI 2OO4 ABOVE** *Cases:* N=324 cancers of the oral cavity, pharynx (397) *Controls:*N=1,545 **Exclusion criteria: SEE ALTIERI 2OO4 ABOVE** **Observation time: SEE ALTIERI 2OO4 ABOVE**	**Exposure: SEE ALTIERI 2OO4 ABOVE** **Measure:**drinks per week, **Reference group**: 1-20 drinks per week **Results:** *Oral Cavity* d/w ca/co Only at meals ca/co outside meals 21–34 34/95 2.5 (1.5-4.2) 9/70 4.0 (0.9–17.1)) 35–55 19/129 3.7 (1.9-7.2) 42/79 13.2 (3.4–50.8)) ≥56 30/64 10.3 (5.3–20.1) 141/113 27.6 (7.3–103.7) *Pharynx* d/w Only at meals ca/co outside meals 21-34 37/295 2.0 (1.1-3.4) 15/70 2.2 (0.8–6.2) 35–55 20/129 2.2 (1.1-4.4) 51/79 4.9 (1.9–12.6) ≥56 32/64 7.1 (3.7-13.8)) 195/113 11.3 (4.5–28.4)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Moreno-Lopez 2000 **Country:** Spain **Study aims:** to discover the role of tobacco and alcohol consumption and of the level of oral hygiene in the appearance of oral cancer **Source of funding:** N/s	**Population:** *Cases:* all those with oral cavity cancer diagnosed in three hospitals in Madrid, histologically confirmed N=75 *Controls:* healthy subjects in health care centres that corresponded to these hospitals, N=150 **Exclusion criteria:** cancer in any location or any medical oral disease **Observation time:** n/s, Response rate: n/s	**Exposure:** *Questionnaire:* standardized questionnaire administered by interviewer *Interviewers blinded*: n/s *Reference period:*n/s *Drink type:* wine, beer, spirits **Measure:**grams per day, **Reference group**: non drinker **Results:** 1-50 28/77 1.55 0.72-3.32 (P<0.05) >50 35/22 6.76 2.96-15.42 (P<0.05), *p*trend.<0.05

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Rodriguez 2004 **Country:** Italy, Switzerland **Study aims:** risk factors for oral cancer in the young	**Population:SEE ALTIERI 2OO4 ABOVE** *Cases:* N=137 *Controls:* N=298 **Exclusion criteria: SEE ALTIERI 2OO4 ABOVE** **Observation time: SEE ALTIERI 2OO4 ABOVE**	**Exposure: SEE ALTIERI 2OO4 ABOVE** **Measure:** drinks per day, **Reference group**: non drinkers **Results:** ca/co <3 20/102 0.70 (0.27-1.78) 3-<6 19/76 0.99 (0.35-2.81) 6-<10 37/40 3.69 (1.23-11.08) ≥10 46/27 4.94 (1.62-15.10) *p*trend.<0.0001)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Schwartz 2001 **Country:** USA **Study aims:** To examine further the relationship between alcohol use, ADH3 genotypes, and oral squamous cell carcinoma risk **Source of funding:** National Institute of Dental and Craniofacial Research, National Cancer Institute	**Population:** *Cases:* residents in Washington state, identified through population-based state Cancer Surveillance System All participating cases and controls asked to provide a sample of exfoliated oral tissue N=407 *Controls:* identified through random-digit telephone dialling of state households N=615 **Exclusion criteria:** cases of lip cancer **Observation time:** Between January 1990 and June 1995 Response rate: cases (54%) controls (63.3%)	**Exposure:** *Questionnaire:* interviewed in-person by trained personnel using a FFQ *Interviewers blinded*: n/s *Reference period:* n/s *Drink type:* n/s **Measure:**drinks per week, **Reference group**: <1 drink per week **Results:** 1–7 1.0 (0.6, 1.5) 8–14 1.7 (1.0, 2.9) 15–42 2.8 (1.7, 4.8) ≥43 4.7 (2.4, 9.4)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Vjajiinac 2006 **Country:** Serbia and Montenegro **Study aims:** To test some hypotheses of risk factors for oropharyngeal malignant tumours (neoplasm of base of tongue, palate and tonsils). **Source of funding:** Ministry of Science, Technology and Development of Serbia	**Population:** *Cases:* consecutive patients diagnosed for the first time as oropharyngeal neoplasm cases at Otorynolaryngology and maxillofacial surgery, Clinical Centre in Belgrade, histologically confirmed N=100 *Controls:* patients treated during same period for some non-malignant diseases of head and neck N=100 **Exclusion criteria:**- None specified **Observation time:** 1998–2000 Response rate: n/s	**Exposure:** *Questionnaire:* interviewed by physician with structural questionnaire *Interviewers blinded*: n/s *Reference period:* lifetime *Drink type:*yes **Measure:**average weekly consumption and duration, **Reference group**: non-drinkers/<19yrs **Results:** Average weekly intake (dl) Duration of drinking (years) ≤1.75 39/37 1.55 (0.72–3.35) 20–39 50/40 1.26 (0.87–1.82) >1.75 42/30 1.98 (1.28–3.05) 40+ 15/10 1.50 (0.73–3.00) *p*trend.< 0.05

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Zavras 2001 **Country:** Greece **Study aims:** to understand the specific risk factors and protective mechanisms potentially involved in the aetiology of OC in this atypical population. **Source of funding:** National Institute of Dental and Craniofacial Research	**Population:** *Cases:* male and female residents of South Greece identified at one of three major university hospitals in Athens, histologically confirmed, N=110 *Controls:* patients of the same institutions, hospitalized for conditions unrelated to cancer N=115 **Exclusion criteria:**trauma patients **Observation time:** Between November 1995 and January 1998 Response rate: 98%	**Exposure:** *Questionnaire:* Trained interviewers used a structured questionnaire specifically designed for study *Interviewers blinded*: n/s *Reference period:* n/s *Drink type:* wine, beer, ouzo/tsipouro, dark liquors **Measure:** drinks per week, **Reference group**:0 drinks per week **Results:** d/w ca/co Men Women 1-28 34/36 1.8 (0.6-4.8) 15/9 1.4 (0.5-4.1) >28-42 10/9 1.6 (0.4-6.2) >42 15/4 5.3 (1.2-24.1) *p*trend.0.08

Descriptive tables for ovarian cancer: cohort studies

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Chang 2007 **Country:** USA **Study aims:** To examine the association between alcohol consumption and risk of ovarian cancer in a prospective cohort in which baseline alcohol consumption was associated with increased breast cancer risk **Source of funding:** National Cancer Institute, and from the California Breast Cancer Research fund	**Population:** California Teachers Study cohort *Source* includes 133,479 active and retired female public school teachers and administrators who were members of State Teachers Retirement System and returned a mailed questionnaire in 1995–1996 *Exclusion criteria:* lived outside California at baseline; prior diagnosis of ovarian cancer or bilateral oophorectomy, aged 85 ≥yrs at baseline; reported never having had a 1stmenstrual period; providedmultiple invalid, inconsistent, or blank responses to questionnaire or reported food consumption judged to be implausibly low/high; invalid, or missing alcohol intake during previous year *Study pop*: 90,371 **Observation time:** 1995-1996 to 31 December 2003, median follow-up 8.1 years; Loss to follow-up: <1% 253 diagnosed with epithelial ovarian cancer	**Exposure:** *Questionnaire:* mailed questionnaire *Repeated during follow-up:* no *Reference period:* preceding year and at ages 18-22 and 30-35 years *Drink type:* beer, wine/champagne, cocktails/liquor **Measure:** grams per day, **Reference group**: none (n=77) **Results:** *Year before baseline* *Ages 30–35 yrs* *Ages 18–22 yrs* <10.0 81 1.04 (0.76-1.42) 101 1.14 (0.83-1.56) 62 0.76 (0.55-1.03) 10.0 < 20.0 72 1.47 (1.06-2.03) 47 1.08 (0.74-1.59) 36 1.26 (0.86-1.84) ≥20.0 23 1.15 (0.71-1.84) 16 0.99 (0.56-1.71) 9 1.00 (0.50-1.99) *p*trend = 0.19 0.99 0.63

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Kelemen 2004 **Country:** USA **Study aims:** To determine if there was an association between alcohol consumption and ovarian cancer, and to test the hypothesis that there could be an interaction between folate and alcohol for risk of ovarian cancer as has been reported for breast cancer. **Source of funding:** National Cancer Institute.	**Population:** Source: 99,826 eligible women between ages of 55-69 yrs randomly selected from Iowa driver's license registry. 41,836 (41.9%) responded to questionnaire. *Exclusion criteria:* history of cancer other than skin cancer; a bilateral oophorectomy at baseline or during follow-up; ovarian tumour of borderline malignancy Study pop:27,205 **Observation time:** 1986 through December 31, 2000, 367,114 person-years Loss to follow-up: 35%; 147 cases	**Exposure:** *Questionnaire:* semi quantitative FFQ *Reference period:* over last 12 months *Drink type* – no *Repeated during follow-up:* no **Measure:** grams per day, **Reference group:**<0.01g/d **Results:** *g/d* *ca* 0.01-3.9 75 0.78 (0.54-1.13) 4.0-9.9 12 0.75 (0.39-1.42) ≥10 12 0.58 (0.30-1.11) *p*trend 0.08

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Schouten 2004 **Country:** Netherlands **Study aims:** To study alcohol consumption in relation to ovarian cancer risk in a prospective cohort study. **Source of funding:** None specified	**Population:** *Source:* Netherlands Cohort Study on diet and cancer initiated in 1986 (n=62.573) postmenopausal women. *Exclusion criteria:* cancer cases (other than skin cancer); undergone an oophorectomy *Study pop*: Case cohort approach for design & analysis, 2,412 women randomly sampled from cohort **Observation time:** 1986-1995, mean 9.3 years of follow-up, Loss to follow-up: n/s; 214 incident cases	**Exposure:** *Questionnaire:*self-administered FFQ *Reference period:*- preceding year *Drink type:*beer, red wine, white wine, sherry, other fortified wines, liqueur, and liquor *Repeated during follow-up:* no **Measure:** grams per day, **Reference group**:non drinkers (less than once a month) **Results:** *g/d* *ca* *all* *Wine* 0.1-4 74 1.13 (0.79-1.63) 1.08 (0.76-1.54) 5-14 28 0.85 (0.53-1.37) 0.97 (0.60-1.58) ≥15 21 0.92 (0.55-1.54) *p*trend 0.54 1.00 (0.57-1.75)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Tworoger 2008 **Country:** USA **Study aims:** to examine the association between caffeine, alcohol intake, cigarette smoking, and ovarian cancer risk, overall and by histologic subtype, in the Nurses' Health Study (NHS). **Source of funding:** National Institutes of Health Grants	**Population:** *Source:* Nurses Health Study established in 1976 when 121,701 U.S. female registered nurses ages 30 to 55 years completed and returned a questionnaire *Exclusion criteria:*those reporting any diagnosis of cancer besides non-melanoma skin cancer; with a history of bilateral oophorectomy; with a history of pelvic irradiation; missing year of birth; implausible dietary intakes *Study pop*: = 80,253 **Observation time:** 1980 to June 1 2004, Loss to follow-up: 4.7% 507 cases (443 invasive and 64 borderline)	**Exposure:** *Questionnaire:* self-administered FFQ *Repeated during follow-up:* yes, every two years *Reference period:* preceding year *Drink type:* beer, wine, spirits **Measure:** grams per day (g/d) and drinks per week (d/w), **Reference group**: <0.1g/d (n=110) for g/d and never (n=49) for d/w **Results:** g/d cad/w ca 0.1–4.9 217 1.05 (0.83–1.33) >0–4 249 0.99 (0.72–1.35) 5.0–14.9 114 0.99 (0.75–1.30) 5–6 80 0.93 (0.65–1.34) 15+ 66 0.99 (0.72–1.36) 1+ d/d 129 0.97 (0.69–1.35) *p*trend 0.910 99

