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Prostate Cancer and Diet in Scottish Men

by

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Ph.D

The University of Edinburgh

2004

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Abstract

Prostate cancer is an important and increasing public health problem in Scotland. It is the second most common cancer in men after lung cancer, with prostate cancer (PCa) incidence and mortality rates continuing to increase rapidly. It is therefore of great importance that opportunities for prevention are examined and identified. Although the aetiology of PCa remains largely unknown, there is gathering evidence that diet may play an important role, with recent epidemiological studies demonstrating associations between fat, animal products and plant-based nutrients (including selenium, isoflavones and tocopherol) and PCa risk.

This thesis examines the association between diet and PCa in Scottish men, based on the PCANDIET study: A population based case-control study of PCa in relation to inherited susceptibility and diet. Data on the habitual diets of 433 cases diagnosed with PCa and 483 controls were collected using a validated food frequency questionnaire. From these, individual daily intakes of specific nutrients and food items (chosen á priori as being hypothesised to be associated with PCa risk) were estimated for the comparison between case and control groups.

Significant odds ratios (ORs) (adjusted for energy intake, age, family history of PCa, Carstairs deprivation index, smoking and EI: BMR ratio) for highest intake versus lowest intake (reference) categories were observed for cholesterol (OR 1.57, 95%CI 1.04-2.37); red meat (OR 1.64, 95%CI 1.09-2.48); vegetables (OR 0.62, 95%CI 0.41-0.93); consumption of alcohol (OR 0.62, 95%CI 0.42-0.90), total alcohol (OR 0.66, 95%CI 0.44-0.99); wine (OR 0.38, 95%CI 0.19-0.74) and spirits (OR 0.48, 95%CI 0.29-0.79). Significant associations were also observed for protein (OR 2.34, 95%CI 1.13-4.87) and red meat (OR 3.74, 95%CI 1.70-8.15) within younger subjects, and for selenium (OR 0.61, 95%CI 0.37-0.99), vegetables (OR 0.60, 95%CI 0.36-0.99), wine (OR 0.21, 95%CI 0.08-0.52) and spirits (OR 0.49, 95%CI 0.26-0.91) within older subjects.

These results suggest that cholesterol and red meat are both associated with a 60% increase in PCa risk, whereas vegetables and alcohol are associated with a 40% reduction in PCa risk. The results also suggest that protein and red meat are associated with over a two-fold and three-fold increase in PCa risk respectively in younger men. Whereas, selenium and vegetables are associated with 40% reduction in PCa risk in older men, in addition to a further reduction in risk of PCa associated with wine and spirits (80% and 50% respectively).

This evidence - the first of its kind in a Scottish population - suggests that the promotion of a healthier diet in a population traditionally known for its bad diet (high in fats and meat products and low in fruit and vegetables) may have a great influence on the incidence of PCa in addition to other known diet related diseases.

Declaration

I, Charlotte Lucinda Heald hereby declare that this thesis was written entirely by myself and that all the work reported herein was performed by myself, except where the contribution of colleagues is acknowledged. This thesis has not been submitted for any other degree or professional qualification.

Date: 1st June 2005

Acknowledgements

I would like to convey my thanks to the following individuals who have helped me in the preparation of my thesis.

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Finally, I am very grateful to **participants of PCANDIET**, without which my thesis would never have happened.

Glossary of abbreviations

95%CI	95% confidence intervals
BrCa	Breast cancer
BMR	Basal metabolic rate
CRUK	Cancer Research UK
DepCat	Carstairs deprivation index
DES	Dietary energy supply
DNS	Dietary and nutritional surveys
EI	Total energy intake
EI:BMR	Energy intake: Basal metabolic rate ratio
EU	European Union
FAO	Food and Agriculture Organisation for the United Nations
FFQ	Food frequency questionnaire
FHPCa	Family history of prostate cancer
FSA	Food Standards Agency
GNP	Gross national product
GP	General practitioner
HEBS	Health Education Board for Scotland
HER	High energy responder
HPLC	High-performance liquid chromatography
LER	Low energy responder
MUFA	Mono unsaturated fatty acids
N/A	Not available
OR	Odds ratio
PCa	Prostate cancer
PCANDIET Study	A population based case-control study of PCa in relation to inherited susceptibility and diet.
PUFA	Poly unsaturated fatty acids
RCT	Randomised controlled trial
Retinol equivalent	The sum of vitamin A provided by preformed retinol and carotenoids[1]
RR	Risk ratio / relative risk
SCG-FFQ	The Scottish Collaborative food frequency questionnaire
SD	Standard deviation
SE	Standard error
SES	Socio-economic status
UK	United Kingdom
US	United States of America
USDA	United States Department of Agriculture

Contents Table

List of tables

List of figures

1 . Chapter 1: Background - Prostate cancer

1.1 Introduction

In common with many other countries, prostate cancer is an important and increasing public health problem in Scotland. It is the second most common male cancer after lung cancer, and accounts for 10% of all male cancer related deaths, making it the third most common cause of cancer death after lung and colorectal cancer[2].

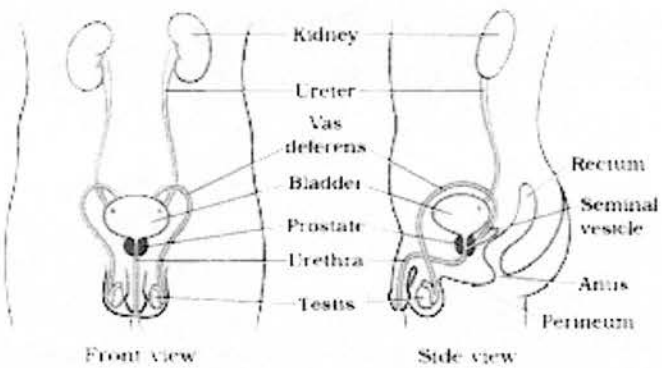
Furthermore, it is very common for the quality of life of men with prostate cancer (PCa) to deteriorate due to the experience of unpleasant side effects of therapy, including urine incontinence and impotence, whereas others may experience years of symptoms related to the slow progression to metastatic disease. PCa has therefore become a major concern for both Scottish men and also health service providers. This is due not only to the increasing burden of PCa, but also the rapidly growing costs for diagnosis and treatment and also the impending possibility of a national PSA screening program (which will most likely lead to an increase in diagnosed cases of PCa requiring treatment). It is therefore of great importance that opportunities for prevention are identified. The most promising of these is diet. There is gathering evidence that diet plays an important role in the aetiology and prevention of PCa, and unlike fixed risk factors such as age and family history of PCa which can not be altered, the exposure to these factors can be modified by changing dietary habits. It is within this context that I have embarked on this thesis. My aim is to investigate certain foods and nutrients commonly consumed by Scottish men and which have been hypothesised to be associated with PCa, in order to examine their association with PCa amongst the Scottish male population. To my knowledge this is the first time that dietary factors for PCa within the Scottish population alone have been investigated.

In this chapter, geographical and temporal trends in PCa incidence and mortality will be discussed and interpreted in terms of the aetiology of PCa and established risk factors will be discussed. A brief overview of the natural history of PCa will also be presented, in order to give a helpful insight into the aetiology of this disease.

1.2 The prostate

The prostate is a small accessory sex gland of the male reproductive tract. It is located at the base of the bladder and surrounds the upper part of the urethra, see Figure 1.1. The main function of the prostate is poorly understood, but it appears to be related to the production of secretions that aid sperm function. The growth and development of the prostate is largely controlled by sex hormones, in particular testosterone[3], which diffuses from plasma into the prostate where it is converted to dihydrotesterone (DHT), a more biologically potent steroid, by the enzyme 5-alpha reductase.

Figure 1.1: Location of the prostate gland



1.3 Natural history of PCa

Most PCa tumours are adenocarcinomas, they range from incidentally discovered, low-grade, microscopic focal tumours to tumours that are highly aggressive locally and have a high potential for metastatic spread. PCa is often asymptomatic, the majority of PCa tumours being relatively slow growing with many remaining dormant until death from other causes intervenes[4]. However, PCa can also present with symptoms of lower urinary tract obstruction, which are indistinguishable from those produced by benign prostatic hyperplasia (BPH)[2], PCa therefore tends to be diagnosed only during routine rectal examination or by the incidental finding of a

tumour when a transurethral resection of the prostate (TURP) is performed for BPH[5]. Increasingly and particularly in the US, PCa is diagnosed as a result of screening by the measurement of serum prostate specific antigen (PSA) and also by digital rectal examination (DRE)[5]. However, as both these diagnostic procedures are prone to low sensitivity and specificity and, for DRE in particular, are subject to human error, it is important that the diagnosis is histologically confirmed[2].

1.3.1 Clinical grading & staging

The histological grade is a strong predictor of the biological behaviour of PCa, including invasiveness and the metastatic potential. Of the many grading systems that have been proposed, the Gleason system[6] is the most commonly used system in the UK and US. It is based on the degree of glandular differentiation, from very well differentiated (Grade 1) to very poorly differentiated (Grade 5).

PCa staging ascertains how far the tumour has spread by determining the anatomic extent and burden of tumour. The Tumour / Node / Metastasis (TNM) classification[7] is considered the international standard for PCa staging. It separately assesses the tumour (T), lymph nodes (N) and metastases (M), and is classified into four stages for both tumour and lymph nodes and two stages for the metastases. See Table 1.1 for summary of TNM classification.

Another staging system which has been used by several US studies on diet and PCa to stratify risk by PCa stage, including Giovannucci et al[8;9] and Whittenmore et al[10], is the Jewett-Whitmore System. This system is classified into grades A to D and was the most common staging system in the US until recent years when it has been increasingly replaced by the more descriptively detailed TMN system. See Table 1.2 for a summary of the Jewett-Whitmore System.

Table 1.1: Summary of TNM classification

Tumour (T)	Lymph Nodes (N)	Distant Metastases (M)
T0 No evidence of tumour	N0 No regional lymph nodes metastasis	M0 No distant metastasis
T1 Incidentally detected and clinically inapparent tumour	N1 Metastasis in a single lymph node (≤ 2 cm)	M1 Distant metastasis
T2 Tumour confined to the prostate capsule (localised)	N2 Metastasis in a single lymph node (2 - 5cm); or multiple lymph node metastases (≤ 5cm)	
T3 Tumour has extended beyond the prostate capsule (locally advanced)	N3 Metastasis in a lymph node (>5cm)	
T4 Invasion of bladder neck, rectum or external sphincter		

N.B. Tumour stages are also categorised (a, b or c) according to the extent of the tumour spread within the area defined by the stage.

Table 1.2: Summary of the Jewett-Whitmore System

Stage	Description	Equivalent TNM Stage
A	Nonpalpable, incidentally detected and clinically inapparent tumour	T1
B	Tumour confined to the prostate capsule	T2
C	Tumour has extended beyond the prostate capsule	T3
D	Tumour has metastasised to regional lymph nodes and/or other parts of the body	T4, N1-3, M1

N.B. Tumour stages are also categorised (0,1,2) according to the extent of the tumour spread within the area defined by the stage.

1.3.2 Latent PCa

As mentioned before, PCa can be asymptomatic, so much so that the estimated number of men with PCa that is never detected or diagnosed during their lifetime is far greater than the number of those with clinically diagnosed PCa.

The term latent PCa is used to describe a tumour that is malignant by histopathological criteria but found only on post-mortem examination of the prostate[11]. These tumours tend to be small, typically unifocal and usually categorised as well to moderately differentiated[11], in this context the terms microfocal and subclinical are also sometimes used. 'Latent' cancers that are detected by chance during a transurethral resection of the prostate (TURP) are also known as incidental PCa. It has been assumed that these tumours are dormant and therefore clinically insignificant[12] as opposed to 'clinically important / significant' tumours which are usually diagnosed as a consequence of procedures used in cases of suspected PCa. However, it is not known whether the origins and natural history of latent PCa are distinct from tumours that become clinically significant or whether they represent a continuum on a linear progression toward aggressive disease[3].

Autopsy studies from different geographical areas around the world suggest that latent PCa may be observed in 20-30% of men in their 50's rising to nearly 80% of men in their 80's[4;13]. These same studies also observed that the prevalence of latent PCa varies slightly across the world, with age-adjusted prevalence being higher for US blacks (37%) and whites (35%) than for native Japanese (21%)[13].

N.B. In order to distinguish between clinically important / significant PCa and latent PCa within this thesis. Clinically apparent / significant PCa from now on will be referred to as PCa, whereas latent PCa will remain termed as latent PCa.

1.4 Incidence and mortality rates

1.4.1 Geographical trends

PCa incidence

Compared to the prevalence of latent PCa, incidence and mortality rates of PCa vary dramatically across the world. There is approximately a 90-fold difference in the incidence of PCa around the world, see Figure 1.2. The lowest age-standardised incidence rates are generally in Asia, in particular the population of Tianjin, China (1.9 per 100,000 per year), and the highest are in North America and Scandinavia, especially for African-American men in the US (137 per 100,000 per year)[14]. The incidence rate within the Scottish male population is ranked in the middle (31.2 per 100,000 per year) just above England and Wales (28.0 per 100,000 per year).

This wide range of incidence, which should be noted includes both clinically significant PCa and incidental tumours usually identified through PSA testing, maybe due to combination of many underlying differences, including genetic susceptibility and exposure to risk factors such as lifestyle and diet. Artifactual reasons such as the variations in diagnostic methods, such as TURP and PSA testing in US and Sweden, and the accuracy of cancer registers may also be a cause of this variation, for example, it has been suggested that the relatively low reported incidence in most African countries may, in part, be due to under-reporting[15].

PCa mortality

International mortality rates of PCa are far lower than those for PCa incidence, there is also considerable less variation between countries, see Figure 1.3, although African-Americans still represent the highest (34.3 per 100,000 person years) and Japanese, the lowest (3.8 per 100,000 person years) age-standardised mortality rates[16]. Mortality data for Tianjin, China were not available. As with PCa incidence, the age-standardised PCa mortality rate within the Scottish population is ranked in the middle (15.0 per 100,000 person years)[17], just below that of England and Wales (16.3 per 100,000 person years)[16], and similar to that of US whites (15.7 per 100,000 person years).

PCa mortality data have the advantage over incidence data of not being distorted by the presence of diagnosed latent (incidental) PCa that should, in principle, not appear on a death certificate. The rates of which are therefore probably more genuinely comparable between countries than those of incidence, as they should not be influenced by the artefactual effects of TURP and PSA testing[18]. However, these too must be interpreted with caution as the underlying cause of death given on the death certificates may be much less accurate for the oldest age groups in which PCa is particularly common[19], death certificates may also be affected by attribution bias in which diagnosis of PCa during life may increase the likelihood of PCa being recorded as a certified underlying cause of death[20].