Descriptive tables for ovarian cancer: case control studies

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Goodman 2003 **Country:** USA **Study aims:** To examine the hypothesis that alcohol consumption is associated with the risk of ovarian cancer **Source of funding:** National Institutes of Health	**Population:** *Cases:* from two population-based cancer registries, in Hawaii and Los Angeles N=558 (127 borderline tumours, 431 invasive carcinomas) *Controls:* representative sample of all households in Hawaii state based on lists of female residents interviewed by Health Surveillance Program N =607 **Exclusion criteria:**prior history of ovarian cancer; more than one intact ovary **Observation time:** 1993 to 1999 Response rate: cases 60%, controls67%	**Exposure:** *Questionnaire:* structured in person interview *Reference period:* lifetime history, drinker defined as woman who drank any type of alcoholic beverage at least once a week for 6 months or more. *Drink type:* – beer, wine, spirits **Measure:**drinks per week, **Reference group**: never drinkers **Results:** Ever 0.88 (0.67-1.16), Former 1.16 (0.82-1.64), Current 0.69 (0.50-0.96) *d/w ca/co Total* *yr ca/co No. of years drinking* <3.5 41/64 0.72 (0.46-1.12) <10 60/98 0.67 (0.46-0.98) 3.5-6.9 39/50 0.86 (0.54-1.38) 10–20 58/68 0.94 (0.62-1.42) 7.0-13.9 67/61 1.14 (0.76-1.72) ≥20 85/72 1.15 (0.78-1.68) *p*trend 0 37 ≥14 56/63 0.84 (0.55-1.28), *p*trend=0 70

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Modugno 2003 **Country:** USA **Study aims:** To examine alcohol consumption as a risk factor for epithelial ovarian cancer according to tumor histology. **Source of funding:** National Cancer Institute	**Population:** *Cases:*women aged 20–69 years diagnosed with EOC identified at 39 hospitals around the Delaware Valley N =767 *Controls:* random-digit dialling from households in same county N =1367 **Exclusion criteria:**none specified **Observation time:** May 1994 to July 1998, Response rate: cases 88%, controls72%	**Exposure:** *Questionnaire:* standardized, 1.5-hour, in-person *Interviewers blinded*: n/s *Reference period:* n/s *Drink type* - no **Measure:**grams per day, **Reference group**:never drinker **Results:** *Current drinkers* / *Former drinkers* Non-Mucinous / Mucinous / Non-Mucinous / Mucinous 24: 0.98 (0.75-1.30) / 0.61 (0.32-1.15) / 1.06(0.78-1.43) / 0.97 (0.54-1.74) ≥24: 0.88 (0.57-1.37) / 1.93 (1.02-3.65) / 1.29 (0.83-2.00) / 0.64 (0.22-1.85)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Petersen 2006 **Country:** USA **Study aims:** To investigate alcohol consumption as a risk factor for ovarian cancer **Source of funding:** National Institutes of Health;	**Design:** population case control **Population:** *Cases:* all women aged 40–79 (1993-1995) or aged 20-75 (1998-2001) with new diagnosis of ovarian cancer reported to state cancer registries N =762 *Controls:* randomly selected from lists of licensed drivers if < 65yrs, and from rosters of Medicare beneficiaries if ≥ 65yrs. N =6,271 **Exclusion criteria:** bilateral oophorectomy **Observation time:** 1993-1995 to 1998-2001 Response rate: cases 66%, controls 80.6%	**Exposure:** *Questionnaire:* structured telephone interview *Interviewers blinded*: yes *Reference period:* information on average alcohol consumption in early adulthood (20–30 years of age) and at 1 or 5 years before a reference date, depending on era of data collection. *Drink type:* beer, wine, spirits **Measure:**drinks per week and day, **Reference group**: non drinker **Results:** *Recent past* / *At 20-30yrs* <1d/w 1.05 (0.75-1.30) / 1.12 (0.88–1.42) 1-6d/w 1.15 (0.75-1.30) / 1.13 (0.90–1.43) ≥1d/d 0.89 (0.70-1.20) *p*trend=0.77 / 1.27 (0.96–1.68) *p*trend=0.11 *Recent past and drink type* Beer / Wine / Spirits <1d/w 1.17 (0.90-1.51) / 1.14 (0.90-1.44) / 0.99 (0.78-1.26) 1-6d/w 1.05 (0.78-1.41) / 1.10 (0.84-1.43) / 1.27 (0.97-1.66) ≥1d/d 0.94 (0.58-1.51) / 1.34 (0.88-2.05) / 1.19 (0.79-1.79) ptrend=0.11 / 0.21 / 0.11

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Riman 2004 **Country:** Sweden **Study aims:** to examine body mass index (BMI), alcohol use, coffee consumption, cigarette smoking, and leisure-time physical activity in relation to epithelial ovarian cancer (EOC) risk **Source of funding:** not specified	**Population:** *Cases:* subjects were 655 newly diagnosed EOC cases and, all 50-74 years *Controls:* 3899 population controls 655 cases 3899 controls **Exclusion criteria:** previous bilateral oophorectomy **Observation time:** 1993 to 1995 Response rate:	**Exposure:** *Questionnaire:* postal questionnaire (plus phone interviews for 11% non respondents) *Interviewers blinded*: *Reference period:* *Drink type:* **Measure:**grams per day, **Reference group**: not specified **Results:** <5 0.94 (0.77-1.14) ≥5 0.99 (0.75-1.29) p for trend 0.80

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Tavani 2001 **Country:** Italy **Study aims:** To investigate the relationship between coffee and alcohol intake and ovarian cancer risk **Source of funding:** Italian Association for Cancer Research	**Population:** *Cases*: selected from major teaching hospitals in four Italian areas: Greater Milan, North-eastern Italy, Central Italy and Southern Italy. N =1031cases (median age 56) *Controls:* women from same geographical areas and admitted to same network of hospitals as cases N =2411controls (median age 57) **Exclusion criteria:** admitted to the hospital for hormonal and gynaecological diseases and if they had undergone bilateral ovariectomy; admitted to the hospital for chronic conditions or digestive tract diseases, related to coffee or alcohol intake **Observation time:** between 1992 and 1999 Response rate: cases 96%, controls 96%	**Exposure:** *Questionnaire:* self administeredstructured questionnaire *Interviewers blinded*: n/s *Reference period:* n/s *Drink type:* wine, beer, grappa, amari and digestives, and spirits **Measure:**grams per day, **Reference group**: never drinkers (life-long alcohol non-drinkers) **Results:** *g/d* *All alcohol* *g/d* *Wine* <12 1.02 (0.80-1.30 ≤13 1.06(0.83-1.35 12-<24 1.29 (1.00-1.67) >13-26 1.37(1.06-1.77) 24-<36 1.04 (0.80-1.36) >26-39 1.07 (0.82-1.39) ≥36 1.09 (0.76-1.57) >39 1.03 (0.70-1.50) *p*trend= 0.409 0.386 Beer drinkers 1.15 (0.94-1.41)Spirits drinkers 1.20 (0.84-1.72)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Webb 2004 **Country:** Australia **Study aims:** to evaluate the association between alcohol intake and ovarian cancer risk in a large population-based case-control study **Source of funding:** Australian National Health and Medical Research Council andQueensland Cancer Fund.	**Population:** *Case*s: ascertained through major treatment centres in the three Australian states (New South Wales, Victoria, & Queensland). N= 696 *Controls:* selected at random from the electoral roll N= 768 **Exclusion criteria:** history of ovarian cancer or bilateral oophorectomy **Observation time:** between August 1990 and December 1993 Response rate: cases 89% controls 73%	**Exposure:** *Questionnaire:* self completed FFQ *Interviewers blinded:* n/s *Reference period:* n/s *Drink type:* red wine, white wine and champagne, beer and spirits. **Measure:** drinks per week, **Reference group**: non-drinkers **Results:** <1 0.79 (0.59-1.05) 1-6 0.66 (0.48-0.90) 1-1.9 0.78 (0.50-1.23) ≥2 0.49 (0.30-0.81) *p*trend 0.003 *Beer* *Wine* *Spirits* <1/wk 1.21 (0.51-1.91) 0.68 (0.77-1.91) 1.16 (0.75-1.80) 1-6 1.28 (0.64-2.10) 0.77 (0.51-1.61) 1.08 (0.64-1.82) ≥1/day 0.94 (0.55-1.61) 0.56 (0.33-0.93) 1.07 (0.59-1.95) *p*trend =0.50.01 0.5

Descriptive tables for pancreatic cancer: cohort studies

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Coughlin 2000 **Country:**USA **Study aims:** To learn more about epidemiology of pancreatic cancer by examining associations with a variety of possible risk factors for death from pancreatic cancer **Source of funding:** n/s	**Population:** *Source:*Cancer Prevention Study II - a prospective mortality study of men and women enrolled by American Cancer Society volunteers from all 50 US states *Exclusion criteria:*Persons <30 years old; Individuals with a self reported history of cancer other than non-melanoma skin cancer *Study pop*: 1.2 million men and women **Observation time:** 1982-1996, Loss to follow up 1.4% 3,751 deaths (1967 men, 1784 women)	**Exposure:** *Questionnaire:* Self administered questionnaire *Repeated during follow-up*: Baseline exposure only *Reference period:*within year before survey *Drink type:* n/s **Measure:**drinks per day (d/d), **Reference group**: None' (not defined) **Results:** Men Women Some 0.9 (0.8-1.1) 0.9 (0.8-1.1) 1d/d 0.9 (0.8-1.1) 0.8 (0.7-1.0) >1d/d 0.9 (0.8-1.1) 0.9 (0.8-1.1)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Heinen 2009 **Country:** Netherlands **Study aims:** to investigate the association between alcohol consumption and the risk of pancreatic cancer in a large prospective cohort study in the Netherlands. **Source of funding:** No funding	**Population:** *Source:* Netherlands Cohort Study began in September 1986 and included initially 58,279 men and 62,573 women aged 55–69 years from 204 Dutch municipalities with computerized population registries *Exclusion criteria:*- incomplete alcohol data *Study pop*: 120,852 **Observation time:** 1986 to December 1999 LFU: <4% 447 incident cases of pancreatic cancer,	**Exposure:** *Questionnaire:* self-administered 150-item semi-quantitative FFQ *Repeated during follow-up*: *Reference period:*during the year preceding the start of the study *Drink type:* beer; red wine; white wine; sherry and other fortified wines; liqueurs containing, (Dutch) gin, brandy, and whiskey **Measure:**grams per day, **Reference group**: Abstainers 73 **Results:** 0.1–<5 93 1.03 (0.74-1.42) 5–<15 82 1.12 (0.79-1.57) 15–<30 50 0.86 (0.58-1.28) ≥30 52 1.57 (1.03-2.39) Continuous (per 10-g/day increment) 1.06 0.98, 1.13

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Jiao 2009 **Country:**US **Study aims:** To further elucidate the relation between alcohol use and pancreatic cancer risk **Source of funding:** National Institutes of Health	**Population:**NIH-AARP Diet and Health Study *Source:* self-administered baseline questionnaire was mailed to 3.5 million AARP members 50-71 yrs who resided in 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, Georgia, and Detroit, Michigan). 617,119 members returned the questionnaires, and 567,169 completed the questionnaire satisfactorily *Exclusion criteria:* moved out of the study areas before returning the questionnaire; questionnaire completed by proxy respondents;prevalent cancer cases identified through cancer registries at baseline, those with extreme energy intake *Study pop*: 470,681 AARP members, 280,084 men and 190,597 women. **Observation time:**1995-1996 toDecember 31, 2003, LFU = 4%, 1,149 cases	**Exposure:** *Questionnaire:* self-administered questionnaire *Repeated during follow-up*: baseline only *Reference period:* over the previous 12 months *Drink type:* beer, wine, and spirits **Measure:** grams per day, **Reference group**: 0-0.9 g/d **Results:** 0 305 1.14 (0.99-1.32) 1–1.99 121 0.92 (0.75-1.12) 2–2.99 41 1.03 (0.75-1.42) 3–3.99 39 1.31 (0.94-1.82) 4–4.99 25 1.54 (1.02-2.31) 5–5.99 10 1.28 (0.68-2.41) ≥6 52 1.55 (1.13-2.13), P for trend 0.01 Continuous(per 10-g/dayincrement)1.06 0.98, 1.13

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Lin 2002 **Country**: Japan **Study aims:** evaluated the associations of such lifestyle factors as alcohol drinking, coffee consumption and medical history with risk of death from pancreatic cancer **Source of funding:** Ministry of Education, Science, Sports and Culture of Japan;	**Population:** *Source:* 127,500 inhabitants who underwent a general health check-up enrolled as basic cohort population from 45 areas in Japan, response rate: >90%, *Exclusion criteria:* with a history of any cancer at baseline and those with unknown smoking status. *Study pop*: 110,792: 46,465 men and 64,327 women **Observation time:** 1988-1990 to 1997, follow-up of 775,697 person-years, LFU: <5%, 225 pancreatic cancer deaths	**Exposure:** *Questionnaire:* Self administered questionnaire *Repeated during follow-up*: Baseline exposure only *Reference period:* amount drunk in last week *Drink type:* n/s **Measure:** grams per day, years of drinking grams, cumulative amount, **Reference group**: non drinkers **Results:** *Daily Amount* *Years of drinking grams* *g/d men women yrs men women* 0-29 1.16 (0.66-2.04) 1.01 (0.53–1.91) 0-19 0.93 0.40–2.14) 1.02 0.44-2.36) 30-59 1.07 (0.56-2.06) 20-39 1.09 (0.60–1.99) 0.77 0.24-2.48) ≥60 0.98 (0.39-2.46) ≥40 0.97 (0.52–1.83) 1.45 0.35-5.96) *p*trend 0.76 *p*trend 0.66 *Cumulative amount (grams) men women* 0–999 0.8 (0.41–1.57) 1.04 (0.50–2.19) 1,000–1,999 1.55 (0.84–2.86) 1.81 (0.25–13.27) ≥2,000 0.61 (0.26–1.44), *p*trend 0.89

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Michaud 2001 **Country:** USA **Study aims:** We examined the relationships of coffee and alcohol intakes and pancreatic cancer risk in the HPFS3, a prospective cohort of men, and in the NHS, a prospective cohort of women **Source of funding:** National Cancer Institute	**Population:** derived from two cohort studies: Health Professionals Follow Up Study (HPFS) and Nurses Health Study (NHS) *Exclusion criteria:* diagnosed with cancer (other than non-melanoma skin cancer) before baseline (1986 HPFS; 1980 NHS); individuals with very high/ low scores for energy. *Study pop*: 47 794 men, 88 799 women **Observation time:** 1986 to January 31, 1998 for men 1980 to June 30, 1996 for women 1,907,222 person years of follow-up, LFU <10% 130 cases of pancreatic cancer diagnosed in men and 158 pancreatic cancer cases in women	**Exposure:** *Questionnaire:* Mailed 131-item semi-quantitative FFQ *Repeated during follow-up*: Information collected at baseline and at four year intervals *Reference period:*over the previous year *Drink type:* n/s **Measure:**grams p/d, **Reference group**: Non drinkers' (not defined) **Results:** HPFS NHS 0.1-4 1.01 0.36-2.83 0.72 0.41-1.30 1.5-4.9 1.44 0.67-3.12 1.07 0.68-1.67 5.0-12.9 1.23 0.59-2.53 0.93 0.61-1.42 ≥30 1.34 0.58-3.08 0.78 0.36-1,68 *p*trend 0.55 *p*trend 0.49 Multivariate RRs for every additional drink/day in pooled analyses: 1.08 (95% CI,0.88–1.33) for beer, 0.91 (95% CI, 0.70 –1.19) for wine, and 0.96 (95% CI, 0.81–1.15) for hard liquor

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Rohrmann 2009 **Country:**Europe **Study aims:** o examine the association of baseline and lifetime ethanol intake with cancer of the pancreas **Source of funding:** European Commission	**Population:** European Prospective Investigation into Cancer and Nutrition (EPIC) conducted in 23 centres in 10 European countries (see Chapter 2.4, Box 2)) *Exclusion criteria:*prevalent cancer cases, missing follow-up information,6,220 subjects without dietary or non-dietary information, 9,674 subjects with extreme ranking ratio for energy intake versus energy expenditure *Study pop*: 478,400 **Observation time:** 1992 and 2000. Median follow-up time of 8.9 years, LFU: n/s; 555 cases	**Exposure:** *Questionnaire:* self-administered questionnaire *Repeated during follow-up*: no *Reference period:*over the previous 12 months and (for lifetime) consumed per week at ages 20, 30, 40, and 50 yrs *Drink type:*beer wine spirits **Measure:** grams per day, **Reference group**: 0.1–4.9 g/d **Results:** 0 78 1.06 (0.79–1.41) 24 0.78 (0.50–1.24) 5–14.9 140 0.98 (0.78–1.24) 113 0.86 (0.66–1.12) 15–29.9 91 1.06 (0.81–1.39) 68 0.87 (0.63–1.20) 30 80 0.98 (0.72–1.32) 58 0.94 (0.64–1.37) Per 10 g/day 1.00 (0.96–1.05) 0.99 (0.94–1.05)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Stevens 2009 **Country:**United Kingdom **Study aims:** to examinethe separate and joint associations of demographic and lifestylefactors with pancreatic cancer **Source of funding:** Cancer Research UK, Medical Research Council, UK, NHS Breast Screening Programme.	**Population:** million women study. *Source:* 1.3 million middle-aged women who had been invited for screening for breast cancer at breast cancer screening centres throughout England and Scotland *Exclusion criteria***:** diagnosed before recruitment with any cancer other than non-melanoma skin cancer *Study pop*: 1.29 million **Observation time:** 1996–2001 to 2006/07, 9.2 million person-years 1,338 incident pancreatic cancer cases and 1,710deaths from the disease	**Exposure:** *Questionnaire:* self-administered questionnaire *Repeated during follow-up*: n/s *Reference period:*n/s *Drink type:*n/s **Measure:** units per week, **Reference group**: **Results:** *incidence* *mortality* None 378/492 1.07 (0.06) 1.10 (0.05) 1-2 382/483 1.00 (0.05) 1.00 (0.05) 3-6 255/334 0.88 (0.06 0.99 (0.06) 14+ 91/114 1.08 (0.11) 1.07 (0.10)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Ye 2002 **Country:** Sweden **Study aims:** To investigate the risk of pancreatic cancer among patients with a discharge diagnosis of alcoholism, alcoholic chronic pancreatitis, or alcoholic liver cirrhosis. **Source of funding:** The Swedish Cancer Society.	**Population:** in-patients with discharge diagnosis of alcoholism (ICD-7 307, 322; ICD-8 291, 303; ICD-9 291, 303, 305A), Cohort = 178 688 men and women , **Exclusion criteria:** Records: (1) erroneous or incomplete national registration numbers; (2) inconsistencies uncovered during record linkage; (3) patients who died during the index hospitalisation; and (4) of patients with prevalent cancers at entry. **Observation time:** 1965-1995, mean duration of follow up 10 years, 1 789 693 person years at risk, no loss to follow up 305 incident cases 254 men, 51 women	**Exposure:** consumption defined by specified ICD-7,8,9 codes into category ‘alcoholism’ **Results:** *Alcoholism* All 1.4 (1.2-1.5) Male 1.3 (1.2-1.5) Female 1.6 (1.2-2.1) *Age at index discharge* *Follow up duration (yr)* <50 1.7 (1.4-2.1) 1–4 1.3 (1.0–1.6) 50-59 1.2 (1.0-1.5) 5–9 1.4 (1.1–1.7) 60-69 1.3 (1.1-1.6) 10–14 1.5 (1.2–1.9) ≥70 1.1 (0.7-1.6) 15–30 1.4 (1.1–1.8) *p*trend 0.02 *p*trend 0.35