Figure 1.2: World age-adjusted Incidence of PCa (1988-1992)[14]

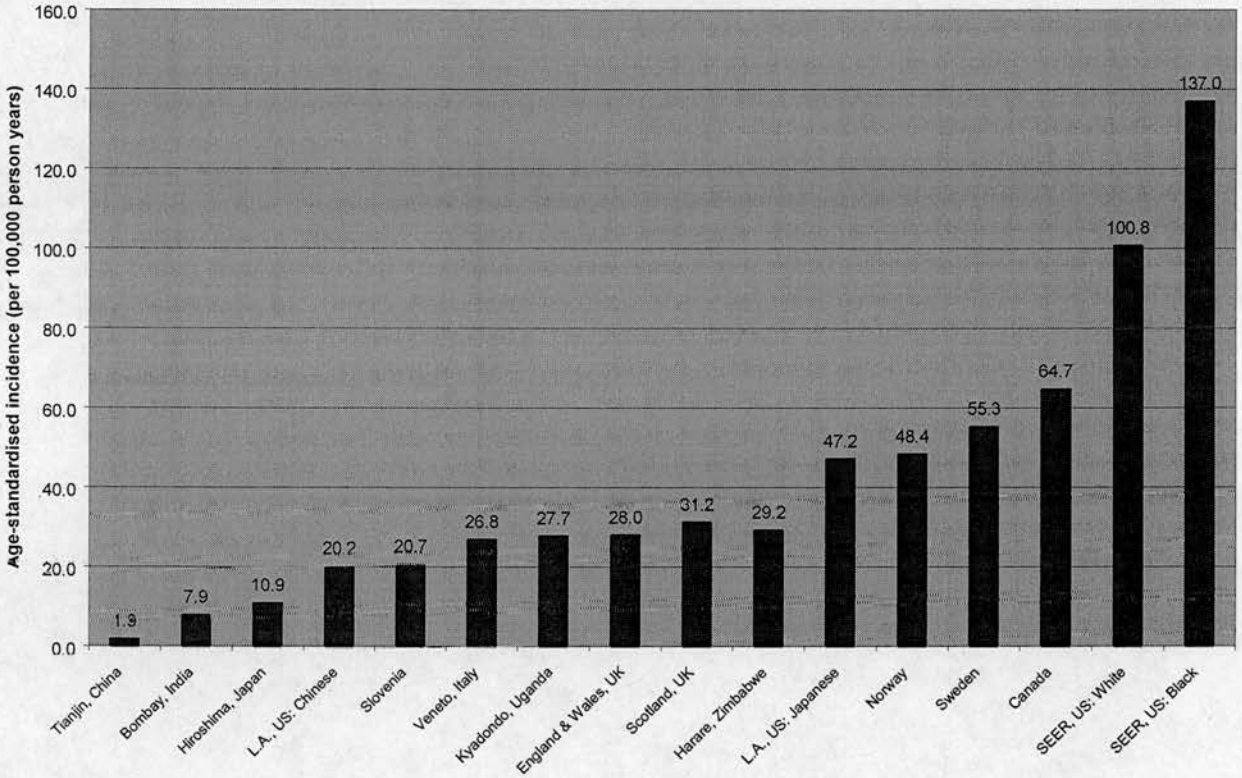
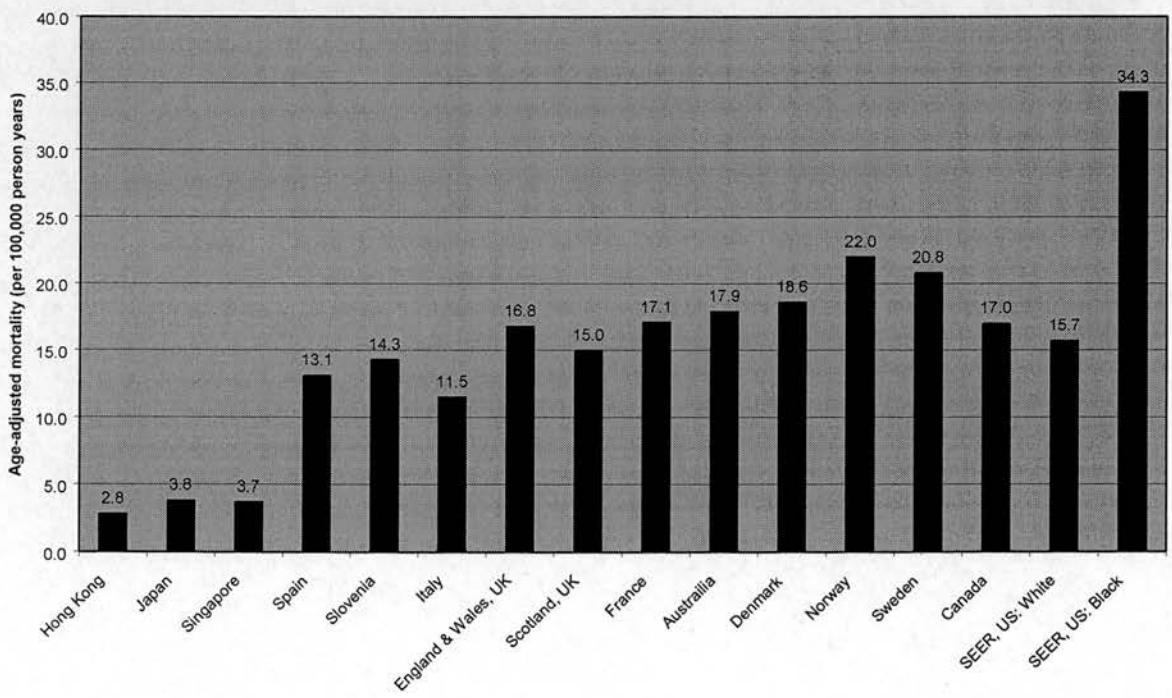


Figure 1.3: World age-adjusted mortality of PCa (1988-1992)[17]



1.4.2 International temporal trends

PCa incidence

The incidence of PCa in most Western countries, including Scotland, has risen sharply during the last decades. In 15 years time, PCa is predicted to be the most common cancer in men[21]. This has mainly been attributed to the ageing population, with fewer men dying from other causes such as cardiovascular disease, and also to improved diagnostic methods, although it is highly possible that an increase in exposure to underlying risk factors is also an influence. Increased use of TURP in the 1980's and PSA testing in the 1990's are responsible for marked increases in incidence of prostate cancer in all Western countries, in particular the US and Sweden[16]. Even Asian countries, where incidence is far lower, have observed a large rise in PCa incidence[16;22], this has been mainly attributed to the 'Westernisation' of these countries. Between 1973 and 1992, increases in incidence has ranged from 25%-113% in high-risk countries (e.g. US and Sweden) to 16%-104% in low risk countries (e.g. Japan and China)[16].

PCa Mortality

PCa mortality in all countries, with the exception of Sweden, has increased between 1973 and 1992, although the rises were less rapid than those of PCa incidence[16]. The changes in mortality rates during this 20 year period ranged from –3.7% in Sweden to nearly 95% in Asian countries, with mortality increasing by 39% in England and Wales[16]. More recent data shows that mortality rates in some countries including the US and England and Wales have started to decrease in the last decade. A decrease in PCa mortality of 6.7% has been observed in the US since 1992[23], whereas in England and Wales age-standardised mortality fell from 27.1 per 100,000 person years in 1992 to 24.7 per 100,000 person years by 1997[24]. Recent mortality rates for Scotland have not yet been published.

The recent decline in mortality rates suggests that earlier diagnosis due to screening and enhanced survival due to improved disease treatment may be influencing PCa mortality, especially among US whites[15]. The suggestion that PSA testing in particular has attributed to this decrease in PCa mortality has been the subject to

much discussion, with the opposing opinion that PSA screening in the US is unlikely to have made a major contribution to this reduction in PCa mortality as it has occurred too soon after the widespread introduction of PSA testing and that similar reductions in PCa mortality have been observed in countries were PSA testing is relatively scarce[24;25].

1.4.3 PCa trends in Scotland

Within the last three decades, PCa incidence in Scotland has increased dramatically. Age-standardised rates have more than doubled from 15.3 per 100,000 person years in 1960 to 35.2 per 100,000 person years by 1994, see Figure 1.4, this rate has increased rapidly within the last decade in particular. PCa mortality in Scotland has also increased, though not as rapidly, with age-standardised rates rising by over a third from 12.5 per 100,000 person years in 1960 to 16.8 per 100,000 person years by 1994, see Figure 1.5.

N.B. Both PCa incidence and mortality age-standardised rates differ slightly from those reported for Scotland in the previous section describing geographical differences, due to the use of different time periods over which the standardised rates were calculated.

The use PSA testing in Scotland has increased recently since its introduction in 1989[25], although it is still restricted to a minority of men[2]. This and the prior increased rates of TURP have been suggested to be the main cause of the observed increase in PCa incidence in Scotland since 1970[25]. Although they do not wholly account for the increase in incidence, suggesting that an increased exposure to underlying risk factors, in particular lifestyle and dietary factors may have attributed to this increase.

So far there is no evidence that the increased detection of PCa due to PSA testing in some parts of Scotland has resulted in substantial reduction in mortality from the disease[25]. As seen in Figure 1.5, mortality has continued to rise since PSA testing was introduced. This maybe due to the aforementioned attenuation bias, or that it is

simply too soon to detect a reduction in mortality resulting from PSA testing, especially in the absence of an organised screening programme[25].

Figure 1.4: Age-standardised PCa incidence (world standard) in Scotland (1960-1992)

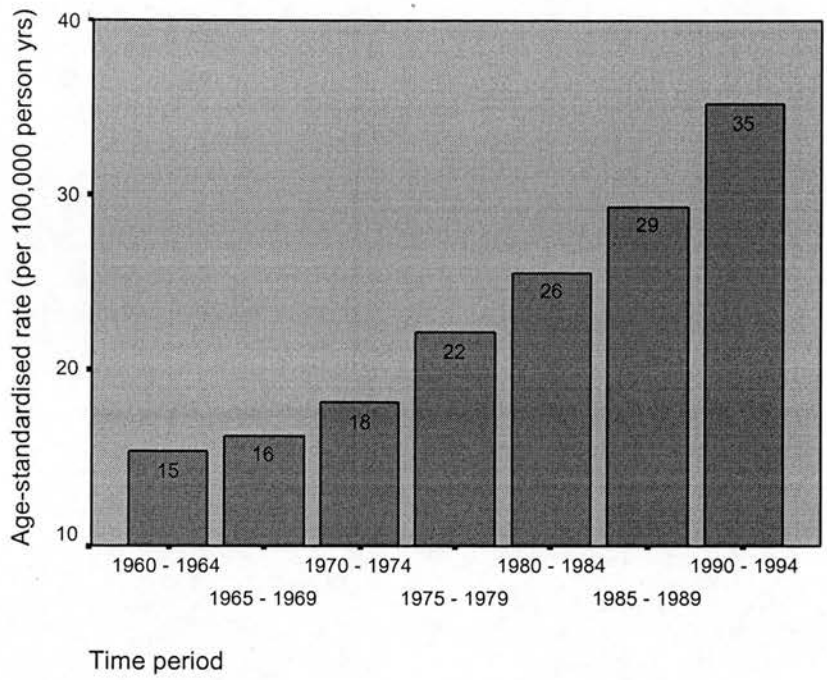
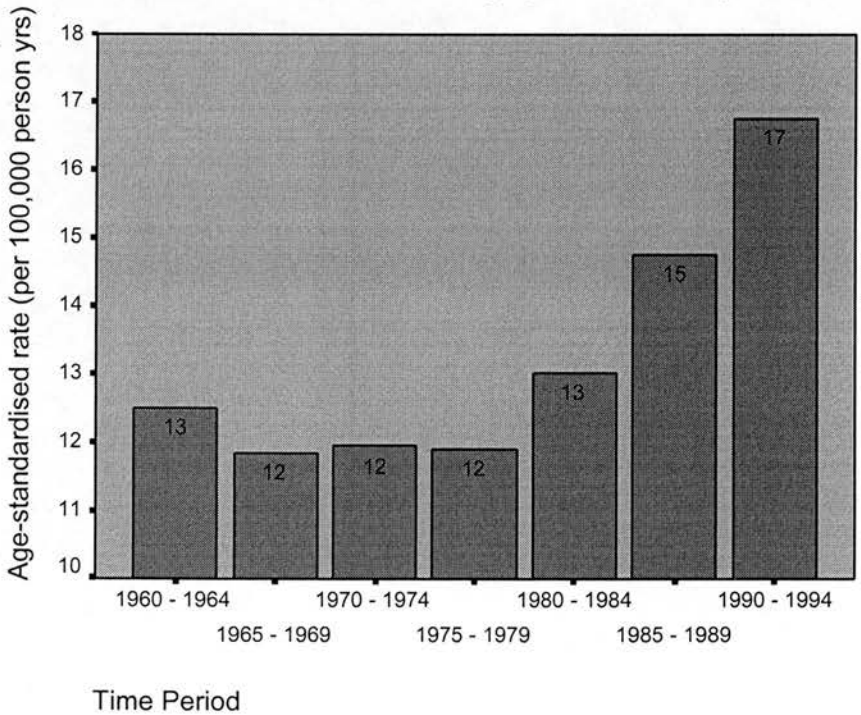


Figure 1.5: Age-standardised PCa mortality (world Standard) in Scotland (1960-1994)



Future trends in Scotland

In Scotland, PCa incidence has been predicted to double by 2014 (if present trends continue) with an increased use of PSA testing adding a further 15%[2], whereas PCa mortality has been predicted to increase by 25% by 2014, with an increased use of PSA testing attributing to a modest reduction of PCa mortality by around 40 deaths per year[2], Table 1.3 shows these trends, with the estimated effect of increased PSA testing, over the next decade in more detail.

Table 1.3: Predicted numbers of cases and deaths in Scotland

Time period	PSA testing effect applied	Cases per year	Deaths per year
1990-94	No	1498	695
1995-96	No	1832	760
1995-9	No	1948	759
	Yes	1948	759
2000-4	No	2849	804
	Yes	2537	791
2005-9	No	3241	877
	Yes	3372	847
2010-12	No	4303	990
	Yes	4494	953

N.B. Data for incidence and mortality in Scotland reported in this section were calculated as part of the Cancer Scenarios for Scotland Study, 2001[26]. A study in which I was involved in the data management and analysis / projection estimations for several main cancer sites including PCa. It should also be noted that the data used in this study were available for years 1960-1996 only. Since it's publication, complete data for the years up until 2000 (PCa cases) and 2002 (mortality data) have become available.

1.5 Established risk factors

The exact underlying reasons for the variation in PCa incidence and mortality, both geographically and temporally, are currently unknown. The variation of incidence in particular is one of the largest amongst cancers and may offer a unique insight into PCa aetiology. However, despite the substantial international prevalence of PCa, age, ethnicity and family history of PCa are the only established risk factors[27]. Evidence for other risk factors, including diet, genetic factors, alcohol, smoking, hormonal factors, sexual behaviour, socio-economic status and occupational exposures, vary from being promising but inconclusive (dietary [28;29] and genetic factors[30]) to conflicting (sexual behaviour[31] and occupational exposures[32]).

1.5.1 Age

PCa is rare before the age of 50, accounting for <0.1% of all cases[33] after which incidence increases rapidly for each subsequent decade of life. Although PCa is typically considered a disease of older men, the high overall frequency in western countries makes PCa a common cancer in men between the ages of 50 and 70.

Figure 1.6 shows the age-specific incidence rates of PCa in Scotland, a rapid increase in incidence with age can be seen after the age of 50 years, which starts to trail off after the age of 80. This same pattern can also be seen in the age-specific mortality rates, see Figure 1.7, although the sharp increase with age starts slightly later and the trend towards a stable rate above the age of 80 does not appear.

N.B. As with the previous data for incidence and mortality in Scotland, the age-specific rates were calculated as part of the Cancer Scenarios for Scotland Study, 2001[26].