Descriptive tables for pancreatic cancer: case control studies

Study and Aims	Study and sample characteristics	Exposure measurement and main results
De Martel 2008 **Country:** USA **Study aims:** To investigate and potentially corroborate a possible association between H. pylori infection and subsequent development of pancreatic cancer **Source of funding:** N/s	**Population:** 128,992 subscribers to Kaiser Permanente Medical Care Program enrolled in a multiphase health check-up from 1964 to 1969 *Cases:* consisted of randomly selected subjects among 507 who developed pancreatic cancer in the cohort. N=104 *Controls:* consisted of pancreatic cancer–free subjects from a pool of 730 controls previously tested for studies conducted on this cohort. N=262 **Exclusion criteria:** none specified **Observation time:** From enrolment until the year 2000, Response rate: none specified	**Exposure: NO DETAILS PROVIDED** *Questionnaire:* *Interviewers blinded*: *Reference period:* *Drink type:* *Quest validated:* **Measure:**drinks per day, **Reference group**: never drinkers **Results:** Former 0.88 (0.22-3.56) ≤2 drinks/d 1.93 (0.99-3.75) >2 drinks/d 0.62 (0.21-1.85)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Hassan 2007 **Country:** USA **Study aims:** To evaluate the independent effects of multiple risk factors for pancreatic cancer and determined whether the magnitude of cigarette smoking was modified by other risk factors in men and women. **Source of funding:** National Institutes of Health/ Texas Tobacco Settlement	**Population:** *Cases:* recruited from population of patients with newly diagnosed pancreaticcancer at cancer centre in Texas N=808 *Controls:* were healthy nonblood relatives, particularly spouses, of patients with cancers other than liver, gastrointestinal, lung or head and neck (smoking-related cancers) who were undergoing treatment at same cancer centre N=808 **Exclusion criteria:** not have ever had cancer; Non U.S. residency and inability to communicate in English **Observation time:** January 2000 through December 2006, Response rate: cases and controls 84%	**Exposure:** *Questionnaire:* personally interviewed by well-trained interviewers, using a structured questionnaire *Interviewers blinded*: n/s *Reference period:* lifetime (consumed at least 4 alcoholic drinks of beer, wine or hard liquor each month for 6 months during their lifetimes *Drink type:* **Measure:**lifetime intake, mL/day, **Reference group**: No (not defined), n= cases114/ controls 463 **Results:** ≤60 355/386 0.9 (0.7–1.2) >60 67/42 1.6 (1.1–2.5)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Talamini 1999 **Country:** Italy **Study aims:** to compare alcohol and smoking as risk factors in the development of chronicpancreatitis and pancreatic cancer **Source of funding:** Italian Cancer Registry and University of Rome	**Population:** *Cases:*All consecutive cases in medical surgical departments in Verona N=630 *Controls:*selected randomly from polling station in Verona, Italy N=700 **Exclusion criteria:**-any patients in whom a pancreatic cancer was diagnosed within two years of diagnosis of chronicpancreatitis **Observation time:** Cases 1971-1995, Controls 1985-1987 Response rate: n/s	**Exposure:** *Questionnaire:* direct interviews at point of diagnosis *Interviewers blinded*: n/s *Reference period:* alcohol intake over the previous 5 years *Drink type:* n/s **Measure:**grams per day, **Reference group**: 0-40g/d **Results:** *Pancreatic Cancer without history of Chronic Pancreatitis versus controls* *g/d* 41-80 0.5 (0.2-1.0), >80 0.4 (0.2-1.0)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Villeneuve 2000 **Country:** Canada **Study aims:** To assess the relationship between tobacco, alcohol and coffee in the aetiology of pancreatic cancer **Source of funding:** Canadian National Enhanced Cancer Surveillance System project.	**Population:** *Cases:* identified from provincial cancer registries in eight of the ten Canadian provinces N=583 *Controls:* random sample from health insurance plans or random digit telephone sample N=4813 **Exclusion criteria:** cases known to be deceased **Observation time:** 1994-1997 Response rates: cases (56%) controls (68%)	**Exposure:** *Questionnaire:* mailed FFQ with telephone follow up, *Interviewers blinded*: n/s *Reference period:* two years before interview *Drink type:* wine, beer and spirits. **Measure:**times per month', **Reference group**: '0-3 times per month' **Results:** Males Females >0-<-3 0.83 0.56-1.25 0.90 0.65-1.25 3-<7 0.86 0.57-1.28 0.59 0.34- 1.02 7-<14 1.20 0.79- 1.80 0.95 0.57-1.56 ≥14 1.36 0.93-2.00

Descriptive tables for prostate cancer: cohort studies

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Albertsen 2002 **Country:** Denmark **Study aims:** to analyse whether alcohol intake is a risk factor in the development of prostate cancer and whether any such relationship depends on the type of alcoholic beverage consumed **Source of funding:** Danish National Board of Health and Danish Ministry of Health	**Population:** *Source:* male participants from three longitudinal studies conducted in Copenhagen, Denmark between 1976 and 1986, two random samples of general population, the other collected from 14 large workplaces *Exclusion criteria:* incomplete data on drinking, smoking and diet *Study pop*: 24, 496, response rate 80% **Observation time:** until 31 December 1998, mean follow up 12.3yr, 159,623 person years, LFU n/s 233 incident cases	**Exposure:** *Questionnaire:* Self administered questionnaire *Repeated during follow-up*:collected every 4 years *Reference period:* in previous year *Drink type:* Beer, Wine, Spirits **Measure:**drinks per week, **Reference group**: <1 drink per week **Results:** 1-6 0.90 0.61-1.34 7-13 0.86 0.57-1.29 14-20 0.91 0.58-1.44 21-41 0.93 0.59-1.47 >41 0.66 0.29-1.49 *p for trend, 0.48*

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Breslow 1999 **Country:** USA **Study aims:** to examine the association between usual alcohol consumption and prostate cancer and to examine the association between distant past alcohol consumption and prostate cancer **Source of funding:** n/s	**Population:** *Source:* NHANES I, nationally representative, cross-sectional survey of the civilian non-institutionalized population of the US, conducted between 1971 and 1975, formed two separate cohorts, one originated in 1971–75; the other originated in 1982–84 *Exclusion criteria:*none specified *Study pop*: Cohort I (*n* = 5766) and Cohort II (*n* = 3775, was the subset of Cohort I alive and free of prostate cancer at their 1982–84 interview who had data on alcohol consumption) **Observation time:** median follow-up 17.1 years, LFU n/s, Cohort I (252 cases), Cohort II (134 cases)	**Exposure:** *Questionnaire:* In-person interview at baseline, then FFQ at follow-up *Repeated during follow-up*: baseline 1971-1975 and then in 1982–84 *Reference period:* at baseline within last 24 hours and at follow up within the last year *Drink type:* Beer, Wine, Spirits **Measure:**drinks per week, **Reference group**: non drinkers, **Results:** Cohort 1 Cohort 2 *caca* >0-1 41 0.97 0.67-1.41 19 0.74 0.44-1.25 2-7 65 0.88 0.64-1.29 29 1.13 0.71-1.80 8-14 25 0.96 0.61-1.44 1 1.05 0.60-1.86 15-21 8 0.85 0.41-1.47 9 1.12 0.55-2.30 22+ 17 1.42 0.84-2.40 2 0.23 0.06-0.95 Distant past drinking *ca* Not heavy at age 25 71 0.99 0.69-1.43 Heavy at age 25 3 0.20 0.06-0.63 Not heavy at age 35 81 1.18 0.80-1.73 Heavy at age 35 5 0.30 0.12-0.77 Not heavy at age 45 79 1.05 0.72-1.54 Heavy at age 45 6 0.39 0.17-0.93 Not heavy at age 55 79 1.13 0.78-1.66 Heavy at age 55 5 0.43 0.17-1.10

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Ellison et al 2000 **Country:** Canada **Study aims:** 'to assess the relation between tea consumption and the risk of developing prostate cancer among men... In addition, we also studied the effects of coffee, cola, and alcohol on prostate cancer risk' **Source of funding:** n/s	**Population:** *Source:* Residents of the ten Canadian provinces were randomly sampled using a three-stage stratified cluster design total of 12 795 people aged 50-84 years, responded to the initial invitation to participate (47% response rate) *Exclusion criteria:*diagnosed with any form of cancer prior to baseline; missing information on tea intake *Study pop*: 3584 **Observation time:** 1970-1972 to 1993, Loss to follow up n/s 154 cases of incident prostate cancer	**Exposure:** *Questionnaire:* one-month food frequency questionnaire, *Repeated during follow-up*: baseline only *Reference period:* *Drink type:* beer, wine and spirit **Measure:**ml/day, **Reference group**: **Results:** *ml/day cases* >0-9.9 38 0.96 0.63-1.47 10.0-24.9 54 0.85 0.50-1.45 >>25.0 22 0.93 0.55-1.57 any 25 0.93 0.63-1.36

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Lund Nilsen 2000 **Country:** Norway, **Study aims:** to examine the association between several lifestyle and socio-economic factors and the development of prostate cancer in a cohort of Norwegian men'. **Source of funding:** Norwegian Cancer Society	**Population:** *Source:* Large health survey in the county of Nord-Trøndelag, Norway, all residents aged ≥20yrs by 31/12/1983 eligible. Of 85 100 eligible persons, 77 310 (90.8%) filled in questionnaire. *Exclusion criteria:*no history of any cancer at study entry *Study pop*: 22 895 men aged ≥40 years **Observation time:** 1984 to 1986 until of 1 January 1996, mean follow-up 9.3 years; 644 cases of incident prostate cancer	**Exposure:** *Questionnaire:* health survey questionnaire *Repeated during follow-up*: baseline only *Reference period:*n/s *Drink type:* beer, wine and spirit **Measure:**drinks per week, **Reference group**: none (not drunk in past 2 weeks but not including teetotallers) **Results:** *p/w cases* 1-4 times 148 0.15 0.94-1.41 >4 times 40 0.90 0.64-1.25, *p* for trend 0.862

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Platz 2004 **Country:** USA **Study aims:** To evaluate the association of alcohol intake and alcohol drinking patterns with prostate cancer in a large cohort study. **Source of funding**: National Cancer Institute, and National Institute on Alcohol Abuse and Alcoholism and National Heart, Lung, and Blood Institute	**Population:** Participants members of the Health Professionals Follow-up Study, an ongoing prospective cohort study of 51,529 men aged 40–75 years in the US Final cohort size, 47,843 men. *Exclusion criteria:* Men who had been diagnosed with cancer (except non-melanoma skin cancer) before 1986 (4.0%) and incomplete diet questionnaires in 1986 (3.1%); **Observation time:** 1986 through to 1998.533 047 person years Follow-up response was 94%. 2,479 cases of incident prostate cancer	**Exposure:** *Questionnaire:* Mailed semi-quantitative FFQ completed *Repeated during follow-up*: at baseline (1986) and in 1990 and 1994. Analysis of alcohol intake from baseline consumption only *Reference period:*over past year *Drink type:* beer, red wine, white wine, and spirits; Questions on frequency of consumption of number of days of the week on which alcohol consumed; whether alcohol intake had changed in past 10 years. **Measure** Grams per day, **Reference group**:0 grams/d (never drinkers incl. former drinkers) **Results:** *Grams per day* *drinking days per week* 0-1-4.9 0.99 (0.86-1.09) 1-2 608 1.05 (0.94-1.16) 5.0-14.9 1.05 (0.94-1.18) 3-4 335 1.05 (0.92-1.20) 15.0-29.9 1.13 (0.98-1.31) 5-6 358 1.19 (1.04-1.35) 30.0-49.9 1.13 (0.96-1.33) 7 393 1.05 (0.92-1.20) *p*-trend 0.10 ≥50 1.00 (0.77-1.31) *p*-trend 0.20 *Advanced cases* *Distant metastatic or fatal cases (ref group: 0–4.9g/d*) 5.0-14.9 175 1.22 (0.96-1.55) 79 1.32 (0.91-1.92) 15.0-29.9 80 1.24 (0.92-1.67) 27 1.01 (0.62-1.63) 30.0-49.9 81 1.17 (0.85-1.61) 38 1.35 (0.83-2.21)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Putnam 2000 **Country:** USA **Study aims:** evaluated role of lifestyle (alcohol, smoking, and physical activity) … factors known to correlate with or modulate endogenous steroid hormones as prostate cancer risk factors in a population-based cohort of Iowa men. **Source of funding:** National Cancer Institute	**Population:** Population-based control group study of 6 cancer sites in Iowa, 1986-1989 Controls: randomly selected from Iowa population by two sampling methods: 1) random sample of all persons 40 to 64 yrs identified through Iowa driver's license records and 2) random sample of all persons 65 yrs and older identified through US Health Care Financing Administration *Exclusion criteria***:** prior history of cancer. *Study population*: 1,601 **Observation time:** 1989-December 31, 1995; 9,509 person-years of follow-up, Loss to follow up 1%; 101 cases of prostate cancer.	**Exposure:** *Questionnaire:* miled food frequency questionnaire, supplemented with telephone interview *Interviewers blinded*:n/a *Reference period:*in the previous year *Drink type:* beer wine and liquor **Measure:** grams per week, **Reference group**: non-drinker **Results:** *ca* <22 14 1.1 (0.6-2.1) 22-92 25 2.6 (1.4-4.6) >92 16 3.1 (1.5-6.3) *p*-trend 0.001

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Rohrmann 2008 **Country:** Europe **Study aims:** To examine whether baseline or average lifetime alcohol consumption was associated with the subsequent risk for prostate cancer. **Source of funding:** n/s	**Population:** *Source:* European Prospective Investigation into Cancer and Nutrition: 10 European countries [Denmark France, Germany, England, Greece, Italy, The Netherlands, Norway, Spain, and Sweden], approx. 500,000 participants. At baseline, men were between 40-65 yrs. Recruited 1992-2000, usually from the general population. *Exclusion criteria:*without prevalent cancers other than non-melanoma skin cancer; missing information on dietary or non-dietary data or if in the top or bottom 1% of the distribution of the ratio of reported energy intake to energy requirement *Study pop*: 142,607 **Observation time:** Period n/s, 1,235,364 person-years of follow-up, loss to follow up: n/s; 2,655 prostate cases	**Exposure:** *Questionnaire:* dietary assessment instruments that were specifically developed for each participating country *Repeated during follow-up*: baseline only *Reference period:*over the previous 12 months *Drink type:* beer and/or cider, wine, sweet liquor, distilled spirits, or fortified wines **Measure:** grams per day at baseline, average lifetime consumption, **Reference group**: 0.1-4.9 g/d (n=615) **Results:** *ca* *Baseline* *ca* *Average lifetime consumption* 0. 204 0.95 (0.81-1.12) 20 0.82 (0.51-1.29) 5-14.9 745 0.99 (0.89-1.11) 482 1.03 (0.88-1.21) 15-29.9 531 0.95 (0.84-1.08) 421 1.08 (0.91-1.27) 30-59.9 422 1.03 (0.90-1.18) 283 1.02 (0.85-1.23) ≥60 138 0.88 (0.72-1.08) 142 1.09 (0.86-1.39)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Sutcliffe 2007 **Country:** USA **Study aims:** To investigate red wine consumption and prostate cancer in the Health Professionals Follow-up Study (HPFS). **Source of funding:** National Institutes of Health	**Population:** *Source:* HPFS is an ongoing, prospective study of 51,529 American male health professionals 40-75 yrs at enrolment in 1986. *Exclusion criteria:* diagnosed with cancer (except nonmelanoma skin cancer); invalid or incomplete baseline food frequency or alcohol information *Study pop:* 45,433 **Observation time:** 1986 to January 31, 2002, Loss to follow up: 6% 348 cases	**Exposure:** *Questionnaire:* semi-quantitative food frequency questionnaire *Repeated during follow-up*: baseline and every 4 years *Reference period:*during the past year *Drink type:* beer red wine white wine liquor, e.g., whiskey, gin **Measure:** grams per day, **Reference group**: No alcohol consumption (n=307) **Results:** *ca* 0.01-1.31 158 0.90 (0.74-1.09) 1.32-2.41 205 1.02 (0.85-1.22) 2.42-7.03 594 1.12 (0.97-1.29) 7.04-16.4 840 1.16 (1.01-1.32) >16.5 798 1.14 (0.99–1.31) *p*-trend 0.003

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Schuurman 1999 **Country:** Holland **Study aims:** To examine alcohol consumption in relation to prostate cancer incidence in the Netherlands Cohort Study **Source of funding:** Dutch Cancer Society	**Population:** *Source:* Cohort consists of 58,279 men; study population consists of sub-cohort sample, which was sampled directly after identification of the total cohort. *Exclusion criteria:*prevalent cancer cases other than skin cancer *Study pop*: Sub-cohort = 1688 **Observation time:** 1986-1992, 6.3 yrs, no loss to follow;680 incident cases	**Exposure:** *Questionnaire:* self-administered 150-item semi quantitative food-frequency questionnaire *Repeated during follow-up*: baseline only *Reference period:*during year preceding study start *Drink type:* **Measure:** grams per day, **Reference group**:abstainers (incl. ex drinkers) **Results:** *g/d ca Prostate ca localised ca advanced* 0.1-4 143 1.1 (0.8-1.5) 59 1.7 (1.0-2.6) 44 1.0 (0.6-1.6) 5-14 161 0.9 (0.7-1.3) 55 1.1 (0.7-1.8) 63 1.1 (0.7-1.6) 15-29 161 1.1 (0.8-1.4) 61 1.4 (0.9-3.3) 49 0.9 (0.6-1.5) ≥30 101 1.1 (0.8-1.6) 33 1.3 (0.8-2.2) 35 1.1 (0.7-1.8) *p*-trend 0.74 0.6 0.67 Total alcohol intake: continuous 10g increment = 1.0 (1.0-1.1)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Sesso 2001 **Country:** USA **Study aims:** To examine the association of total and beverage-specificalcohol consumption with prostate cancer risk using data fromthe Harvard Alumni Study, a prospective cohort study of middle-agedand older men **Source of funding:** National Cancer Instituteand the National Heart, Lung, and Blood Institute	**Population:** *Source:* Men matriculating as undergraduates at Harvard University, USA 1916-1950. First mailed a health questionnaire to surviving alumni in either 1962 or 1966, and then periodically to all surviving alumni. For this study, information from 12,805 men who returned the 1988 questionnaire *Exclusion criteria:* Any historyof physician-diagnosed cancer; Incomplete data on alcohol consumption and other potential risk factors *Study pop*: cohort size = 8,935, mean age 66 years **Observation time:** From 1988 to end of 1993 median follow-up of 5.0 years, Loss to follow up 15%; 366 cases	**Exposure:** *Questionnaire:* Mailed questionnaire *Repeated during follow-up*: baseline only *Reference period:*n/s *Drink type:* wine, beer, and spirits **Measure:** units of alcohol, **Reference group**: Almost never (not defined) **Results:** Total Alcohol 1 month-<3 p/week 1.33 (0.88-2.01) 3 p/week-<1p/day 1.65 (1.12-2.44) 1p/day-<3p/day 1.85 (1.29-2.64) ≥3p/day 1.33 (0.86-2.05) ptrend 0.40

Descriptive tables for prostate cancer: case control Studies

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Barba 2004 **Country:** USA **Study aims:** We examined the association between lifetime alcohol intake, duration of alcohol use, and drinks per day with risk of prostate cancer in western New York.' **Source of funding:** Department of Defence, Prostate Cancer Program and the National Cancer Institute, and in part by an American Italian Cancer Foundation Fellowship	**Population:** *Cases:* drawn from hospitals in Western New York. N=96 *Controls:* selected from a list of individuals holding a New York State driver's license. Those aged >65 selected from rolls of the Health Care Financial Administration, N=317 **Exclusion criteria:** men with previous history of cancer (except non-melanoma skin cancer), or on hormonal or chemotherapy treatment (current or in the 6 months prior to diagnosis); chronic or acute liver diseases; cases 35-65 yrs also required to have driver's license, because driver's license records used to identify age-matched controls. **Observation time:** December 1998-April 2001. Response rate: cases 70%, controls 60%	**Exposure:** *Questionnaire:* Trained interviewers during in-person computer assisted interviews and with self-administered questionnaires. Detailed information on alcohol consumption throughout the lifetime was collected using the Cognitive Lifetime Drinking History *Interviewers blinded*: n/a *Reference period:* n/s *Drink type:* wine, beer, and spirits **Measure:** ounces, **Reference group**: Lifetime : ≤2647 ounces; total drinking years: >53 yrs; drinks per day: ≤2d/d **Results:** *ca/co Lifetime ethanol intake* ≤2647.62-11048.28 34/90 1.20 (0.65-2.23) >11048.28 25/92 0.83 (0.43-1.60) *ca/co Total drinking years* *ca/co Drinks per day* 42–53 27/94 1.44 (0.66–3.14) >2 26/54 1.38 (0.76–2.51) ≤42 47 92 2.16 (0.98–4.78)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Chang 2005 **Country:** Sweden **Study aims:** …whether the association of alcohol consumption with prostate cancer risk varies between localized and advanced cases, or between sporadic and familial cases. **Source of funding:** Swedish Cancer Society	**Population:** *Cases:* identified from four of six regional cancer registries covering northern, central, Stockholm, and southeastern health care regions in Sweden, approx. 67% of Sweden's total population, N=1,895 *Controls:* identified through Swedish Population Registry database, and frequency-matched by age (five-year categories) to expected distribution of incident cases, N=1,684 **Exclusion criteria:** none specified **Observation time:** 1st July 2001 to 1 March 2002. Response rate: cases 79%, controls 67%	**Exposure:** *Questionnaire:* Completed self-administered questionnaire *Interviewers blinded*: n/a *Reference period:* drinking in the last year *Drink type:* wine, beer, and spirits **Measure:** grams per week, **Reference group**:Non-drinkers **Results:** 0.1-45.0 1.1 (0.8-1.4) 45.1-90.0 1.2 (0.9-1.5) 90.1-135.0 1.3 (0.9-1.7) ≥135.1 1.3 (1.0-1.7) *p*trend *0.06* *Localized (804) Advanced (593) Sporadic (387) Familial (634)* 0.1–45.0 1.5 (1.1-2.1) 0.8 (0.6-1.0) 0.9 (0.7-1.3) 1.0 (0.7-1.5) 45.1–90.0 1.4 (1.0-2.0) 0.9 (0.7-1.2) 1.1 (0.8-1.5) 1.2 (0.8-1.8) 90.1–135.0 1.4 (1.0-2.1) 1.1 (0.8-1.5) 1.3 (0.9-1.8) 1.2 (0.8-1.9) ≥135.1 1.4 (1.0-2.0) 0.9 (0.7-1.2) 1.1 (0.8-1.5) 1.2 (0.8-1.8)