Figure 1.6: Age-specific PCa incidence in Scotland (1960-1994)

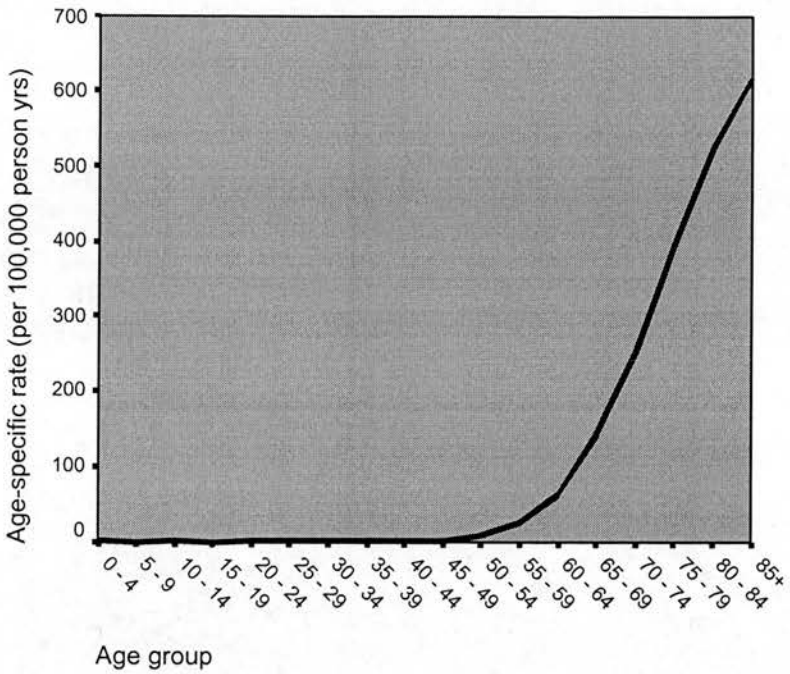
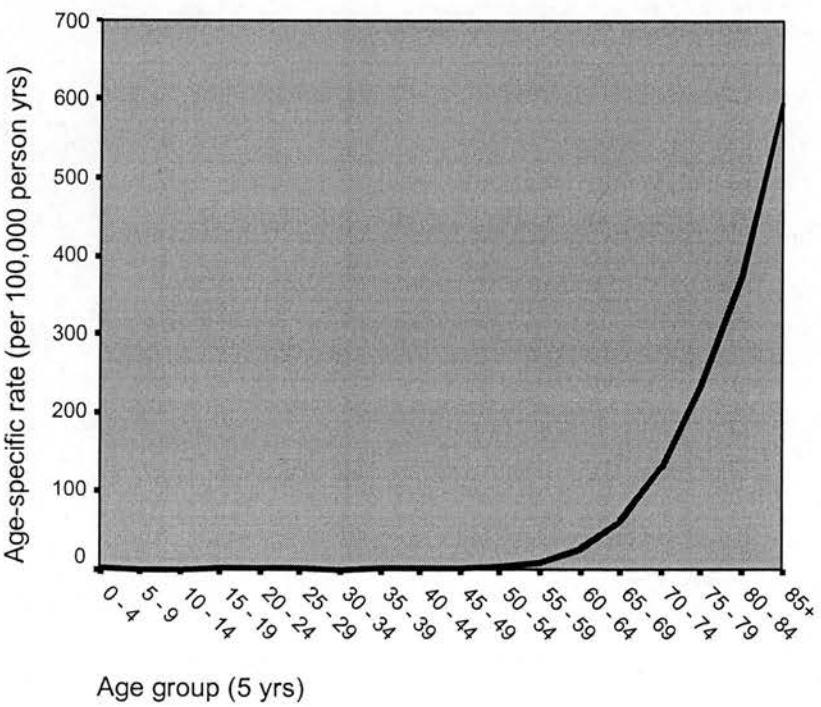


Figure 1.7: Age-specific PCa mortality in Scotland (1960-1994)



1.5.2 Family history of PCa

Many epidemiological studies, as reviewed by Ross & Schottenfield[34] and Stanford and Ostrander[35], have consistently observed that men with a first degree relative diagnosed with PCa have approximately twice the risk of developing PCa than do men without affected relatives, particularly among young-onset cases[36]. The risk is higher still for men with more than one affected relative and for men with a relative who developed PCa at a young age[34]. This pattern of familial PCa accounts for approximately 10-20% of PCa cases in the US[35]. This clustering of PCa in families may be due to shared genetic susceptibility as well as common environmental exposures or by chance alone given the high incidence of this cancer[33].

Although an increasing number of candidate high-penetrance genes for hereditary susceptibility have been identified (as reported by Stanford and Ostrander[35]) such as the HPC1 gene, only 5-10% of PCa cases may arise from these genes[30]. Other genetic factors, in combination with possible environmental / dietary risk factors, may be of greater importance. These include genetic polymorphisms that are far more common in the population than the high-penetrance PCa susceptibility genes[30]. For example, the Androgen Receptor gene (AR gene), which is polymorphic with a highly variable number of the trinucleotide microsatellite repeats CAG and GGC, has been observed to have a significant association with PCa, as reviewed in Coughlin & Hall[30]. Other genetic polymorphisms that may be associated with PCa risk include 5 α-Reductase Type II gene (SRD5A2) and the Vitamin D Receptor gene (VDR)[30].

1.5.3 *Ethnicity*

The international variation in PCa incidence and mortality may also be attributed to variation of PCa risk between different ethnic groups. This variation is also seen between ethnic groups within countries, such as the US. African-Americans are prone to the highest risks of PCa, with both PCa incidence and mortality rates being far higher than for US whites[16]. Socio-economic status and education factors are not associated with the increased incidence, presentation at a more advanced stage and an overall worse prognosis in African-Americans compared to their white

counterparts [3]. The underlying causes of these ethnic differences within the US remain unknown.

Many studies of migrant populations moving from areas of low PCa risk to countries with higher PCa risk show an upward shift in both PCa incidence and mortality rates[37]. More recent migration studies have shown that when Japanese people emigrate from Japan to the US, PCa incidence in these people increases, although this increase is only to about 50% of the rate for US whites[38;39]. Although some of the difference in incidence between native Japanese and Japanese-Americans will be due to differences in health care between countries[40], the result of migrant studies appear to show a real shift in incidence toward rates in the new host country. This provides evidence that the international and ethnic differences in PCa incidence are not entirely based on genetic disposition, but on environmental and lifestyle factors too.

1.6 Conclusion

As discussed above, observed geographical and temporal trends in PCa incidence and mortality cannot be explained by genetic factors, ethnicity and differences in health care / cancer registration alone. It is therefore very possible that lifestyle and, in particular, dietary factors may also attribute to these variations, thereby suggesting that they play a major role in the aetiology of PCa. It is these factors that will be considered in the next chapter.

2 . Chapter 2: Background - Diet

2.1 Introduction

This chapter will first examine briefly the international variations and temporal trends in diet in the context of PCa incidence and mortality, before introducing the concept of nutritional epidemiology. Individual dietary factors will be discussed in the next chapter.

2.2 Geographical variations of diet

The consumption of major food groups varies considerably across the world. International food consumption data, as reviewed by the Food and Agriculture Organisation for the United Nations (FAO)[41] and by the World Cancer Fund[42], show that in most Asian countries cereals are the staple food, with more than half of total energy being supplied by cereals (e.g. 67.9% of the Dietary Energy Supply (DES) in China[41]). In addition, Asian diets tend to contain few animal foods and only small amounts of vegetable and fruits, the majority of Asian populations also consume low-fat diets[42]. Whereas in Westernised countries, where the consumption of meat and dairy products is high (e.g. 25% of DES in the US[41]), cereals, although still an important source of energy, provide less than one quarter of DES[41]. In addition, western diets tend to contain high levels of fat, in particular animal fats (total fat supply: 154 g/day per capita in the US, compared to 52 g/day per capita in China[41]). Fruit and vegetable intake is relatively high, accounting for up to 6% of DES in the US and Mediterranean countries[42], whereas Alcohol consumption is high ranging from 5% of DES in the US to 8% of DES in Germany and Portugal[42].

N.B. The food consumption information above was extracted from food balance sheets containing information about average food availability per head. These are calculated by the FAO from the food produced and imported for countries as a whole (minus food exported, fed to animals, or otherwise not available to humans), divided by the number of people the respective country. Although food supply data is, in general, a relatively accurate proxy for actual food consumption[42], it does tend to overestimate food consumption in westernised countries, where substantial amounts of food are wasted or fed to pets, and can underestimate food consumption in developing countries where people tend to grow their own food.

The supply of various foods has been expressed as a percentage of total dietary energy supply (DES). This is because the amounts of different foods reported represent the commodities as produced, with no correction for the inedible portion nor for wastage and losses, thereby leading to varying levels of overestimation in the foods reported. However, the nutrient and energy content of foods has been calculated to account for this, therefore by expressing the data as the percentage contribution of each food group to the DES, these errors are attenuated and the distortion of the reported dietary profile is reduced[42].

2.3 International temporal trends in diet

Over the last couple of decades food consumption throughout the world has changed markedly. Since 1960, the food consumption in Asian countries has changed dramatically, reflecting the rapid industrialisation and urbanisation. Most of these countries have shown a decrease in cereal consumption, whereas meat intake has risen considerably, for example by over 300% in both China and Japan[42], fat consumption, in particular animal fats, has also increased accordingly. Food consumption in most Westernised countries has remained relatively stable, in particular for meat and fat intake[42].

2.4 Diet in Scotland

The Scottish diet is one of the worst in Western countries, it is high in fat, sugar and salt but low in fruit and vegetables and complex carbohydrates. After smoking, it is the most significant cause of Scotland's poor health record, contributing to a range of serious illnesses including coronary heart disease, stroke, diabetes and certain cancers[43] and has recently started to take over from more traditional public health concerns[44].

2.4.1 Components of the Scottish diet

The FAO food balance sheets show that the UK diet has one of the highest proportions of animal products and lowest proportion of fruit and vegetables in Europe. Recent Diet and Nutrition Surveys[45-47] and National Food Surveys[48] confirm these findings. For example, UK men consume on average 1602g of meat produce per week, compared to only 962g of vegetables[45]. For dairy products, 976g of semi-skimmed milk (the most commonly consumed type of milk) and 36g of animal-based fat spreads (which are rich in saturated and trans-fatty acids, but low in poly-unsaturated fatty acids) are consumed by men per week[45]. Alcohol consumption within the UK is also relatively high in relation to other countries, although it is still lower than that of other European countries (21.9g/day[46] compared to approximately 27g/day in France and Italy[42]).

For Scotland in particular, the consumption of meat products is high (1784g per week within meat consumers), with just over half of men (54%) reporting to eat meat two to four times a week[44]. The consumption of vegetables in Scotland is nearly half that of consumption in London and the South-East (1025g compared to 2029g per week)[45], with only 35% of Scottish men reporting to eat five or more helpings of green vegetables per week[44]. The intake of animal-based fat spreads is also far higher in Scottish men compared to those in London and the South-East[45]. Alcohol consumption is similar to that of the UK average[46]. A more detailed account of dietary intake can be found under the respective dietary factors in the next chapter.

2.4.2 Social class variations

Reported regional differences in food consumption, such as lower consumption of green and root vegetables in Greater Glasgow compared to the rest of Scotland[44], may in part reflect the impact of different behavioural patterns linked to social classes and socio-economic status[49]. The Scottish Health Survey[44] reported that the consumption of 'healthy' foods was far more prevalent among informants in Social Classes I and II than among those in Classes IV and V. In particular, half of men in Social Classes I and II consumed green vegetables five or more times a week compared to only a third of men in Social Classes IV and V. Similar differences were observed for using semi-skimmed / skimmed milk and consuming fruit, raw vegetables, oily fish and wholemeal bread. Whereas, two thirds of men in Social Classes IV and V consumed fried food two or more times a week, compared to just over a third of men in Social Classes I and II. Men in Social Classes IV and V were also more likely to consume red meat two or more times a week than men in Social Classes I and II. Higher intakes of energy, protein, fat, carbohydrates and alcohol, and lower intakes of vitamin E, retinol and beta-carotene have also been reported in manual, compared to non-manual workers[50].

2.4.3 Temporal trends

The last couple of decades have seen a substantial change in dietary habits and food consumption patterns within the United Kingdom. These changes, termed the 'Consumption Revolution'[51] are suggested to have been caused by fundamental changes in the attitudes and social behaviour of UK households in addition to economic factors such as the growth in household income.

Since 1970, the meat consumption in general has declined steadily, in particular red meat[52], see Figure 2.1. Recently, poultry has become a major component of meat intake and is now more important than beef. For fat spreads consumption, there has been a general decrease in the consumption of full-fat and animal fat products, whereas the consumption of low- / reduced-fat spreads has increased dramatically since their introduction in the early 1980's[52], see Figure 2.2.

For Scotland, within the last decade in particular, although patterns of general dietary consumption have tended to remain stable, the consumption of several food groups has been observed to change. Whilst the consumption of meat products has been observed to have declined slightly, see Table 2.1, the amount of men consuming whole milk and butter have halved, with semi-skimmed milk consumption increasing substantially[45;53]. The consumption of vegetables has in general remained constant, although the number of men consuming carrots has increased, as has the number of men consuming fruit, especially apples and pears[45;53]. This finding has been confirmed by the Scottish Health Surveys of 1995 and 1998, which found that 45% of men reported eating fruit at least once a day in 1998, compared to 39% in 1995[44]. However these observations should be interpreted with caution as only two data points are available and therefore it is difficult to interpret whether the observations do indeed infer a trend. It should also be noted that the sizes of study populations for the Dietary and Nutritional Surveys (DNS)[45;53] used are very small and therefore may not provide an accurate summary of the food consumption of the Scottish population as a whole.

Figure 2.1: Meat consumption in the United Kingdom, by time period (extracted from National Food Survey data[52])

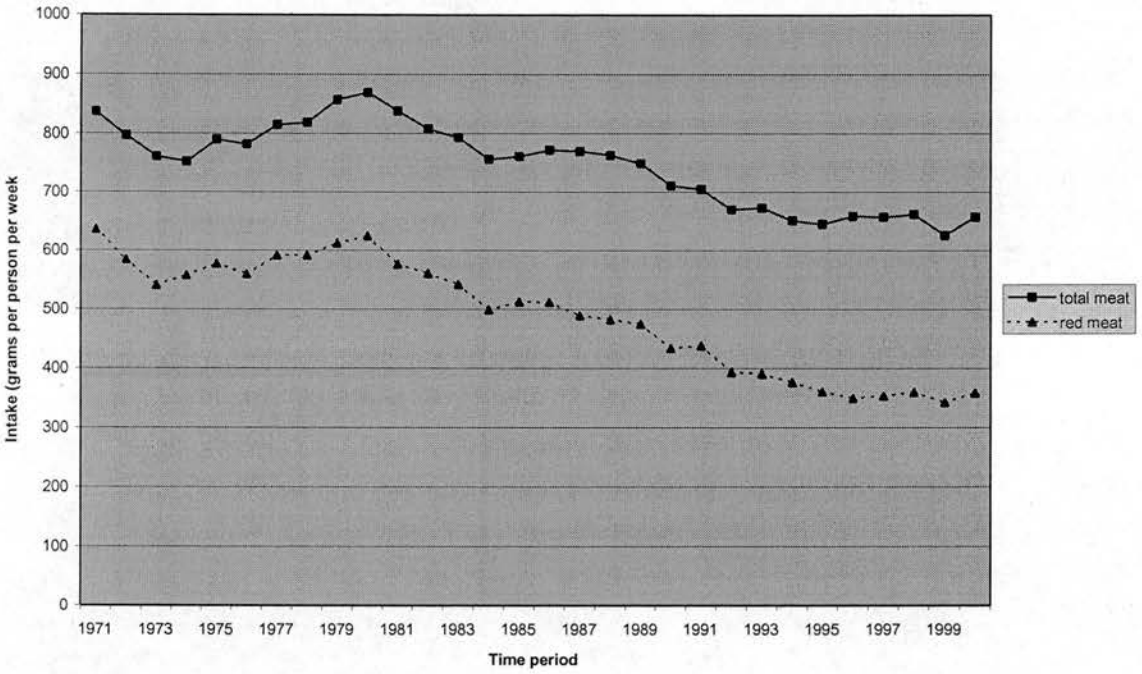


Figure 2.2: Fat spread consumption in the United Kingdom, by time period (extracted from National Food Survey data[52])

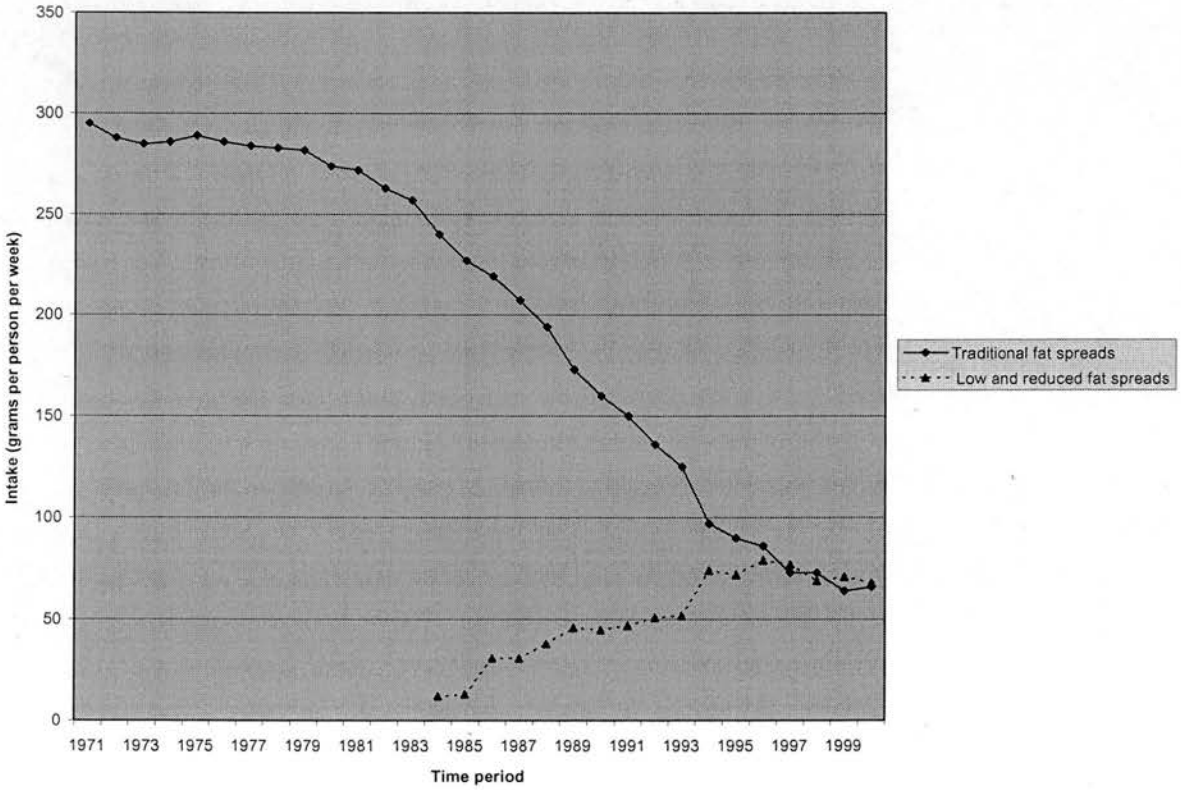


Table 2.1: Food groups consumption within the Scottish population for the first[53] and second[45] Diet and Nutrition Survey of British Adults (DNS).