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Crispo 2004 **Country:** Italy **Study aims:** To examine the association between alcohol and the risk of prostate cancer/benign prostatic hyperplasia in a population with a wide range of alcohol consumption, **Source of funding:** Italian Association for Cancer Research, Italian League Against Cancer, and European Research Advisory Board	**Population:** *Cases:* those admitted to major teaching and general hospitals in four areas of Italy N=1294; *Controls:* selected from patients admitted to same hospitals with conditions, unrelated to known or potential risk factors for prostatic disease and long-term diet modification N=1451 **Exclusion criteria:**patients admitted for diseases related to alcohol drinking, **Observation time:** 1991 to 2002 Response rate: <5% of both cases and controls refused to participate	**Exposure:** *Questionnaire:* Interviewed during hospital stay, using structured questionnaire *Interviewers blinded*: n/s *Reference period:* up to 1 year before diagnosis *Drink type:* wine, beer, and spirits) **Measure:** drinks per week, duration of drinking, age at starting, **Reference group**:drinks per week, duration of drinking, abstainers; age at starting - ≤16 yrs **Results:** *drinks per week* <3 0.89 (0.61-1.29) 3-4 0.90 (0.61-1.32) 5-6 1.13 (0.74-1.74) 7-8 0.95 (0.60-1.49) ≥9 0.85 (0.54-1.35) *p*trend=0.819 *yr* *Duration of drinking* *yr Age at starting* <35 254/185 1.14 (0.63-2.08) 17–19 233/230 1.36 (1.05-1.75) 35-44 488/416 1.11 (0.63-1.97) 20–22 408/366 1.13 (0.91-1.42) ≥45 618/611 0.95 (0.54-1.68) ≥23 337/334 1.19 (0.94-1.51) *p*trend= 0.224 0.314

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Hodge 2004 **Country:** Australia **Study aims:** to test several hypotheses relating to risk factors for prostate cancer, including diet, particularly with respect to early onset, clinically significant disease **Source of funding:** National Health and Medical Research Council, Tattersall's and The Whitten Foundation	**Population:** *Cases:* aged <70 yrs at diagnosis and registered to vote in Melbourne, Sydney or Perth, Australia, N=858 *Controls:* randomly selected from State Electoral Rolls, N=905 **Exclusion criteria:** excluded tumours that were described as low-grade or had Gleason scores <5. **Observation time:** between 1994 and 1997 Response rate: 65% cases and 50%controls	**Exposure:** *Questionnaire:* Face to face interviews were with an administered food frequency questionnaire *Interviewers blinded*: n/s *Reference period:* n/s *Drink type:* beer, wine, spirits **Measure:** grams per day, **Reference group**: 0-19 grams per day **Results:** 20-39 1.0 (0.8-1.3) 40-59 1.0 (0.7-1.3) 60+ 1.0 (0.7-1.4) *p*-trend 0.91

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Schoonen 2005 **Country:** USA, **Study aims:** to gain knowledge about the relationship between alcohol intake and prostate cancer **Source of funding:** National Cancer Institute, NIH, Department of Health and Human Services	**Population:** *Cases:* were newly diagnosed prostate cancer identified from the Seattle cancer registry and from eligible cases, a random 75% sample was selected. N=753 (82.1%) *Controls* were selected using randomly telephone dialling and were frequency-matched to cases by 5-year age group N= 703 (75%) **Exclusion criteria:** did not have a residential telephone number; aged >64 years **Observation time:** Between January 1, 1993 and December 311996	**Exposure:** *Questionnaire:* In-person interview conducted by trained male interviewers, including a validated self-administered food frequency questionnaire *Interviewers blinded*: n/s *Reference period:* For men who drank >12 alcoholic drinks throughout their lives, lifetime information on alcohol consumption was recorded per beverage, for each period of drinking pattern and number of drinks recorded for every period *Drink type:* beer, spirits and wine **Measure:**drinks per week, lifetime duration, total cumulative consumption, **Reference group**: non-drinker' **Results:** *ca/co* *Lifetime intake* >0-6000 186/170 1.12 (0.75-1.68) 6001 122/138 0.89 (0.57-1.37) 12001 138/139 0.97 (0.63-1.51) ≥24001 235/170 1.29 (0.84-1.97) *p*trend = 0.33 *years* *ca/co* *Lifetime duration* *d/w* *Drinks per week-lifetime average* <31 149/153 1.11 (0.72-1.70) 1-7 266/264 0.94 (0.68-1.31) 31–35 132/123 1.06 (0.68-1.66) 8-14 166/145 1.06 (0.73-1.54) 36–40 166/168 0.95 (0.62-1.45) ≥15 195163 1.08 (0.84-1.97) ≥ 41 234/173 1.15 (0.75-1.76) *P*trend = 0.97= 0.32 *d/w* *Wine* *Beer* *Spirits* Ever 0.74 (0.59-0.93) 1.17 (0.93-1.49) 1.16 (0.92-1.47) 1-7 0.73 (0.48-1.10) 1.14 (0.79-1.67) 1.16 (0.76-1.78) 8-14 0.56 (0.32-0.98) 1.17 (0.72-1.89) 1.22 (0.71-2.11) ≥15 0.63 (0.31-1.27) 1.16 (0.71-1.91) 1.42 (0.83-2.43) *P*trend= 0.41 0.88 0.39

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Sharpe &Siemiatycki 2001 **Country:** Canada **Study aims:** 'to assess occupational exposures, but which also included information on lifelong alcohol consumption' **Source of funding**: National Health Research and Development Program of Canada, National Cancer Institute of Canada, and Health Canada	**Population:** *Cases:* 'virtually' all (97%) incident cancer cases occurring in men aged 35-70 yrs diagnosed at all large hospitals in metropolitan Montreal N=449 (80.6% response rate) *Controls*: selected from electoral lists and by random digit dialling. A second control group was selected from pool of all other cancer cases in overall study that were accrued during the same years as prostate cancer cases. N= 533, Cancer controls = 674 (72.0% response rate) **Exclusion criteria:** n/s for population controls. For cancer controls, sites considered to be related to alcohol use were excluded; i.e., cancers of the oesophagus, stomach, liver, sigmoid colon, rectosigmoid junction, rectum, but not colon cancer **Observation time:** 1979 and 1985	**Exposure:** *Questionnaire:* Structured questionnaire, carried out by team of three interviewers *Interviewers blinded*: not blinded to whether subject was a cancer patient or a population control, but were blinded to type of cancer that participant had *Reference period:* lifetime consumption *Drink type:* beer, wine, and spirits **Measure:**drink status, age started drinking, duration of daily drinking **Reference group**: those who never drank weekly **Results:** Drank weekly, never daily 1.6 (1.1-2.4) Drank daily 1.6 (1.1-2.3) *Yrs age at starting daily drinking* *Duration of daily drinking* <15 17/10 3.8 (1.6-9.3) Drank for < 20 yrs 32/41 1.3 (0.7-2.4) 15-19 51/68 1.4 (0.8-2.4) Drank for 20-39 yrs 64/110 1.1 (0.7-1.8) 20-24 49/51 1.6 (0.9-2.7) Drank for ≥ 39 yrs 88/65 2.0 (1.2-3.1) *p*trend =0.01 ≥ 25 68/87 1.2 (0.8-2.0) *p*trend 0.0009

Study and Aims	Study and sample characteristics	Exposure measurement and main results
Villeneuve 1999 **Country:** Canada, **Study aims:** To evaluate the relationship between prostate cancer and several potential lifestyle risk factors. **Source of funding:** None specified	**Population:** *Cases:* identified from provincial cancer registries in eight of ten Canadian provinces. N=1623 (response rate 69%) *Controls*: drawn from provincial health insurance plans, ministry of finance data or random digit telephone dialling, depending on province, sample, based on expected age distribution of all registry cancer cases, and not just prostate cancer, N=1623 (response rate 69%) **Exclusion criteria:** prostate cancer cases diagnosed < 50yrs; people aged ≥74 years **Observation time:** Between 1994 and 1997.	**Exposure:** *Questionnaire:* Mailed questionnaires, with telephone follow-up *Interviewers blinded*: n/s *Reference period:*2 years before interview Drink type: wine, beer and liquor **Measure:**drinks per day status, age started drinking, duration of daily drinking, **Reference group**:non-drinkers **Results:** Up to 1 1.1 (0.9-1.3) 1-<4 1.1 (0.9-1.4) ≥4 1.1 (0.8-1.6) *p*trend 0.70

Appendix E: Excluded references

EXPOSURE

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Appendix F: Previous and revised factors for converting alcohol volume to units*

Drink	Volume reported	Original unit conversion factor	Usual volume (ml)	Average ABV[1]	Revised unit conversion factor
Normal strength beer, lager, stout, cider, shandy (less than 6% ABV)	Half pint	1.0	*284*	4.0%	1.0
	Can or bottle	Amount in pints multiplied by 2	330	4.5%	Amount in pints multiplied by 2.5
	Small can (size unknown)	1.0		4.5%	1.5
	Large can/bottle (size unknown)	2.0		4.5%	2.0
Strong beer, lager, stout, cider, shandy (6% ABV or more)	Half pint	1.5	*284*	6.5%	2
	Can or bottle	Amount in pints multiplied by 3	330	6.5%	Amount in pints multiplied by 4
	Small can (size unknown)	1.5		6.5%	2
	Large can/bottle (size unknown)	3.0 a		6.5%	3.0
Wine	Glass (size unspecified) b	1.0		12.5%	2.0
	glass - 125ml		125	12.5%	1.5
	glass - 175ml		175	12.5%	2.0
	glass - 250ml/small can		250	12.5%	3.0
	bottle	6.0	750	12.5%	9.4
Sherry, vermouth and other fortified wines	Glass	1.0	50	17.0%	1.0
Spirits	Glass (single measure)	1.0	25	40.0%	1.0
	bottle				
Alcopops	Small can or bottle	1.0	50	5.0%	1.5

*Source: adapted from Table 1 in Goddard (2007) and Corbett et al (2009)

[1]The predominant measure of alcoholic strength in use in the UK is alcohol by volume (ABV) which is the percentage of the drink by volume that is pure ethyl alcohol.

Appendix G Scottish Health Survey sample sizes, 2003, 2008, 2009

Table G.1 SHeS sample sizes, weighted and un-weighted, 2003, 2008, 2009, men and by age-group

Bases (weighted):								
	16-24	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**≥75**	**Total**
Men 2003	536	596	755	665	566	404	258	3780
Men 2008	405	475	559	549	478	326	218	3011
Men 2009	514	564	631	648	563	386	257	3563
Bases (unweighted):								
Men 2003	309	446	726	610	630	507	323	3551
Men 2008	220	312	456	530	523	451	304	2796
Men 2009	261	404	548	601	575	516	361	3266

Table G.2 SHeS sample sizes, weighted and un-weighted, 2003, 2008, 2009, women and by age-group

Bases (weighted):								
	16-24	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**≥75**	**Total**
Women 2003	505	655	805	685	599	491	467	4209
Women 2008	402	487	614	585	502	382	348	3319
Women 2009	501	571	694	700	590	450	408	3913
Bases (unweighted):								
Women 2003	366	598	879	788	774	579	492	4476
Women 2008	305	450	646	627	630	513	408	3579
Women 2009	376	580	779	733	735	550	479	4232

Appendix H: Alcohol related cancer trends in Scotland, European Age Standardised Rates by gender, 1985-2008

Table G.1 European age-standardised incidence rates (EASRs)[1] for cancers of the UADT by gender, 1985-2008. (Source ISD 2010b)

	Men				Women			
	Oral Cavity	**Pharynx**	**Larynx**	**Oesophagus**	**Oral Cavity**	**Pharynx**	**Larynx**	**Oesophagus**
1985	6.1	1.1	8.2	12.90	2.2	0.4	1.5	6.10
1986	5.2	1.1	8.5	11.90	2.3	0.3	1.6	5.90
1987	5.9	1.1	7.1	13.50	3	0.3	1.6	6.90
1988	6.3	1.1	8.4	13.00	2.8	0.4	1.6	7.10
1989	6.3	1.8	8.1	13.40	2.8	0.5	1.8	7.40
1990	6.9	1.8	8.6	15.00	2.7	0.4	2.4	7.50
1991	7.1	1.3	9.5	13.70	3.2	0.6	1.5	7.50
1992	7.1	1.5	10.2	14.80	3	0.5	1.8	8.10
1993	7.5	1.6	9.8	16.90	2.9	0.4	1.6	9.20
1994	7.5	1.4	9.3	17.10	3.4	0.5	1.9	8.40
1995	7.9	1.8	8.2	17.10	3.7	0.9	1.8	8.40
1996	8.2	2.1	10.5	18.50	3.9	0.9	2.9	8.70
1997	8.1	2.7	8.5	16.60	3.1	0.8	1.8	7.90
1998	8.9	1.7	9.3	17.60	4.2	0.3	1.8	7.10
1999	9	2.5	10.2	16.80	3.5	0.9	2	8.20
2000	8.4	2.7	9.3	16.50	3.7	0.8	2	7.00
2001	8.1	2.3	9.6	17.40	4.4	0.8	1.9	6.90
2002	9	2.4	8.5	18.40	3.6	1	1.7	7.40
2003	9.2	2	8.2	17.80	4	0.9	1.9	7.00
2004	9.2	2.6	8.4	18.30	4.2	0.9	2	7.90
2005	8.8	2.5	7.7	17.40	4	0.8	1.7	7.20
2006	9.2	3	8.3	17.60	3.8	0.7	2.2	7.00
2007	9.2	3	8.4	17.5	4.3	0.9	1.5	6.7
2008	8.7		7.3	17.5	4		1.7	6.4

[1]EASR: age-standardised incidence rate per 100,000 person-years at risk (European standard population)

Source: Scottish Cancer Registry, ISD. Data extracted: September 2010

Table G.2 European age-standardised incidence rates (EASRs) [1] for alcohol related gastrointestinal cancers of the UADT by gender, 1985-2008. (Source ISD 2010b)

	Men					Women				
	Liver	**Pancreas**	**Gastric**	**Colon**	**Rectal**	**Liver**	**Pancreas**	**Gastric**	**Colon**	**Rectal**
1985	3.8	11.5	31	33.4	19.5	1.5	8.8	14.8	28.8	11.1
1986	3.9	12.1	28.8	34.5	19.9	1.7	9.1	13.4	28.8	11.8
1987	4.7	12.3	28.6	33.4	19.6	1.5	7.8	13.1	28.6	12.4
1988	3.9	12.3	28.6	32.9	18.7	1.8	8.2	12.5	28.1	11.8
1989	4.3	12.0	28	36.8	19.1	1.8	8.2	11.6	30.5	10.9
1990	4.4	12.8	25.8	36.8	20.6	1.8	8.7	11.2	31	12
1991	4.6	11.1	25.3	38	22.4	1.9	7.6	11.4	28.5	11.2
1992	5	12.5	26.4	38	23.1	2.3	8.4	10.9	27.8	11.3
1993	4.5	10.8	22.1	41.2	22.1	2.3	8.3	9.9	31.4	11.5
1994	4.6	10.5	23.8	40.2	22.7	1.8	8.3	10.6	30.7	12.4
1995	4.8	10.1	22.9	40	22	1.8	7.4	10.7	31.3	11.3
1996	6.1	12.3	22	43.6	26	2.7	8.6	10.1	31.9	13.4
1997	6.1	11.3	21.9	41.2	26.2	2.4	8.2	10.6	27.9	12.5
1998	6.1	10.5	19.8	39.8	26.3	2.4	8.8	8.9	26.7	13
1999	5.6	9.8	19.5	40.1	26.2	2.5	8.3	9.5	28.9	12.2
2000	5.4	11.6	20.9	42.5	25.4	3	7.8	9	30.1	12.6
2001	5.8	9.6	19.4	41	24.8	2.6	7.8	8.9	30.2	12.6
2002	5.8	10.1	18.7	38.1	25.4	2.3	7.6	8.2	28.2	12.3
2003	6.4	10.6	17.1	41.9	23.8	2.9	9.0	7.6	26.4	12.3
2004	7	9.8	17.4	40	24.8	3	7.6	7.6	27.3	12.1
2005	7.1	9.7	15.3	37.8	24.8	2.8	8.5	7.6	26.8	12
2006	7.9	9.9	15.8	38.8	22.7	3	7.7	6.7	27.6	12.2
2007	8.7	10.3	14.2	40.1	23.8	2.9	8	6.8	29.2	12.3
2008	7.3	10.9	16	41.5	24.6	2.8	7.8	6.4	29.8	12.8

[1]EASR: age-standardised incidence rate per 100,000 person-years at risk (European standard population)
Source: Scottish Cancer Registry, ISD. Data extracted: September 2010

Table G3 European age-standardised incidence rates (EASRs)[1] for prostate, bladder, kidney, breast, lung and ovarian cancer, by gender, 1985-2008. (Source ISD 2010b)

	Men				Women				
	Lung	**Bladder**	**Kidney**	**Prostate**	**Lung**	**Bladder**	**Kidney**	**Ovarian**	**Breast**
1985	133	32.2	9.90	46.0	44.8	9.7	5.1	16.5	84.6
1986	126.2	34.5	9.40	47.8	43.4	10.5	4.3	17.9	87.2
1987	127.8	35.6	9.80	48.6	45.8	10.4	5.2	17.6	89.3
1988	122.5	34.6	9.50	49.1	45.8	10.3	5.7	18.3	91.1
1989	119.5	32.9	9.60	49.8	45.7	10.9	5.6	17.4	93.1
1990	116.6	35.5	10.10	52.5	49.1	10.4	6.3	18.5	100.8
1991	118.1	32.2	12.10	52	48.7	11.2	5.4	19.3	108.6
1992	119.8	36.4	10.90	55.8	52.1	10.7	6	18.8	110.7
1993	117	35.6	10.70	67.8	50	11.4	5.6	17.9	106.5
1994	112.7	37.7	12.00	70.3	50.6	10.9	6.9	19.1	104.7
1995	107.7	35.4	12.50	74	51.5	11.8	6.2	17.9	110.5
1996	107.6	34.9	13.10	81.4	56.2	11.5	7.4	20.8	109.8
1997	101.7	30.4	12.70	71.6	53.5	9.9	6.8	21.3	112.6
1998	99	22.9	13.70	71.4	53.3	7.7	6.8	18.4	115.3
1999	94.1	21.2	14.00	73.3	51	6	6.5	18.2	118.4
2000	90.9	18.2	12.60	73.9	53.8	5.7	7.2	19.6	119.4
2001	89.5	18.2	13.20	77.8	49.1	6.6	6.6	18	113.2
2002	91.6	18.6	12.70	85.4	53.6	5.9	7.1	18.7	116.1
2003	85.7	17.7	12.90	86.2	52.7	5.8	7	18.9	120
2004	85.7	18.3	14.00	91.2	56.2	6.4	7	18.2	120.9
2005	83.9	15.9	14.00	83.9	54.7	5.8	7.2	18.1	120.8
2006	83.5	15.6	14.90	87.3	56.7	5.5	7.3	16.2	122.6
2007	82	15.6	15.3	85.6	58.2	5.5	8.8	17.8	121.9
2008	77.2	14.8	15	84.3	57.5	5.7	8.7	17.2	122.8

[1]EASR: age-standardised incidence rate per 100,000 person-years at risk (European standard population)

Source: Scottish Cancer Registry, ISD. Data extracted: September 2010

Appendix I: Age standardised incidence ratios, by cancer type, gender and Carstairs (2001) deprivation quintiles

Table H1 Male age standardised incidence ratios (with 95% confidence intervals), by cancer type, and Carstairs (2001) deprivation quintiles.