Food Group	% of men reported to have consumed food	
	1st DNS[53] 1986-1987	2nd DNS[45] 2000-2001
Bacon and Ham	79%	77%
Beef and Veal	84%	80%
Whole Milk	80%	40%
Semi-skimmed milk	40%	75%
Butter	58%	32%
Leafy green vegetables	38%	38%
Carrots	36%	47%
Tomatoes (raw)	61%	58%
Apples and Pears	45%	54%

2.5 Nutritional epidemiology

The assessment of diet and its use in epidemiological studies to investigate the aetiology of chronic disease, especially cancer, has progressed substantially over the past twenty years. The recent development of nutritional epidemiology, both in terms of an expansion of the literature and in improvements in the methodological basis of nutritional epidemiology, has been motivated by the evidence of large world-wide variations in cancer incidence and mortality suggesting that these variations could be related to differences in diet and lifestyle between populations[54]. Nutritional epidemiological studies, which, in the context of the classical definition of epidemiology, may be defined as the study of the nutritional determinants of disease and their distribution within a population[55], have contributed immensely in providing useful insights into the association between diet and cancer aetiology. It is indeed of general consensus that diet plays a major role in cancer aetiology, although exactly which of the dietary components are associated with cancer aetiology remain unresolved.

Unlike other exposures of risk, such as smoking, the complex nature of diet poses a particularly difficult challenge to epidemiologists[56]. The effects of individual dietary components on cancer are notoriously difficult to detect due to the high degree of co-variance and interaction. And even when an association is observed, the relative risk of developing cancer rarely exceeds 2.0 or lies below 0.5. This is, in part, due to the methods used to assess diet, which are generally unable to distinguish precisely between different components of the diet within a population. It is this lack of accurate and practical methods to assess diet which is probably the most serious limitation to nutritional epidemiological research.

2.5.1 Diet assessment

There are four main methods of dietary assessment, Diet Recalls (usually 24 hours), and Diet Records assess current intake only, whilst Diet Histories and Food Frequency Questionnaires (FFQs) can focus on usual intake both post and present. As the main factors of interest in epidemiological studies tend to occur in the past, usually at a point in time that coincides with the induction of the disease[57], or as a

long-term exposure[58], it is the latter two methods which are most appropriate in epidemiological research, in particular the FFQ. In addition to this, retrospective methods, especially the FFQ, are usually quick and cheap to administer, also they need only low subject motivation and can be used to assess subjects with low literacy and numeracy skills.

FFQs are the most widely used technique for assessing diet in epidemiology studies. They consist of a list of food items (varying in length, depending on the study and hypothesis being tested) for which subjects are asked about the frequency and portion usually consumed. These FFQs can be either interviewer- or self-administered and can be formulated to measure diet in the past.

However, most methods of diet assessment have the inherent problem in that they depend entirely on individuals' ability to recall accurately the frequency and quantity of food and drink they usually consume. With the exception of diet records where subjects are asked to record their intake as they eat, this is a potential source of between-subject variation other than dietary intake, in particular memory and conceptualisation skills, which may contribute to measurement errors. This is a particular problem in the young and elderly who are less likely to recall diet accurately. Bingham *et al*[57] suggest that subjects over the age of 60 should be given a simple mental ability test to ensure that basic memory skills are intact. However, unless memory is associated with the disease of interest, the distribution of people with good and bad memories should be randomly spaced throughout the study population, leading to random misclassification at most[57]. Another major problem of diet assessment is illustrated by the Heisenberg Uncertainty Principle, "...as you stop something to measure it, you change its behaviour...". It has been well documented that subjects consciously and/or unconsciously distort their reported diet [57;59]. Various reasons include the unwillingness to confess consumption of certain types of food (e.g. sweets and alcohol) and the wish to report a diet that they believe will be acceptable in the eyes of the interviewer.

Individual nutrient intakes can be estimated from dietary assessment methods using food composition tables. These food tables tend to be nationally based, in order to

assess the nutritional components of foods and brands commonly eaten in the respective country. In the UK, the most commonly used food composition table is McCance and Widdowson's The Compostition of Foods (5th edition)[60] and related supplements[61-69], whereas in the US it is the USDA Composition of Foods: Raw, Processed and Prepared (Agricultural Handbook No. 8)[70]. Supplemental food databases may also be used to estimate nutrients that are not adequately covered by the main food tables, such as the Isoflavone Food Database[71] which contains food composition data for isoflavones in foods and brands commonly eaten in Scotland. Food composition tables can also be an important source of potential error, as the nutrient composition of each food item, in particular processed and convenience foods, can vary between brands and also when and where it was produced or processed. This is particularly true of isoflavones, the main source of which is soy - a commonly used bulking agent for processed foods in the UK. The amount of isoflavones in these foods can vary due to soy flour or soy protein concentrate being added in differing amounts according to the product and brand [72]. Additionally, substantial variation in isoflavone content of soybeans and soy products may occur because of genetic differences of various varieties, season of harvesting, where the soybeans are grown, maturity, and food-processing procedures[73;74].

Lastly, random measurement errors, unassociated with the true dietary intakes being measured, can cause the estimates of relative risk or other measures of diet-disease association to be weakened (an effect known as attenuation bias) and reduce the statistical power of epidemiological studies[75]. At the same time, a tendency for the assessment method to over- or under-estimate dietary intakes systematically at a group level may lead to a distortion of the scale on which differences in dietary intakes are measured [76;77]. Both random and systemic measurement errors can thus compromise the interpretation and estimation of relative risk. The assessment of the validity of the diet assessment method to be used (i.e. how accurately it measures true dietary intake) is therefore essential.

2.5.2 Diet validation

Various methods have been used to assess the performance of diet assessment methods to estimate dietary intake accurately. Within the diet assessment method itself, markers of internal validity can be incorporated by including questions that ask for the same information in different ways. The answers of which can be compared for consistency.

The reproducibility of measurements made by the diet assessment method on two or more separate occasions can produce a useful preliminary estimation of diet assessment performance. However, care must be taken in deciding the period of time between administrations of the diet assessment. Too short, and the subjects may tend to remember their previous responses. Too long, and true changes in dietary intake may contribute to a reduced reproducibility.

The comparison of individual nutrient intakes with an independent 'standard' measure of diet can be used to assess the validity of the diet assessment method. However, as there is no perfect measure of dietary intake, it is important that the measurement errors of both assessment methods be as independent and uncorrelated as possible to avoid spuriously high estimates of validity[77]. With the FFQ, the most feasible comparison method, which is likely to have the least correlated errors, is the Diet Record. The major sources of measurement error associated with FFQs (restrictions imposed by a fixed list of foods, memory, perception of portion sizes and interpretation of questions) are minimally shared by diet records. As diet records are open-ended, they allow direct assessment of portion sizes by measurement of weight or dimensions and they do not depend on memory[58]. However, one source of error likely to remain correlated is that of the food composition data. Nutrient intakes are usually calculated from each assessment method using a similar body of published data. Therefore, for nutrients whose content varies greatly in individual food items, the calculated values from the diet record may be incorrect, but still correlated with the FFQ. An alternative to the use of diet records as a standard is the collection of multiple 24-hours recalls. Although the errors of 24-hour recalls are more likely to be correlated with those of FFQs (both rely on memory and perception

of serving sizes), they may be the only feasible standard available, especially if subjects have low literacy skills or low compliance.

The use of biomarkers as a standard in the validation of diet assessment methods has the main advantage in that the potential sources of random error occurring with biomarkers are different from those of diet assessment methods. Therefore, it is fair to assume that the errors are independent between the two measurements[76]. They are also objective indicators of dietary intake, and therefore not effected by recall and observer bias[78]. However, these biomarkers are unlikely to be influenced by habitual dietary intake alone, physiological, absorption and metabolic processes of the body are also factors which may vary between individuals[78]. Other potential sources of variation include genetic and lifestyle differences, daily variation in dietary intake, which will cause temporal fluctuation in biomarker levels, and technical error associated with laboratory measurements. The net effect of these factors is to weaken the association between dietary intake and biomarkers. The observed correlation between biomarker and diet assessment measurements can therefore be interpreted only as a lower limit for the true correlation between diet and biomarkers, even if adjustments are made for the attenuating effects due to variation in the biomarker over time[76]. Another limitation is the lack of suitable biomarkers for many dietary factors of major interest including the intake of total fat and carbohydrates. For other nutrients where biomarkers do exist, homeostatic regulation is so strong that the biomarker's association with dietary intake is weakened dramatically, making the biomarker of minimal use to validation studies. Such highly regulated nutrients include plasma levels of retinol and calcium[79].

Validation studies usually take place on a random sample of 100-200 of the main study population[79]. In the analysis of the validation data, it is important to adjust nutrient intakes for variables that are ultimately controlled for in an epidemiological analysis, for example age, sex and EI[79;80]. As dietary intake values and biomarker levels tend to be skewed, it is also important that transformations to increase normality should be considered, alternatively, non-parametric tests could be used such as the Spearman's Rank correlations.

2.5.3 Other important methodological and epidemiological considerations

Study design

The two main types of analytical epidemiological study designs, cohort and case-control studies, have been used extensively to test hypotheses and confirm findings gained from previous ecological and geographical studies regarding dietary factors associated with PCa.

The case-control study tends to be the most commonly used study design, particularly in older studies, due to its relatively short completion time and the lesser expense entailed compared to cohort studies. However, there are many potential methodological limitations attached to this design, such as the potential for disease status to influence dietary intake and recall bias, these limitations will be discussed further in the next section.

In cohort studies, the exposure of interest is usually measured at the beginning of follow-up and therefore before the disease / outcome of interest occurs, thereby reducing the likelihood of recall bias. These studies also provide an absolute measure of risk, whereas a case-control study can only provide estimates of relative risk. All these determinants make the cohort study design a more robust method of assessing dietary factors associated with PCa. However, cohort studies may also be subject to misclassification, as dietary information is usually collected at a single point in adult life, and so will not be able to take into account any temporal changes in dietary habits, they also tend to be expensive and time consuming. Several studies have used cohort analysis methods in randomised controlled trials (RCTs) to examine the association between baseline characteristics and PCa, whereby the analysis is stratified by the intervention arm or is included as a potential confounding factor. These RCTs include the α-tocopherol and β-carotene RCT study (ATBC) [81;82] and the Physicans' Health Study[83].

Another type of study design that has been used in a number of nutritional epidemiological studies is the nested case-control study, in which a case-control analysis is conducted with a cohort study or RCT (i.e. cases and controls are selected from the cohort population). This type of study is particularly useful if complex and

expensive procedures are being used to collect data. It has been used in several cohort studies, including the Health Professionals Follow-up Study[84] and the CLUE I & II cohort studies[85;86], and also in RCT studies, including the Physicians Health Study[87;88], the Carotene and Retinol Efficacy Trial (CARET)[89] and the α-tocopherol and β-carotene RCT study (ATBC)[90;91]. A similar design is the case-cohort approach, as used in the Netherlands Cohort Study[92-95] this method differs from the normal nested case-control method, as whilst cases are derived from the entire cohort (providing numerator information for calculation of cancer incidence rates), the accumulated person years at risk in the total cohort are estimated using a random sub-cohort sample (providing denominator information for the rates)[95].

Statistical power and study size

The sample size of a study is an important determinant of statistical power - the probability that the study can demonstrate a significant association when a true association exists. The larger the study, the stronger the statistical power, therefore it is of utmost importance that the study size be as large as possible, in particular as most dietary assessment methods are susceptible to at least some degree of measurement error, whilst also taking into account practical and economical constraints. Several other factors may also affect the power of a study, including the strength of the true association, the frequency of the outcome, as given by the number of cases and controls and the prevalence of exposure among the subjects.

The issue of statistical power is of important consideration when reviewing the literature on dietary factors for PCa, as the number of subjects recruited in recent epidemiological studies investigating dietary factors varies substantially.

Subject selection

The way in which subjects are selected must be carefully considered in order to reduce selection bias. Selection bias occurs when there is a difference in the characteristics of those people who were selected for a study and those who were not, and where those characteristics are related to the exposure or outcome of interest. The effect of selection bias is to lead to an incorrect estimate of risk. It is particularly a problem for case-control studies where it gives rise to non-comparability between

cases and controls, i.e. the controls are not representative of the population that produced the cases. An ideal case-control study, where there is no selection bias, is one where:

- There is a clearly defined population (reference population)
- All cases in that population are included in the study
- Controls are a random sample of that population

Hospital-based case-control studies are particularly prone to selection bias, especially if admission to hospital for other conditions is related to exposure status. Also people in hospital often do not represent the general population, they tend to be poorer, smoke and drink more, and live in worse conditions than the population of potential hospital users. Most recent case-control studies investigating dietary factors for PCa have been population- rather than hospital-based.

Epidemiological studies investigating risk factors for PCa tend to identify cases through either population-based cancer registries or by hospital admission data, once identified and recruited, it is very important that the PCa diagnosis is confirmed histologically and/or pathologically, in order to avoid subject misclassification.

As mentioned previously, the 'clinical' PCa is of far greater epidemiological and aetiological importance than 'latent' or incidental PCa. It is therefore of great importance, especially in countries such as the US where PCa screening is common, that a distinction is made between clinical PCa and 'latent' PCa detected by screening. Some US studies, for example Giovannucci et al[8;9;96;97] omitted A_1 stage PCa, thereby concentrating on 'clinical' PCa only. It is also quite possible that many of the 'disease-free' controls recruited in to case-control studies may have, as yet, undiagnosed asymptomatic PCa, which can lead to errors due to subject misclassification. One solution to this is to use Benign Prostatic Hyperplasia (BPH) patients (i.e. diagnosed with BPH as a consequence of TURP in which no PCa was detected) as controls, thereby ensuring that the control group is PCa free.

Another interesting line of investigation that may give a further insight it to PCa aetiology is that of studying the effect of dietary intake on PCa according to cancer

stage (localised Vs advanced) and grade (well differentiated Vs undifferentiated). These categories, which have been discussed previously in Chapter 1, give an indication of the progression and /or aggressiveness of the tumour. Cases with advanced tumours are of particular importance as it is these cancers which are most likely to be fatal and also have a greater burden on health service provision, they are also most likely to be the most distinct from controls who have the potential for undiagnosed latent tumours[98] and most importantly, are possibly most related to environmental exposures such as diet, compared to the latent form of disease.

Subject participation

The success of any epidemiological study, in particular case-control studies, in accurately investigating the association of exposure and disease depends on achieving a high response / participation rate amongst the potential subjects. High rates of non-participation (i.e. subjects who refuse to take part in the study or do not respond), in addition to reducing statistical power of the study if the non-participants are not replaced, may allow for selection and/or non-responder bias. This is especially true if the exposure of interest differs between participants and non-participants or if participation rates differ between cases and controls. It is therefore of utmost importance that special care is taken to ensure that response rates are as high as possible and comparable for case and controls. The use of reminder letters and methods that ensure that data collection is as easy and non-invasive for the subjects as possible may help to increase participation rates.

Information bias

Errors leading to inaccurate information being collected on the exposure of interest and/or the disease may cause the estimate of the strength of the association between dietary factors and PCa to be biased. The extent and direction of this bias will depend upon the nature of the misclassification involved. Non-differential misclassification, in which the probability of exposure being misclassified is the same regardless of disease status, has been discussed previously in context with the dietary assessment method within the diet assessment section. The other main type of information bias is differential misclassification, in particular recall bias, especially within case-control

studies whereby cases recollect their eating behaviour differently from controls. This can be particular serious when trying to study a possible risk factor that the general public are aware of. Observer bias is another type of differential misclassification and can occur when information of disease status influences that of exposure. It is more likely to occur with an increased element of subjective judgement that is required in order to classify exposure / disease status, especially if the observer is aware of the disease / exposure status. Observer bias can be reduced by blinding the observers to the disease / exposure status, and also by reducing the subjective element by provided observers with clear instructions and criteria for obtaining information. Both these types of differential misclassification can bias the estimates of the association in either direction and, hence, it can be responsible for associations that prove to be spurious.

Confounding

Confounding occurs when an estimate of the association between an exposure and an outcome is mixed up with the real effect of another exposure on the same outcome and which is correlated with the first exposure. Therefore, a potential confounder is any factor which is believed to have a real effect on the risk of the disease under investigation (including factors, such as age and social class, that are good proxy measures of more direct unknown causes) and is correlated with the exposure of interest. Potential confounders which are specific to studies investigating dietary factors include the following:

Age and ethnicity

As mentioned previously, age is one of the 'confirmed' factors associated with increased risk of PCa. The process of ageing is also associated with economic, psychological and social changes that can affect dietary habits and impair nutrient intake. It is therefore very probable that age is a confounding factor for the association between dietary intake and PCa, and so must be adjusted for, either by age- or age-frequency matching controls to cases, by stratifying the analysis by age group or by including age in the final multi-variable statistical model. Within studies containing various ethnic or racial groups, it is also important that ethnicity, another

'confirmed' risk factor for PCa, is controlled for, as dietary intake can also vary between different ethnic groups.

Total energy intake

Probably the most important potential confounding factor that must be controlled for in any dietary study is total energy intake. Total energy intake is highly correlated with many dietary components, in particular fat, carbohydrates and protein, due to the high energy content of these components. It is therefore difficult to separate the intrinsic effects of high-energy dietary components from those associated with higher energy intake, unless total energy intake is controlled for. Even with dietary components that do not contribute to energy intake, total energy intake is still an issue as it is also a proxy for the total amount of food consumed[80], this is especially important if total energy intake is associated with the disease under study.

Due to methodological limitations in early / non-validated dietary assessment methods, initial epidemiological studies were unable to assess total energy intake accurately, therefore making the precise adjustment for energy intake impossible.

Unlike age and ethnicity, controlling for total energy intake can only take place at the analysis stage. Several methods used to control for total energy intake have been reviewed by Willet[80], they include: The Nutrient Density Method, in which nutrient intake is expressed as a percentage of total energy intake; the Energy- Adjusted or Residual Method, in which 'energy-adjusted' nutrient intakes are computed as the residual from the regression model with total caloric intake as the independent variable and absolute nutrient intake as the dependent variable, thereby providing a measure of individual nutrient intake uncorrelated with total energy intake; and the Standard Multivariate Model, in which total energy is adjusted for by including it in the final model.

3 . Chapter 3: Dietary factors

3.1 Introduction

The reported geographical and temporal variations in both PCa and dietary intake, as discussed in Chapters 1 and 2, suggest a correlation between PCa and diet. More over, PCa incidence in several countries show a high correlation with corresponding rates of several other cancers thought to be related to dietary factors, such as breast, ovarian and colorectal cancers[28].

Evidence of an association between PCa and diet was first reported in the mid 1970's by ecological studies observing significant correlations between PCa mortality and dietary intake, in particular a positive correlation with fat consumption[54;99;100]. In the light of these observations, the PCa-Diet hypothesis that fat intake is associated with increased risk of PCa was proposed. Subsequent ecological[101] and other epidemiological studies alluding to other dietary factors have lead to more hypotheses being suggested, such as that plant-based nutrients, including beta-carotene and isoflavones, have a protective effect against PCa.

It is these dietary factors hypothesed to be associated with PCa that will be discussed in this chapter. The first section will discuss the literature review methodology, followed by a discussion of each proposed dietary factor and their respective literature. The chapter will close with a general discussion of the dietary factors and issues regarding the literature.

3.1.1 Review papers and meta-analyses

Many recent papers have reviewed dietary factors associated with PCa, the most notable being the general reviews of Kolonel[28], Giles and Ireland[29] and the World Cancer Research Fund[42], who have given a comprehensive though not necessarily systematic review of the literature up till 1996. Important review papers for individual dietary factors will be discussed in the following sections. However, only three meta-analyses of dietary factors associated with PCa have been published,

including alcohol consumption[102], linoleic acid intake[103] and tomato products and lycopene[104].

3.1.2 Literature search

Search strategy

A literature search of Medline® and the Web of Science® using the keywords: Prostate Cancer (and associated MeSH subject headings), Diet (and associated MeSH subject headings) and the respective risk factor under study, was undertaken to identify epidemiological studies investigating dietary factors associated with PCa, see Table 3.1. Search results were limited to humans, English language and for years 1980 to May 2004. Additional studies were identified through previous reviews on nutrition and PCa[28;29] and citations of study papers.

Studies were restricted to analytical epidemiological studies that measured dietary intakes, studies based solely on serum nutrient concentrations were excluded from the review. Details regarding the study design, size and methodology, as well as estimates of risk and the respective confidence intervals or p-values of the dietary factors examined, were extracted. Where results for advanced PCa were given as a subset of the study, these results were also extracted along with the results for all cases. Care was taken to include all reported null findings and also to note the confounding variables each odds/risk ratio were adjusted for. Associations were deemed to be positive if risk estimates were ≥ 1.3, and inverse if risk estimates were ≤ 0.8.

Methodology criteria

A total of eighty-six epidemiological studies (excluding ecological studies) examining the association between dietary factors and PCa were identified. This wealth of epidemiological studies of varying types of designs, methodologies and sizes has given rise to much conflicting evidence, making it increasingly difficult to allow for a definitive answer to be made about the effect of diet on PCa risk. Therefore, in order to omit studies from this literature review whose methodology were deemed inadequate for examining the nutritional aspects of PCa accurately

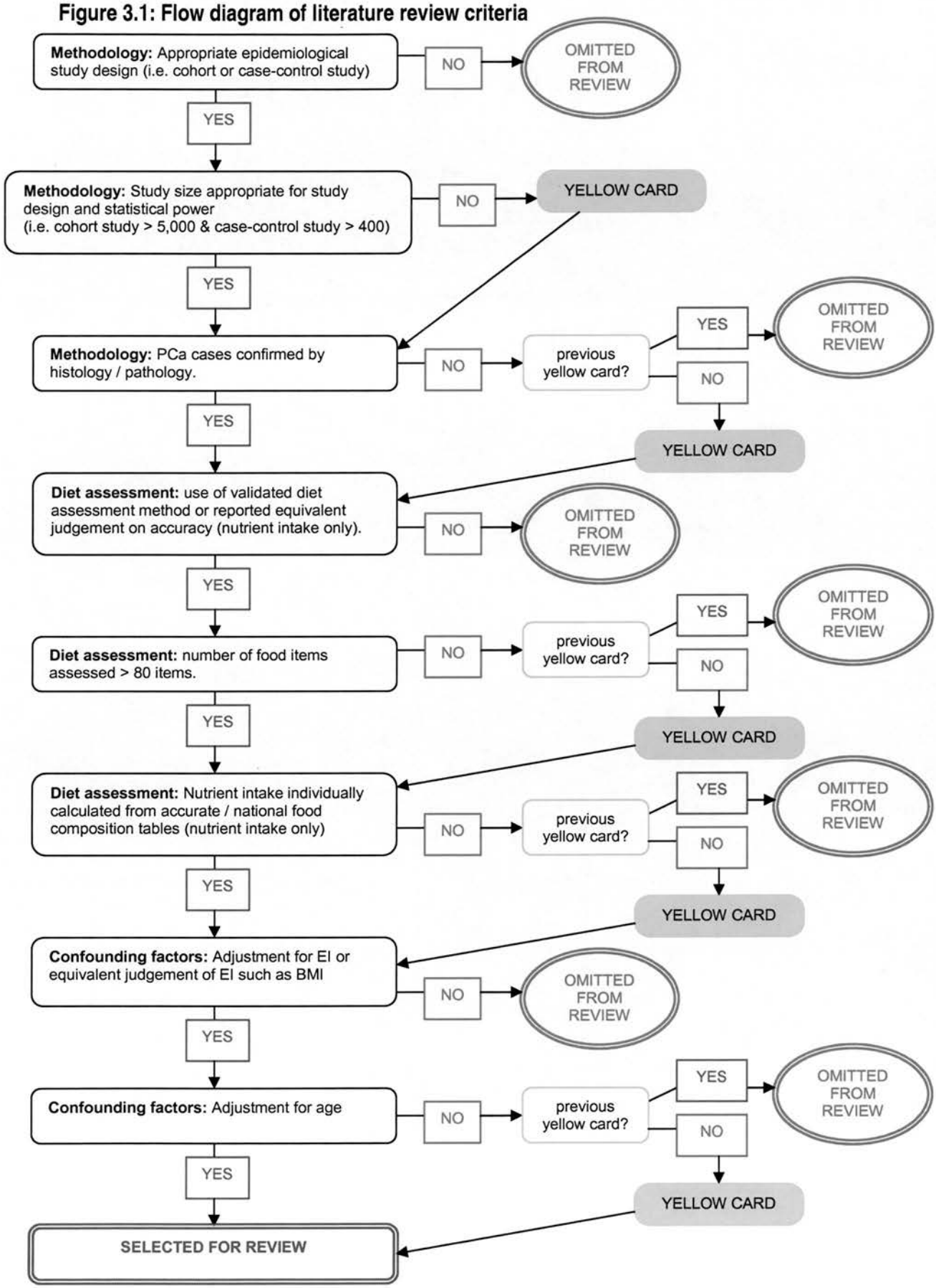
(thereby allowing for the possibility of spurious results to be observed), a rigorous methodology criteria was used. Those studies not fulfilling two or more of the criteria, particularly those that did not use a validated diet assessment method nor adjusted for energy intake were omitted, see Figure 3.1.

For those studies examining individual food groups and items, including alcohol, rather than nutrient intakes, the diet assessment criterion was disregarded, as a fully comprehensive and validated diet assessment method and food tables were not a necessary requirement to measure individual food items.

Table 3.1: Keywords used in the literature search

Dietary Factor	Key words
Fat	Fat, Saturated fat, Unsaturated fat, MUFA / mono unsaturated fatty acids, PUFA / poly unsaturated fatty acids, Cholesterol
Animal products	Animal products, Meat, Dairy products, Milk, Eggs Calcium, Retinol, Vitamin A
Fruit and vegetables	Fruit, Vegetables
Carotenoids	Carotenoids, Carotenes, β-carotene, lycopene
Vitamin E	Vitamin E, Tocopherol
Selenium	Selenium
Phyto-oestrogens	Phyto-oestrogens, Isoflavones, Lignans, Soy / Soya, Soy beans / Soya beans Daidzein, Genistein, Enterolactone, Equol
Alcohol	Alcohol, Beer, Wine, Liquor, Spirits

Figure 3.1: Flow diagram of literature review criteria



3.2 Fat

The relationship between fat consumption and PCa has been explored by numerous studies over the last three decades. However the role of dietary fat in PCa remains unclear.

Several early epidemiological studies demonstrated an association between PCa and fat intake, suggesting that increased fat intake is associated with an increased risk in PCa. However, more recently, as the literature on fat consumption and PCa expanded, and the design and methodology of such studies improved, the evidence of a fat-PCa association has become less consistent.

3.2.1 Fat in the diet

The average daily intake of total fat in the UK is 86.5g and 74.7g for men aged 19-64 years[46] and ≥ 65 years[105] respectively, and provides for nearly 40% of the total energy intake[53], see Table 3.2. These intakes are similar to those of US men[106], as is the proportion of total energy, but is approximately twice the average daily intake of men in China[107]. The same pattern is seen in the fat components, especially saturated fat and cholesterol, whereas poly unsaturated fatty acids (PUFA) remains similar between the UK / US and China.

The main sources of fat include dairy products, such as butter and margarine, meat products and oils. Fat is also found in nuts, fatty fish and cereal products such as cakes and biscuits.

Table 3.2: Average daily fat intakes, from various dietary consumption data:

Fat component	Gregory et al, 1990[53] men only (16-64 yrs)		Henderson et al, 2003[46] Men only (19-64 yrs)		Finch et al, 1998[105] men only (≥ 65yrs)		MAFF Nation Food Survey, 2000[48] men & women, all ages		USDA, 1997[106] US men		Chen et al, 1993[107] Chinese men (18-45 yrs)
	UK (low – high 2.5%)	Scotland (SE)	UK (low – high 2.5%)	Scotland (SD)	UK (low – high 2.5%)	Scotland & North (SD)	UK	Scotland	≥20yrs	≥ 70 yrs	
Total Fat (g)	102.3 (49.8-155.8)	93.4 (2.88)	86.5 (37.8-150.5)	88.1 (28.73)	74.7 (34.6-123.3)	73.4 (23.7)	74	71	92.7	68.6	51.2
Saturated Fat (g)	42.0 (19.1-69.4)	38.5 (1.27)	32.5 (12.9-62.3)	32.0 (11.86)	30.6 (12.6-57.6)	30.0 (12.2)	29.3	28.8	31.3	22.8	14.5
MUFA (g)	31.4 (15.6-49.5)	29.1 (0.90)	29.1[1] (12.9-51.0)	29.9[1] (9.36	23.2[1] (11.1-39.2)	23.1[1] (7.4)	26.4	25.0	35.8	26.4	22.2
PUFA (g)	15.75 (n/a)	13.83 (0.70)	15.17[1] (n/a)	16.68 (n/a)	12.20[1] (4.11-26.17)	11.79[1] (5.27)	13.4	12.0	13.9	18.4	14.3
Cholesterol (mg)	390 (151-741)	367 (17.2)	n/a	n/a	n/a	n/a	223	222	331	270	179

N.B.
[1] = cis-MUFA & cis-PUFA only
n/a = not available

3.2.2 Components of fat

The main components of fat are organic compounds called fatty acids (FAs). Fats can be categorised into three major classes, according to the main type of FAs of which they are composed, and which in turn depend on the presence and number of carbon-carbon double bonds:

1) Saturated FAs, which contain no carbon-carbon double bonds, an example of which is stearic acid, found in animal fats.

2) Mono-unsaturated FAs (MUFAs), which contain one carbon-carbon double bond and include oleic acid which is found in olive oil.