Cancer type	Carstairs Quintile	Obs.	Exp.	SIR	95% CI	P-value
Bladder	1 (least deprived	54	75.1	0.72	0.54-0.94	*0.013*
	2	78	87.0	0.90	0.71-1.12	*0.366*
	3	114	96.0	1.19	0.98-1.43	*0.081*
	4	114	103.2	1.10	0.91-1.33	*0.312*
	5 (most deprived)	229	113.5	2.02	1.77-2.30	*0.000*
Colon	1 (least deprived	87	155.7	0.56	0.45-0.69	*0.000*
	2	105	159.0	0.66	0.54-0.80	*0.000*
	3	146	161.5	0.90	0.76-1.06	*0.235*
	4	166	157.3	1.06	0.90-1.23	*0.506*
	5 (most deprived)	271	175.5	1.54	1.37-1.74	*0.000*
Gastric	1 (least deprived	40	56.9	0.70	0.50-0.96	*0.023*
	2	57	70.8	0.81	0.61-1.04	*0.107*
	3	71	81.5	0.87	0.68-1.10	*0.267*
	4	119	95.2	1.25	1.04-1.50	*0.020*
	5 (most deprived)	178	112.4	1.58	1.36-1.83	*0.000*
Hypopharynx	1 (least deprived	11	1.8	5.98	2.97-10.74	*0.000*
	2	14	2.3	6.15	3.35-10.35	*0.000*
	3	21	2.7	7.87	4.86-12.05	*0.000*
	4	16	3.2	5.04	2.87-8.2	*0.000*
	5 (most deprived)	48	4.2	11.36	8.38-15.08	*0.000*
Kidney	1 (least deprived	17	58.4	0.29	0.17-0.47	*0.000*
	2	36	55.7	0.65	0.45-0.90	*0.007*
	3	46	54.5	0.84	0.62-1.13	*0.277*
	4	49	54.0	0.91	0.67-1.20	*0.549*
	5 (most deprived)	84	54.5	1.54	1.23-1.91	*0.000*
Larynx	1 (least deprived	47	18.3	2.57	1.89-3.42	*0.000*
	2	67	29.0	2.31	1.79-2.94	*0.000*
	3	102	36.5	2.80	2.28-3.39	*0.000*
	4	139	44.5	3.12	2.62-3.69	*0.000*
	5 (most deprived)	247	63.6	3.89	3.42-4.40	*0.000*
Liver	1 (least deprived	52	19.0	2.74	2.05-3.59	*0.000*
	2	61	22.0	2.77	2.12-3.56	*0.000*
	3	83	23.2	3.58	2.85-4.44	*0.000*
	4	83	30.9	2.68	2.14-3.33	*0.000*
	5 (most deprived)	159	36.1	4.40	3.74-5.14	*0.000*
Lung	1 (least deprived	236	218.0	1.08	0.95-1.23	*0.238*

Cancer type	Carstairs Quintile	Obs.	Exp.	SIR	95% CI	P-value
	2	409	326.1	1.25	1.14-1.38	0.000
	3	581	388.9	1.49	1.37-1.62	0.000
	4	711	465.9	1.53	1.42-1.64	0.000
	5 (most deprived)	1493	630.6	2.37	2.25-2.49	0.000
Oesophagus	1 (least deprived	61	50.6	1.21	0.92-1.55	0.170
	2	89	65.3	1.36	1.09-1.68	0.006
	3	122	69.9	1.75	1.45-2.09	0.000
	4	149	76.5	1.95	1.65-2.29	0.000
	5 (most deprived)	248	90.4	2.74	2.41-3.11	0.000
Oral	1 (least deprived	69	22.9	3.01	2.34-3.81	0.000
	2	117	29.1	4.03	3.33-4.83	0.000
	3	155	33.9	4.57	3.88-5.35	0.000
	4	185	38.5	4.81	4.14-5.56	0.000
	5 (most deprived)	323	59.5	5.43	4.85-6.06	0.000
Pancreas	1 (least deprived	34	43.5	0.78	0.54-1.09	0.164
	2	45	40.0	1.13	0.82-1.51	0.465
	3	52	43.1	1.21	0.90-1.58	0.206
	4	71	46.9	1.51	1.18-1.91	0.001
	5 (most deprived)	125	53.2	2.35	1.96-2.80	0.000
Pharynx	1 (least deprived	10	5.6	1.77	0.84-3.27	0.123
	2	29	7.2	4.02	2.69-5.79	0.000
	3	42	10.1	4.17	3.01-5.64	0.000
	4	52	11.2	4.66	3.48-6.12	0.000
	5 (most deprived)	86	14.6	5.88	4.70-7.27	0.000
Prostate	1 (least deprived	126	355.3	0.35	0.3-0.42	0.000
	2	201	322.2	0.62	0.54-0.72	0.000
	3	227	307.6	0.74	0.65-0.84	0.000
	4	249	294.2	0.85	0.74-0.96	0.008
	5 (most deprived)	393	276.3	1.42	1.29-1.57	0.000
Rectal	1 (least deprived	53	96.7	0.55	0.41-0.72	0.000
	2	89	98.9	0.90	0.72-1.11	0.346
	3	101	102.3	0.99	0.80-1.20	0.946
	4	111	100.1	1.11	0.91-1.34	0.300
	5 (most deprived)	184	111.5	1.65	1.42-1.91	0.000

Abbreviations: Obs= observed cases, Exp= expected cases

Table H2 Female age standardised incidence ratios (with 95% confidence intervals), by cancer type, and Carstairs (2001) deprivation quintiles**.**

Cancer type	Carstairs Quintile	Obs.	Exp.	SIR	95% CI	P-value
Bladder	1 (least deprived	10	8.0	1.26	0.60-2.32	0.555
	2	15	9.2	1.63	0.901-2.7	0.096
	3	15	10.1	1.49	0.83-2.46	0.177
	4	27	12.1	2.24	1.47-3.26	0.000
	5 (most deprived)	48	13.1	3.66	2.69-4.85	0.000
Breast	1 (least deprived	100	193.9	0.52	0.42-0.63	0.000
	2	135	195.9	0.69	0.58-0.82	0.000
	3	155	189.1	0.82	0.70-0.96	0.012
	4	224	184.7	1.21	1.06-1.38	0.006
	5 (most deprived)	293	178.7	1.64	1.46-1.84	0.000
Colon	1 (least deprived	32	40.6	0.79	0.54-1.11	0.196
	2	41	41.8	0.98	0.70-1.33	0.984
	3	51	39.9	1.28	0.95-1.68	0.101
	4	53	37.1	1.43	1.07-1.87	0.016
	5 (most deprived)	67	38.5	1.74	1.35-2.21	0.000
Gastric	1 (least deprived	7	10.7	0.65	0.26-1.35	0.319
	2	8	10.6	0.76	0.32-1.50	0.542
	3	13	12.4	1.05	0.55-1.79	0.945
	4	13	13.8	0.94	0.50-1.62	0.979
	5 (most deprived)	42	16.3	2.57	1.85-3.48	0.000
Hypopharynx	1 (least deprived	3	0.3	11.54	2.18-34.16	0.007
	2	4	0.4	11.38	2.96-29.42	0.002
	3	2	0.3	6.17	0.58-22.67	0.090
	4	4	0.5	8.50	2.21-21.97	0.004
	5 (most deprived)	14	0.6	23.16	12.62-38.97	0.000
Kidney	1 (least deprived	4	8.8	0.46	0.12-1.18	0.125
	2	6	8.9	0.67	0.24-1.48	0.430
	3	9	9.1	0.99	0.45-1.9	0.838
	4	14	10.2	1.38	0.75-2.31	0.297
	5 (most deprived)	22	9.9	2.23	1.39-3.37	0.001
Larynx	1 (least deprived	5	1.2	4.09	1.29-9.63	0.018
	2	12	1.9	6.46	3.32-11.33	0.000
	3	13	2.2	5.91	3.13-10.13	0.000
	4	19	3.0	6.35	3.82-9.93	0.000
	5 (most deprived)	53	5.1	10.32	7.73-13.50	0.000
Liver	1 (least deprived	8	2.7	3.01	1.28-5.95	0.013
	2	10	3.0	3.30	1.57-6.09	0.003
	3	13	3.4	3.84	2.04-6.59	0.000
	4	17	3.7	4.64	2.70-7.45	0.000
	5 (most deprived)	22	4.2	5.18	3.24-7.85	0.000

Cancer type	Carstairs Quintile	Obs.	Exp.	SIR	95% CI	P-value
Lung	1 (least deprived	91	53.5	1.70	1.37-2.09	0.000
	2	157	57.2	2.74	2.33-3.21	0.000
	3	189	67.8	2.79	2.40-3.22	0.000
	4	248	80.8	3.07	2.70-3.48	0.000
	5 (most deprived)	423	110.9	3.81	3.46-4.20	0.000
Oesophagus	1 (least deprived	21	8.9	2.36	1.46-3.61	0.001
	2	33	10.1	3.28	2.25-4.60	0.000
	3	23	9.6	2.39	1.51-3.59	0.000
	4	37	11.0	3.36	2.36-4.63	0.000
	5 (most deprived)	64	12.4	5.15	3.96-6.58	0.000
Oral	1 (least deprived	18	4.3	4.24	2.50-6.71	0.000
	2	29	4.6	6.33	4.23-9.09	0.000
	3	42	4.9	8.65	6.23-11.71	0.000
	4	60	5.8	10.38	7.92-13.36	0.000
	5 (most deprived)	71	7.2	9.87	7.71-12.45	0.000
Ovarian	1 (least deprived	20	27.1	0.74	0.45-1.14	0.199
	2	21	27.0	0.78	0.48-1.19	0.283
	3	39	27.0	1.44	1.03-1.97	0.035
	4	29	26.6	1.09	0.73-1.56	0.699
	5 (most deprived)	56	26.0	2.15	1.63-2.80	0.000
Pancreas	1 (least deprived	10	9.6	1.05	0.50-1.93	0.971
	2	15	10.3	1.45	0.81-2.40	0.202
	3	21	11.7	1.80	1.11-2.75	0.018
	4	26	11.7	2.22	1.45-3.25	0.000
	5 (most deprived)	45	12.9	3.49	2.54-4.67	0.000
Pharynx	1 (least deprived	5	1.0	4.82	1.52-11.35	0.010
	2	16	0.9	17.56	10.01-28.58	0.000
	3	14	1.0	13.45	7.33-22.63	0.000
	4	19	1.2	16.00	9.61-25.03	0.000
	5 (most deprived)	26	1.5	16.92	11.04-24.83	0.000
Rectal	1 (least deprived	12	17.2	0.70	0.36-1.22	0.249
	2	23	17.2	1.34	0.85-2.01	0.205
	3	26	16.6	1.57	1.02-2.30	0.040
	4	19	16.9	1.13	0.68-1.76	0.664
	5 (most deprived)	34	16.5	2.06	1.43-2.89	0.000

Abbreviations: Obs= observed cases, Exp= expected cases, SIR= standardised incidence ratio