3) Poly-unsaturated FAs (PUFAs), which contain two or more carbon-carbon double bonds. These include: linoleic acid, found in various vegetable oils; α-linolenic acid, found in both vegetable oils and animal products; and eicosapentaenoic acid (EPA), found in fish oils. PUFAs can be classified further according to the position of the first carbon-carbon double bond, for example: omega-3 FAs, such as α-linolenic acid and eicosapentaenoic acid, and omega-6 fatty acids, such as linoleic acid.

MUFA and PUFA can also occur in two different geometric arrangements, *cis-* and *trans-*. The most common form is *cis-*, whilst *trans-* fatty acids are mainly produced during the manufacturing process of vegetable and fish oil products such as margarine.

Another component of fat is cholesterol, a sterol compound found only in foods of animal origin. Eggs and offal are the main dietary source of cholesterol. Dietary cholesterol is similar in structure to bile acids, sex hormones and vitamin D and is an important precursor in their production by the body.

Fatty acids can differ in their biologic properties depending on the degree of saturation and length of the carbon chain and the position of the first carbon-carbon double bond. Hence, it has been suggested that different fatty acids have different

roles in health and disease, and therefore the various components of fat should not be expected to carry the same risk for cancer[108].

3.2.3 Function of fat and possible biological mechanisms of PCa aetiology

Fat provides a concentrated source of energy, one gram of fat provides 37kJ (9kcal) which is more than double of that provided by either protein or carbohydrate (17kJ/g (4kcal) and 16kJ/g (3.75kcal) respectively)[109]. It is this high energy content that makes fat intake so highly correlated with total energy intake. It is therefore difficult to separate the intrinsic effects of fat intake from those associated with higher energy intake.

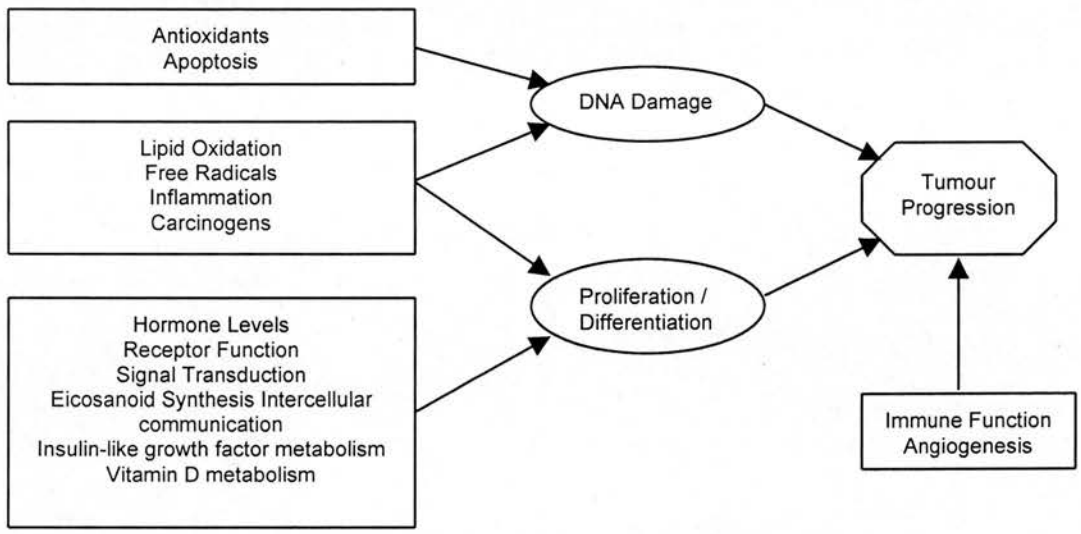
At the cellular level, fatty acids (as part of phospholipids) are an integral component of cellular membranes that function to maintain cellular integrity and regulate the activities of many membrane enzymes. In addition, cholesterol is also a precursor of sex hormones and bile acids. Humans can synthesise most of their necessary fatty acids, with the exception of linoleic and α-linolenic acids (that are therefore called essential fatty acids). These essential fatty acids are obtained from a variety of dietary sources, including vegetable oils, red meat and dairy products. Linoleic acid can be further metabolised to arachidonic acid, an important precursor for the biosynthesis of eicosanoids (e.g. prostaglandins).

Fats, along with other dietary factors, affect several physiologic and cellular processes that could influence, either positively or inversely, the development of PCa. Figure 3.2 summarises these processes. The effect of fat on male sex hormone levels has long been suggested as a possible biological pathway for PCa development. High dietary fat intake, especially saturated fat, has been observed increase circulating levels of endogenous androgens, such as testosterone[110], which in turn have been observed to have a positive effect on PCa risk[111]. Dietary fat has also been observed to affect the hormonal regulation of genes and gene expression[112].

Other possible mechanisms, as reviewed by Kolonel et al[113] include DNA damage due to the oxidation of PUFAs by free radicals, the disruption of normal cellular growth and communication by FAs, the influence of FAs, in particular arachidonic

acid (metabolite of linoleic acid) on inflammation, immune responses and prostaglandin production, all of which may play a role in PCa, and tumour growth and metastasis.

Figure 3.2: Cellular constituents and processes that may mediate the effects of dietary factors on carcinogenesis



3.2.4 Literature review

The following section will discuss the findings of recent studies investigating the association between fat intake and PCa.

Review papers and meta-analyses

Several recent papers have reviewed the association between fat intake and PCa[108;113-117], although the majority of these reviews discussed in depth the available evidence on fat intake and PCa risk, not one of these gave a systematic and complete review of all studies, with the possible exception of Kolonel et al[108;113]. The consensus among these reviews was that dietary fat may indeed be related to PCa risk, although the specific fat components that are responsible are not yet clear, and could involve the interplay of fat with other dietary factors, such as antioxidants or with genetic factors.

To date, only one meta-analysis has been undertaken to examine the effect of linoleic acid on PCa risk only[103], for which a combined relative risk of 1.27 (95%CI 0.97-1.66) and 0.83 (95%CI 0.56-1.24) were observed for three case-control studies and two cohort studies respectively.

Analytical epidemiological Studies

A total of thirty-six analytical epidemiological studies (published between 1983 – May 2004) were identified as examining the association between fat intake and PCa. Of these, fourteen were omitted from the literature review for not fulfilling the methodology criteria, see Table 3.3. Of the remaining studies, twelve were case-control studies, two were nested case-control studies and five were cohort studies.

Table 3.3: Methodology criteria and omitted studies

	Criteria	Studies not fulfilling criteria and which were subsequently omitted from review
1.	Study size appropriate for study design, statistical power and/or diet assessment method.	Heshmat et al, 1985[118] Ohno et al, 1988[119] Bravo et al, 1991[120] Walker et al, 1992[121] Vlajinac et al, 1997[122] Lee et al, 1998[123]
2.	PCa cases histologically or pathologically confirmed.	Ross et al, 1987[124]
3.	Use of validated dietary assessment method.	Graham et al, 1983[125] Heshmat et al, 1985[118] Ross et al, 1987[124] Kolonel et al, 1988[126] Ohno et al, 1988[119] Fincham et al, 1990 [127] Bravo et al, 1991[120] West et al, 1991[98] Walker et al, 1992[121] Vlajinac et al, 1997[122] Lee et al, 1998[123] Hayes et al, 1999[128] de Stephani et al, 2000[129]
4.	Dietary assessment method contains an appropriate number of food items to estimate nutrient intake accurately.	Graham et al, 1983[125] Heshmat et al, 1985[118] Ross et al, 1987[124] Kolonel et al, 1988[126] Ohno et al, 1988[119] Fincham et al, 1990[127] Bravo et al, 1991[120] Walker et al,1992[121] Deneo-Pellegrini et al, 1999[130] Hayes et al, 1999[128] de Stephani et al, 2000[129]
5.	Nutrient intake individually calculated using accurate, complete and internationally recognised food composition tables.	Graham et al, 1983[125] Heshmat et al, 1985[118] Ross et al, 1987[124] Bravo et al, 1991[120] Deneo-Pellegrini et al, 1999[130]
6.	ORs / RRs adjusted for energy intake (or an equivalent judgement of energy intake, i.e. BMI, height, weight).	Graham et al, 1983[125] Ross et al, 1987[124] Kolonel et al, 1988[126] Ohno et al, 1988[119] Fincham et al, 1990[127] Bravo et al, 1991[120] Walker et al, 1992[121]

Total fat

A total of sixteen reviewed studies reported the association between total fat intake and PCa, the findings of these studies are summarised in Table 3.4. The majority of the nine case-control studies that investigated this relationship reported no association [131-136]. However, Whittenmore et al[10] reported a significant positive association with PCa risk (OR 1.4, 95%CI 1.1 – 1.8), whereas two Canadian studies[137;138] reported a non-significant inverse association with PCa risk.

No association between total fat intake and PCa risk was reported by the only nested case-control study[93] and also by two out of the five cohort studies[82;96] that investigated the effect of total fat intake on PCa risk. Of the remaining three cohort studies, non-significant positive / inverse associations were reported by Giovannucci et al[9] and Veierod et al[139], and Hsieh et al[140] respectively.

Significant to borderline significant positive associations with advanced PCa were reported in all of the six studies that investigated the effect of total fat on advanced PCa[9;10;96;136], with the exception of Hodge et al[141] and Schuurman et al[93] who observed no association. The estimated relative risks of which ranged from 1.3 (95%CI 1.0-1.7)[96] to 2.0 (95%CI 1.0-3.9)[136]. Schuurman et al[93] also examined the effect of total fat on latent cancers, as with advanced tumours no association was found.

Table 3.4: Summary of results from epidemiological studies of total fat and PCa

Study, year, location	Subjects	Fat Variable	Odds / Risk Ratio[$@] (95%CI)	Notes
Case – control studies				
Rohan *et al*[137] 1995 Canada	207 Cases 207 Pop Ctrls	Total Fat	0.7 (0.4-1.3)	ORs adjusted for EI, age, FHPCa Age frequency matched
Whittenmore *et al*[10] 1995 US & Hawaii	1,655 Cases 1,645 Pop Ctrls Multi-Ethnic	Total Fat All Adv	 1.4 (1.1-1.8) 1.5 (1.0-2.2)	Men aged ≤ 84 yrs Stratified by ethnicity ORs adjusted for age residence & education (EI adjusted ORs not presented) Age frequency, race & residence matched
Andersson *et al*[131] 1996 Sweden	526 Cases 536 Pop Ctrls	Total Fat All Adv	 1.1 (0.8-1.5) 1.2 (0.8-1.8)	Men aged <80 yrs ORs adjusted for EI (residual) & age Age frequency matched
Ghadirian *et al*[138] 1996 Canada	232 Cases 231 Pop Ctrls	Total Fat	0.8 (0.5-1.5)	Men aged 35-84 yrs ORs adjusted for EI, age & FHPCa Age frequency & residence matched
Key *et al*[132] 1997 England	328 Cases 328 Pop Ctrls	Total Fat	0.9 (0.6-1.4)	Men aged <75 yrs ORs adjusted for EI & SES Age frequency matched
Meyer et al[133] 1997 Canada	215 incidental cases 593 Hosp Ctrls	Total Fat	1.0 (0.6-1.9)	Men aged ≥ 45 yrs. ORs adjusted for age, EI, study group, FHPCa & education. Study population: BPH & PSA screening patients
Villeneuve et al[134] 1999 Canada	1623 Cases 1623 Pop Ctrls	Total Fat	1.2 (0.9-1.5)	Men aged 50-74 yrs. ORs adjusted for age, residence, smoking, BMI, other food grps, income & FHPCa. Age frequency matched.
Ramon *et al*[135] 2000 Spain	217 Cases 434 Hosp / Pop Ctrls	Total Fat	1.2 (0.9-1.6)	Men aged ≤ 80 yrs ORs adjusted for EI, age, residence, FHPCa Age frequency & region matched
Kristal et al[136] 2002 US	605 Cases 592 Pop Ctrls	Total Fat Local Adv	 1.1 (0.7-1.7) 2.0 (1.0-3.9)	Men aged 40-64yrs ORs adjusted for EI, age, race, FHPCa, education, BMI, PSA testing Age frequency matched
Hodge et al[141] 2004 Australia	858 Adv Cases (≥ gleason score 5) 905 Pop Ctrls	Total Fat	1.0 (0.8-1.4)	Men aged < 70 yrs ORs adjusted for: EI (residual), age, study centre, year, FHPCa, SES Age frequency matched
Nested case - control studies				
Schuurman *et al*[93] 1999 Netherlands	642 Cases 1525 Ctrls from 58,279 men	Total Fat All Adv Latent	 1.1 (0.8-1.5) 1.0 (0.9-1.1) 1.1 (0.9-1.2)	RRs adjusted for EI, age, FHPCa & SES Adv & Latent RRs = per 10g increment Netherlands Cohort Study

Cont.

Table 3.4, cont.: Summary of results from epidemiological studies of total fat and PCa

Study, year, location	Subjects	Fat Variable	Odds / Risk Ratio[$@] (95%CI)	Notes
Cohort studies				
Giovannucci *et al*[6] 1993 US	47,855 Men	Total Fat All	1.3 (0.9-1.9)	RRs adjusted for EI, age, ancestry & BMI
	300 Non stage A_1 cases	Adv	1.7 (1.0-2.9)	Health Professional Follow-up Study
Veierod *et al*[139] 1997 Norway	25,708 Men	Total Fat	1.3 (0.6-2.8)	Men aged 16-56 at baseline RRs adjusted for EI & age
	72 Cases			
Giovannucci *et al*[96] 1998 US	47,781 Men	Total Fat All	1.1 (0.9-1.3)	RRs adjusted for EI, age All & Adv RRs = per 33g increment
	1414 Non stage A_1 cases	Adv	1.3 (1.0-1.7)	Health Professional Follow-up Study.
Chan et al[82] 2000 Finland	27,062 Men	Total Fat	1.1 (0.7-1.7)	Men aged 50-69 yrs at baseline. RRs adjusted for age, EI, intervention arm, smoking, education & BMI.
	184 clinically apparent cases (stages 2-4)			Cohort study from the ATBC RCT study.
Hsieh et al[140] 2003 US	444 men	Total Fat	0.7 (0.3-1.8)	Men aged 46-92 yrs RRs adjusted for age & EI (residual)
	68 cases (PSA screened)			N.B. cases included both prevalent & incident cases

N.B
[$] Odds / Risk ratio for highest relative to lowest percentile, except where stated
[@] Odds / Risk ratios based on all PCa cases, except where stated
Hosp Ctrls = hospital controls, Pop Ctrls = population controls
EI = Energy Intake, PCa = prostate cancer, OR = Odds Ratio, RR = Rate Ratio, SES = Socio-economic status, FHPCa = Family history of PCa, All = All PCa, Adv = Advanced PCa only, Agg = Aggressive PCa only, Local = Localised PCa only.

Animal and saturated fat

Thirteen studies have reported on the association between PCa and animal and/or saturated fat intake. The findings for these studies are summarised in Table 3.5.

As with total fat, the majority of the ten case-control studies that investigated this relationship observed no association[131-133;135;136;142]. Two Canadian case-control studies[137;138] reported non-significant inverse associations with PCa risk, whereas Whittenmore et al[10] and Ramon et al[135] reported significant positive associations with saturated fat (OR 1.6, 95%CI 1.1-2.4) and animal fat (OR 2.1, 95%CI 1.3-3.2) respectively. No association was also reported by the only nested case-control study[93] , whereas the two cohort studies[9;139] reported weak non-significant inverse associations.

No association between saturated fat and advanced PCa was observed by the majority of the six studies that investigated this association[9;93;131;143], with the exception of Whittenmore et al[10] who reported a significant positive association (OR 2.8, 95%CI 1.5-5.2). Schuurman *et al*[93] also examined the effect of saturated fat on latent cancers, as with advanced tumours no association was found.

Cholesterol

Only two case-control studies have reported on the association between PCa and cholesterol intake[131;135]. The finding for these studies are summarised in Table 3.5. No association between cholesterol and PCa / advanced PCa was observed.

Table 3.5: Summary of results from epidemiological studies of saturated fat, animal fat and cholesterol and PCa

Study, year, location	Subjects	Fat Variable	Odds / Risk Ratio[$@] (95%CI)	Notes
Case – control studies				
Whittenmore *et al*[10] 1995 US & Hawaii	1,655 Cases 1,645 Pop Ctrls Multi-Ethnic	Saturated Fat All Adv	 1.6 (1.1-2.4) 2.8 (1.5-5.2)	Men aged ≤ 84 yrs Stratified by ethnicity ORs adjusted for age residence & education (EI adjusted ORs not presented) Age frequency, race & residence matched
Rohan *et al*[137] 1995 Canada	207 Cases 207 Pop Ctrls	Saturated Fat Animal Fat	0.6 (0.3-1.0) 0.7 (0.4-1.2)	ORs adjusted for EI, age, FHPCa Age frequency matched
Andersson *et al*[131] 1996 Sweden	526 Cases 536 Pop Ctrls	Saturated Fat All Adv Cholesterol All Adv	 1.1 (0.8-1.6) 1.2 (0.8-1.8) 1.0 (0.7-1.3) 1.0 (0.7-1.5)	Men aged <80 yrs ORs adjusted for EI (residual) & age Age frequency matched
Ghadirian *et al*[138] 1996 Canada	232 Cases 231 Pop Ctrls	Saturated Fat Animal Fat	0.7 (0.4-1.2) 0.8 (0.4-1.3)	Men aged 35-84 yrs ORs adjusted for EI, age & FHPCa Age frequency & residence matched
Key *et al*[132] 1997 England	328 Cases 328 Pop Ctrls	Saturated FAs	1.1 (0.7-1.7)	Men aged <75 yrs ORs adjusted for EI & SES Age frequency matched
Meyer et al[133] 1997 Canada	215 incidental cases 593 Hosp Ctrls	Saturated Fat Animal Fat	0.8 (0.4-1.5) 0.9 (0.5-1.7)	Men aged ≥ 45 yrs. ORs adjusted for age, EI, study group, FHPCa & education. Study population: BPH & PSA screening patients
Tzonou *et al*[142] 1999 Greece	320 Cases 246 Hosp Ctrls	Saturated Fat	1.1 (0.9-1.5)	ORs adjusted for EI & age Age frequency matched OR = per increment of 1 SD of daily intake
Ramon *et al*[135] 2000 Spain	217 Cases 434 Hosp / Pop Ctrls	Saturated Fat Animal Fat Cholesterol	1.0 (0.7-1.4) 2.1 (1.3-3.2) 0.9 (0.6-1.3)	Men aged ≤ 80 yrs ORs adjusted for EI, age, residence, FHPCa Age frequency & region matched
Kristal et al[136] 2002 US	605 Cases 592 Pop Ctrls	Saturated Fat Local Adv	 1.1 (0.7-1.7) 1.8 (0.9-3.6)	Men aged 40-64yrs ORs adjusted for EI, age, race, FHPCa, education, BMI, PSA testing Age frequency matched
Hodge et al[141] 2004 Australia	858 Adv Cases (≥ gleason score 5) 905 Pop Ctrls	Saturated Fat	1.0 (0.7-1.4)	Men aged < 70 yrs ORs adjusted for: EI (residual), age, study centre, year, FHPCa, SES Age frequency matched

Cont.

Table 3.5, cont. : Summary of results from epidemiological studies of saturated fat, animal fat and cholesterol and PCa

Study, year, location	Subjects	Fat Variable	Odds / Risk Ratio[$@] (95%CI)	Notes
Nested case - control studies				
Schuurman *et al*[63] 1999 Netherlands	642 Cases 1525 Ctrls from 58,279 men	Saturated FAs All Adv Latent	 1.2 (0.8-1.8) 1.0 (0.8-1.3) 1.0 (0.7-1.4)	RRs adjusted for EI, age, FHPCa & SES Adv & Latent RRs = per 10g increment Netherlands Cohort Study
Cohort studies				
Giovannucci *et al*[9] 1993 US	47,855 Men 300 Non stage A_1 cases	Saturated Fat All Adv	 0.8 (0.5-1.8) 1.0 (0.4-2.2)	RRs adjusted for EI, age, ancestry, BMI & other fat components Health Professional Follow-up Study
Veierod *et al*[139] 1997 Norway	25,708 Men 72 Cases	Saturated Fat	0.7 (0.3-1.5)	Men aged 16-56 at baseline RRs adjusted for EI & age

N.B
[$] Odds / Risk ratio for highest relative to lowest quartile, except where stated
[@] Odds / Risk ratios based on all PCa cases, except where stated
Hosp Ctrls = hospital controls, Pop Ctrls = population controls
EI = Energy Intake, PCa = prostate cancer, OR = Odds Ratio, RR = Rate Ratio, SES = Socio-economic status, FHPCa = Family history of PCa, All = All PCa, Adv = Advanced PCa only, Agg = Aggressive PCa only, Local = Localised PCa only.

Unsaturated fatty acids (FAs)

Unlike other components of fat, it is only since the mid 1990's that unsaturated fat intake has been examined with regards to PCa risk. Most of the research has been focused on total MUFA and PUFA. More recently research has spread to more specific fatty acids such as α-linolenic and linoleic FAs and EPA and DHA, as research and measurement methodology has improved and new aetiological pathways for individual FAs suggested.

Nine case-control studies, two nested case-control studies and two cohort studies have reported on the association between MUFA and PUFA and PCa. Several of these studies have also examined specific FAs. The findings of these studies are found in Table 3.6.

MUFA

No association between MUFA intake and PCa risk was reported in the majority of eight case-control studies[131;132;135;136;142;144], with the remaining two studies reporting weak non-significant inverse associations[137;138]. However Norrish et al[144] reported a significant inverse association with MUFA rich oils (OR 0.5,95%CI 0.3-0.9). Whereas positive associations were reported by the nested case-control study and two cohort studies that examined MUFA intake, including Giovannucci et al[9] who reported a borderline significant positive association (OR 1.9, 95%CI 1.0-3.5).

Of the four studies which examined the association between MUFA and advanced PCa, Andersson et al[131] and Hodge et al[141] reported no association, whereas Kristal et al[136] and Giovannucci et al[9] reported positive associations of which one was borderline significant (OR 2.0, 95%CI 1.0-3.9).

PUFA

No association between PUFA intake and PCa risk was reported in the seven case-control studies[131;132;135-137] that investigated PUFA intake, with the exception of Ghadirian et al[138] and Tzonou et al[142] who reported a non-significant and significant positive association respectively (OR 1.8, 95%CI 1.1-2.8[142]). A weak non-significant inverse association was reported by the one nested case-control study to examine

PUFA intake[93], whereas the one cohort study[139] to examine PUFA intake reported a non-significant positive association. Schuurman *et* al[93] also examined PUFAs according to their geometric structure, both *Cis*-PUFA and *Trans*-PUFA intake were observed to have no association with PCa.

No association was also reported between PUFA intake and advanced PCa [131;136;141].

Specific FAs

In order to elucidate the association between PUFAs and PCa risk further, seven studies have also examined the effect that specific FAs may have on PCa. The findings of these studies are also summarised on Table 3.6.

The omega-6 FAs, including linoleic acid and arachidonic acid, were reported to have no association with PCa risk in both of the two case-control studies which examined these FAs[131;135], no associations with PCa were also reported in the two nested case-control studies[91;93] and cohort study[9], with the exception of a weak non-significant inverse association between linoleic acid and PCa[93] and a weak non-significant positive association between arachidonic acid and PCa[91]. No association with these FAs and advanced PCa were also reported with the exception of Giovannucci et al[9] who reported a non-significant inverse association.

For the omega-3 FAs, no association was reported between both EPA and DHA and PCa risk in the one case-control and two nested case-control studies that examined these FAs[91;93;136], with the exception of Mannisto et al[91] who reported a weak non-significant positive association with DHA. For advanced PCa, Hodge et al[141] reported a weak non-significant association and no association with EPA and DHA respectively. The evidence for α-linolenic acid is less conclusive, of the two case-control studies, two nested case-control studies and one cohort study to investigate α-linolenic acid, two reported no association[91;131], a further two studies[9;135] reported a positive association, one of which was significant (OR 2.5, 95%CI1.8-3.4[135]), whereas Schuurman et al[93] reported a weak borderline significant inverse association (OR 0.8, 95%CI 0.7-1.0). Of the two case-control studies and one cohort study that examined the association between α-linolenic acid and advanced PCa, Andersson et

al [131] and Hodge et al[141] reported weak inverse associations with advanced PCa, one of which was borderline significant (OR 0.8, 95%CI 0.6-1.0[141]), whereas Giovannucci et al[9] reported a significant positive association with advanced PCa (OR 3.4, 95%CI 1.7-7.0).

Of the remaining FAs examined, no significant associations were reported between PCa risk and stearic acid[91;93], oleic acid[91;93;141;144], palmitoleic acid[91;141] and palmitic acid[91;93].

Table 3.6: Summary of results from epidemiological studies of unsaturated fat, specific fatty acids and PCa

Study, year, location	Subjects	Fat Variable	Odds / Risk Ratio[$@] (95%CI)	Notes
Case – Control Studies				
Rohan *et al*[137]	207 Cases	MUFA	0.8 (0.4-1.4)	ORs adjusted for EI, age, FHPCa
1995	207 Pop Ctrls	PUFA	1.2 (0.7-2.1)	Age frequency matched
Canada				
Andersson *et al*[131]	526 Cases	MUFA		Men aged <80 yrs
1996	536 Pop Ctrls	All	1.1 (0.8-1.6)	ORs adjusted for EI (residual) & age
Sweden		Adv	1.2 (0.8-1.7)	Age frequency matched
		PUFA		
		All	1.0 (0.7-1.4)	
		Adv	1.0 (0.7-1.4)	
		Linoleic FA		
		All	1.2 (0.8-1.7)	
		Adv	1.2 (0.8-1.8)	
		α-linolenic FA		
		All	0.9 (0.7-1.3)	
		Adv	0.8 (0.5-1.2)	
Ghadirian *et al*[138]	232 Cases	MUFA	0.8 (0.5-1.4)	Men aged 35-84 yrs
1996	231 Pop Ctrls	PUFA	1.5 (0.7-2.9)	ORs adjusted for EI, age & FHPCa
Canada				Age frequency & residence matched
Key *et al*[132]	328 Cases	MUFA	0.9 (0.6-1.4)	Men aged <75 yrs
1997	328 Pop Ctrls	PUFA	0.9 (0.6-1.4)	ORs adjusted for EI & SES
England				Age frequency matched
Tzonou *et al*[142]	320 Cases	MUFA	1.1 (0.8-1.5)	ORs adjusted for EI & age
1999	246 Hosp Ctrls	PUFA	1.8 (1.1-2.8)	Age frequency matched
Greece				OR = per increment of 1 SD of daily intake
Norrish *et al*[144]	317 Cases	MUFA rich oils	0.5 (0.3-0.9)	Men aged 40 – 80 yrs
2000	480 Pop Ctrls	Total MUFA	n/s	ORs adjusted for EI, age & SES
New Zealand		Animal MUFA	n/s	Age frequency matched
		Oleic FA	n/s	ORs for MUFA & oleic FA not presented
Ramon *et al*[135]	217 Cases	MUFA	1.2 (0.9-1.9)	Men aged ≤ 80 yrs
2000	434 Hosp /	PUFA	0.9 (0.6-1.2)	ORs adjusted for EI, age, residence,
Spain	Pop Ctrls	Omega-6 FAs	1.0 (0.7-1.4)	FHPCa
		α-linolenic FA	2.5 (1.8-3.4)	Age frequency & region matched
Kristal et al[136]	605 Cases	MUFA		Men aged 40-64yrs
2002	592 Pop Ctrls	Local	1.0 (0.7-1.7)	ORs adjusted for EI, age, race, FHPCa,
US		Adv	2.0 (1.0-3.9)	education, BMI, PSA testing
		PUFA		Age frequency matched
		Local	0.9 (0.6-1.4)	
		Adv	1.2 (0.6-2.1)	
		EPA & DHA		
		Local	1.1 (0.7-1.6)	
		Adv	0.8 (0.4-1.6)	
Hodge et al[141]	858 Cases	MUFA	0.8 (0.6-1.1)	Men aged < 70 yrs
2004	(≥ gleason	PUFA	1.0 (0.7-1.3)	ORs adjusted for: EI (residual), age, study
Australia	score 5)	Palmitoleic acid	0.8 (0.6-1.1)	centre, year, FHPCa, SES
	905 Pop Ctrls	Oleic acid	0.9 (0.5-1.0)	Age frequency matched
		Linoleic acid	1.0 (0.7-1.3)	
		α-linolenic FA	0.8 (0.6-1.0)	
		Arachidonic acid	1.0 (0.7-1.4)	
		EPA	0.8 (0.6-1.1)	
		DHA	1.0 (0.7-1.4)	

Table 3.6, cont.: Summary of results from epidemiological studies of unsaturated fat, specific fatty acids and PCa

Study, year, location	Subjects	Fat Variable	Odds / Risk Ratio[$@] (95%CI)	Notes
Nested case - control studies				
Schuurman *et al*[93] 1999 Netherlands	58,279 Men 642 Cases	MUFA PUFA *Trans*-FAs *Cis*-FAs Palmitic Acid Stearic Acid Oleic Acid Linoleic Acid Linolenic Acid Arachidonic Acid EPA DHA	1.3 (0.8-2.1) 0.8 (0.6-1.1) 1.0 (0.7-1.4) 0.8 (0.5-1.2) 1.1 (0.8-1.7) 1.2 (0.8-1.9) 1.4 (0.9-2.2) 0.8 (0.6-1.1) 0.8 (0.7-1.0) 1.2 (0.9-1.7) 1.0 (0.7-1.4) 1.0 (0.8-1.4)	Latent & Advanced PCa RRs similar to those of All PCa RRs adjusted for EI, age, FHPCa & SES Netherlands Cohort Study
Mannisto et al[91] 2003 Finland	198 Cases 198 Ctrls from 29,133 male smokers	Myristic Acid Palmitic Acid Palmitoleic Acid Stearic Acid Oleic Acid Linoleic Acid α-Linolenic Acid Arachidonic Acid EPA DHA	1.2 (0.7-2.0) 0.8 (0.5-1.4) 0.9 (0.5-1.6) 1.1 (0.7-2.0) 1.0 (0.5-1.7) 0.9 (0.5-1.6) 1.2 (0.6-2.1) 1.3 (0.8-2.2) 1.2 (0.7-2.2) 1.3 (0.7-2.3)	Men aged 50-69 yrs ORs adjusted for: EI (residual), (residence, education, BMI, alcohol, smoking did not effect ORs) Age matched ATBC RCT Study
Cohort Studies				
Giovannucci *et al*[9] 1993 USA	47,855 Men 300 Cases	MUFA All Adv Linoleic acid All Adv α-linolenic acid All Adv	 1.9 (1.0-3.5) 1.6 (0.6-4.0) 0.9 (0.6-1.4) 0.6 (0.3-1.3) 1.3 (0.8-1.9) 3.4 (1.7-7.0)	RRs adjusted for EI, age, ancestry, BMI & other fat components Health Professional Follow-up Study
Veierod *et al*[139] 1997 Norway	25,708 Men 72 Cases	MUFA PUFA	1.4 (0.6-3.0) 1.4 (0.6-3.0)	RRs adjusted for EI & age

N.B
[$] Odds ratio for highest relative to lowest quartile, except where stated
[@] Odds / Risk ratios based on all PCa cases, except where stated
EI = Energy Intake, PCa = prostate cancer, OR = Odds Ratio, RR = Rate Ratio, SES = Socio-economic status, FHPCa = Family history of PCa, All = All PCa, Adv = Advanced PCa only, Agg = Aggressive PCa only, Local = Localised PCa only, n/s = Non-significant
FA = Fatty acid, MUFA = Mono Unsaturated Fatty Acid, PUFA = Poly Unsaturated Fatty Acid, EPA = Eicosapentainoic acid, DHA = Docosahexaenoic acid

3.2.5 Discussion

The evidence gathered from this systematic literature review, unlike previous literature review papers[108;113-117], concludes that, in general, fat and its components have no effect on PCa risk and therefore does not support the Fat-PCa Hypothesis that fat and its components are associated with increased PCa risk, with the possible exception of the effect of total fat on advanced PCa, for which a significant positive association was consistently observed, and α-linolenic acid which the findings are less conclusive with both significant inverse and positive associations being observed for both all PCa and advanced PCa. It should also be noted that MUFA rich oils were observed to have a significant protective effect against PCa[144]. However, care must be taken with the interpretation of this finding, as the observed protective effect could be attributed to non MUFA components of these vegetable oils, as well as residual confounding by the strongly protective Mediterranean / healthy dietary pattern associated with mono-unsaturated fat-rich vegetable oil consumption[144]. This could also be the underlying reason behind the varying observed effect of α-linolenic acid, as this FA is found both in animal and vegetable sources, thereby allowing for the possibility that α-linolenic acid may be correlated with other dietary factors associated with a protective effect against or positive risk for PCa depending on whether intake is from a vegetable or animal source respectively.

Although evidence from many animal and *invitro* studies (as reviewed by Kolonel et al[108]) support the Fat – PCa Hypothesis by observing increased tumour growth with high fat intake[145], or inhibition of tumour growth with a lower fat intake[146;147], several recent animal and *invitro* studies have failed to reproduce these findings[148-150]. It is of great interest that a recent animal study examining the relationship between PCa and energy and fat intake observed that tumour growth was reduced by the restriction of total energy intake rather than fat intake, and that tumour growth was independent of the proportion of fat in the diet as long as the total energy intake was restricted[151]. This therefore suggests that energy intake, not just fat, may affect prostatic tumour growth and also that fat in combination with some other unknown dietary component may encourage tumour growth[152].

3.3 Animal based products

3.3.1 Introduction

The relationship between meat, poultry, fish and dairy product consumption and PCa has been examined over the last two decades. Due to the strong association with fat intake (animal products are the main contributor of total and saturated fat intake), the consumption of animal products was thought to reflect the effect of dietary fat on PCa. However, recent evidence has shown that other constituents of meat and dairy products may also contribute to the carcinogenic effect on PCa.

Meat, poultry and fish contain around 20% protein, whilst fat content ranges from less then 4% fat for lean poultry and fish to 30-40% fat for fatty meat from domesticated farmed animals[42]. In meat, this fat content is made up of approximately 40-50% saturated FAs, poultry contains a relatively lower proportion of saturated FAs (35%) and a higher proportion of PUFAs (15-30% as compared with 10%), whereas fish contains only 20-25% saturated FAs[42]. Oily fish are also a rich source of omega-3 fatty acids. Meat and poultry are also rich sources of iron, zinc, selenium and the B vitamin group, liver is a rich source of retinol in particular. Fish contains relatively lower levels of iron, zinc and the B vitamins, but are a rich source of retinol and vitamin D[42]. Milk, in particular cows' milk, contains approximately 3% protein and 4% fat, of which approximately two-thirds is saturated FAs. Dairy products are rich sources of calcium and also good sources of riboflavin, vitamin B_{12} and retinol, particularly in full-fat dairy products[42]. Eggs are moderate sources of protein, fat and retinol.

N.B. The word meat can relate to either all non-fish and non-poultry meat or include poultry. This ambiguity can present difficulties when comparing results from different studies. In this study review, the term meat refers to non-fish and non-poultry meat unless otherwise stated, in particular beef, lamb and pork.

The consumption of meat, poultry and dairy products varies considerably world-wide this variation, in particular that for Scottish men, has been discussed in Chapter 2. This section will therefore concentrate on the background of the nutrients associated with animal products, in addition to a systematic review of the literature.

3.3.2 Specific nutrients associated with animal products

Calcium

Calcium is a mineral found in both animal and some plant foods. Rich sources of calcium include dairy products and small fish (when eaten with their bones). Calcium plays an important role in various functions in the body, such as nerve and muscle activity and bone metabolism. It also is involved with cell proliferation and differentiation. Calcium metabolism is controlled by various factors including vitamin D and its metabolite 1,25 dihydroxyvitamin D_3 (1,25 D), which in turn effects levels of circulating 1,25 D[153].

In the UK, the average daily intake of calcium is estimated to be 1016mg and 836mg for men aged 19-64[47] and 65 years and over[105] respectively, whereas in Scotland the average daily intake of calcium is estimated to be 1063mg and 777mg for men aged 19-64[47] and 65 years and over[105] respectively (see Table 3.7). This is relatively high compared to the average daily intake of calcium in the US and China where intake is estimated to be at 886mg and 746mg for US men aged ≥ 20years and ≥ 70 years respectively[106] and 582mg for Chinese men [107].

Table 3.7: Average daily animal based nutrient intakes, from various dietary consumption data:

Nutrient	Henderson et al, 2003[47] Men only (19-64 yrs)		Gregory et al, 1990[53] men only (16-64 yrs)		Finch et al, 1998[105] men only (≥ 65yrs)		MAFF Nation Food Survey, 2000[48] men & women, all ages		USDA, 1997[106] men only		Chen et al, 1993[107] men only (18-45 yrs)
	UK (low – high 2.5%)	Scotland (SD)	UK (low – high 2.5%)	Scotland (SE)	UK (low – high 2.5%)	Scotland & North (SD)	UK	Scotland	≥20yrs	≥ 70 yrs	
Calcium	1016 (410-1794)	1063 (394.1)	937 (409-1597)	881 (35.7)	836 (338-1448)	777 (302)	860	850	886	746	582
Vitamin A (μg)	991[1] (219-4124)	1028[1] (1598)	1628[1] (290-6964)	1303[1] (149)	1173[1] (255-6565)	1096[1] (1291)	780[2]	700[2]	1133[1]	1356[1]	n/a
Pre-formed Retinol (μg)	571 (81-3659)	n/a	1226 (190-6564)	945 (143)	847 (154-5921)	771 (1254)	500	460	n/a	n/a	337[1]

N.B.
[1] Retinol Equivalents
[2] Vitamin A Activity, expressed as retinol equivalents

Vitamin A / retinol

Vitamin A, also known as retinol, is a fat-soluble vitamin found in animal products such as liver, milk, eggs and fish liver oils. The term vitamin A applies correctly only to retinol, however, vitamin A intake is generally used to mean the dietary intake of both retinol (pre-formed retinol) and also pro-vitamin A carotenoids, such as β-carotene that are metabolised by the body into retinol[1]. This section focuses mainly on retinol, the pro-vitamin A carotenoids are discussed in the following section.

As summarised in Table 3.7, the average daily intake of preformed retinol (from food sources only) in the UK is 571μg and 847μg for men aged 19-64 years[47] and ≥ 65 years[105] respectively, where as in Scotland the average daily preformed retinol intake is slightly lower at 945μg and 771μg for men aged 16-64 years[53] and ≥ 65 years[105] respectively. This is similar to that observed in other Western countries, and is more than twice as much as that observed in Far Eastern countries such as China[107].

The average daily intake of vitamin A in UK (food sources only, measured as retinol equivalents) is 911μg and 1173μg for men aged 16-64 years[47] and ≥ 65 years[105] respectively, where as in Scotland the average daily vitamin A intake is 1028μg and 1096μg for men aged 19-64 years[47] and ≥ 65 years[105] respectively. These intake are similar to the daily average of vitamin A intake in the US, which is 1133μg and 1356μg for men aged ≥ 20 years and ≥ 70 years respectively[106].

Vitamin A and its precursors, as well as its role in the visual process, are essential for the normal growth and physiologic function of the prostate[42]. Since the discovery of vitamin A, the observation that the main effects of its deficiency are hyperplasia and loss of differentiation of the squamous epithelium has raised speculation that vitamin A may be involved with carcinogenesis. Several early epidemiological studies have observed an inverse association between vitamin A intake and a number of cancers including PCa[119;154], however due to methodological limitations these studies have not been included in the following study review.

3.3.3 Potential bio-mechanisms for PCa aetiology

The aetiological mechanism behind the association between meat and dairy products consumption and PCa is not fully understood. Initially this association was thought to reflect a high exposure to dietary fat, in particular saturated fats, since both meat and dairy products are the major sources of dietary fat. However, due to the inconsistent findings in recent studies on dietary fat and PCa (as reviewed previously), other potential bio-mechanisms have been considered, please refer to Figure 3.2 for an outline of these bio-mechanisms.

The bio-mechanisms involved with meat and meat products have been examined in a review by Kolonel[108]. Firstly, due to the inverse correlations observed between meat and plant food consumption patterns, diets high in meat and other animal products may be relatively deficient in certain anti-carcinogenic compounds found in plant foods, such as β-carotene, lycopene and tocopherol. And secondly, cooking meats at high temperatures (the most common method of cooking meat) can result in the formation of heterocyclic amines and polycyclic aromatic hydrocarbons - potent carcinogens which may induce cancer directly by the formation of DNA adducts[108].

In addition to the bio-mechanisms involved with dietary fat, dairy products also are thought to effect PCa aetiology via calcium intake and the vitamin D metabolic pathway. Vitamin D and its metabolite 1,25 D are anticarcinogenic and have been shown to inhibit PCa cell growth and development[155]. As noted earlier, 1,25 D regulates calcium metabolism and consequently, dietary calcium can suppress circulating 1,25 D levels. Therefore a high intake of dietary calcium may increase PCa risk by lowering the level of anti-carcinogenic 1,25 D. Milk intake has also been linked to higher levels of circulating insulin-like growth factor 1, which in turn has been observed to increase PCa risk[156-158]. However the hypothesis that dairy products increase PCa risk by increasing levels of insulin-like growth factor 1 is very speculative and requires further study[153].

3.3.4 Literature review

Review papers

Several recent papers have reviewed the association between animal products, including vitamin A and calcium, and PCa risk[108;143;153;159]. Although the majority of these reviews discussed in depth the available evidence, not one of these gave a systematic and complete review of all studies. The consensus amongst these reviews confirmed the association between meat and dairy consumption and PCa risk, whereas the evidence for the association of calcium and vitamin A with PCa risk is less conclusive. No meta-analyses on the effect of animal product consumption on PCa risk have been published.

A total of forty-six analytical epidemiological studies have been identified for examining the association between the consumption of animal products and their associated nutrients and PCa. Seventeen studies out of the forty-six studies, as shown in Table 3.8, did not fulfil the methodological criteria and were therefore omitted, a further four studies that examined both animal products and their associated nutrients, were omitted for the review of calcium and/or vitamin A, but were included in the food group review due to not fulfilling the diet assessment and food table criteria which is an important criteria for nutrient analyses but not so for food group analyses . Of the remaining studies, eighteen were case-control studies, two were nested case-control studies and nine were cohort studies.

Table 3.8: Methodology criteria and omitted studies

	Criteria	Studies not fulfilling criteria and which were subsequently omitted from review
1.	Study size appropriate for study design, statistical power and/or diet assessment method.	Heshmat et al, 1985[118] Ohno et al, 1988[119] Oishi et al, 1988[154] Bravo et al, 1991[120] La Vecchia et al, 1991[160] Walker et al, 1992[161] Vlajinac et al, 1997[122] Lu et al, 2001[162]
2.	PCa cases histologically or pathologically confirmed.	All studies fulfilled this criteria
3.	Use of validated dietary assessment method.	Graham et al, 1983[125] Heshmat et al, 1985[118] Kolonel et al, 1987[163] Ohno et al, 1988[119] Oishi et al, 1988[154] Bravo et al, 1991[120] La Vecchia et al, 1991[160] West et al, 1991[98] Vlajinac et al, 1997[122] Hayes et al, 1999[128] (vitamin A only) Lu et al, 2001[162] Tavani et al, 2001[164] Mills et al, 1989[165] Severson et al, 1989[166] Hsing et al, 1990[167] Le Marchand et al, 1994[168] Chan et al, 2001[83] (calcium only) Rodriguez et al, 2003[169] (calcium only)
4.	Dietary assessment method contains an appropriate number of food items to estimate nutrient intake accurately.	Graham et al, 1983[125] Heshmat et al, 1985[118] Ohno et al, 1988[119] Oishi et al, 1988[154] Bravo et al, 1991[120] Walker et al, 1992[161] Deneo-Pellegrini et al, 1999[130] (vitamin A only) Hayes et al, 1999[128] (vitamin A only) Lu et al, 2001[162] Tavani et al, 2001[164] Mills et al, 1989[165] Severson et al, 1989[166] Hsing et al, 1990[167] Le Marchand et al, 1994[168]
5.	Nutrient intake individually calculated using accurate, complete and internationally recognised food composition tables.	Graham et al, 1983[125] Heshmat et al, 1985[118] Kolonel et al, 1987[163] Ohno et al, 1988[119] Bravo et al, 1991[120] Deneo-Pellegrini et al, 1999[130] (Vitamin A only) Mills et al, 1989[165] Severson et al, 1989[166] Hsing et al, 1990[167] Le Marchand et al, 1994[168]

Table 3.8, cont.: Methodology criteria and omitted studies

	Criteria	Studies not fulfilling criteria and which were subsequently omitted from review
6.	ORs / RRs adjusted for energy intake (or an equivalent judgement of energy intake, i.e. BMI, height, weight).	Graham et al, 1983[125] Kolonel et al, 1987[163] Ohno et al, 1988[119] Oishi et al, 1988[154] Bravo et al, 1991[120] La Vecchia et al, 1991[160] Walker et al, 1992[161] Tavani et al, 2001[164] Mills et al, 1989[165] Severson et al, 1989[166] Hsing et al, 1990[167] Le Marchand et al, 1994[168] Chan et al, 2001[83] (calcium only)
7.	ORs / RRs adjusted for age.	Graham et al, 1983[125] Heshmat et al, 1985[118] Oishi et al, 1988[154] Bravo et al, 1991[120] Walker et al, 1992[161] Vlajinac et al, 1997[122] Rodriguez et al, 2003[169] (calcium only)

3.3.5 Meat products

Total meat

A total of ten case-control studies, one nested case-control study and one cohort study examined the association between total meat intake and PCa. The findings from these studies are summarised in Table 3.9. Most studies reported positive associations[128;130;161;170;171] two of which were significant / borderline significant (OR 1.4, 95%CI 1.0-2.0[161], OR 1.4, 95%CI 1.0-2.0[171] and OR 1.4, p≤ 0.05[128]), Talamini et al[161] also reported an even stronger significant association in older men (OR 2.1, 95%CI 1.0-4.0) . Berndt et al[172] examined the association between animal protein and PCa, no association was observed.

Three studies also examined the relationship between meat intake and advanced PCa, both Chan et al[171] and Hayes et al[128] continued to observe significant positive associations (OR 1.6, 95%C.I. 1.02-2.5, and OR 1.8, p≤0.05, respectively), whilst Michaud et al[173] continued to observe no association.

Red meat

A total of three case-control studies and two cohort studies examined the association between red meat consumption and PCa. The findings from these studies are summarised in Table 3.9. The majority of case-control studies reported positive associations[128;130], one of which was significant (OR 1.4, p≤0.05)[128]. However this association was not reported in the two cohort studies which reported no significant associations[82;173].

Both of the two studies that examined the association between red meat and advanced PCa reported a positive association[128;173], one of which was significant (OR 1.8, p≤0.05)[128].

Individual meat items

Most of the studies also examined a variety of individual meat items including beef, pork, poultry, fish, white meat and processed and cured meats. None of which reported any significant associations with the exception of Jain et al[174] who reported

a borderline significant inverse association between fish consumption and PCa risk (OR 0.7, 95 %CI 0.5-1.00) and Schuurman et al[94] who reported a borderline positive association with cured meat (OR 1.4, 95%CI 1.0-1.9).

Cooking method and heterocyclic amines

Two case-control studies examined the association between cooking methods and PCa. Key et al[132]observed no association between grilled / roasted meat and PCa, whereas Norrish et al[175] observed negative non-significant associations between meat doneness and PCa for both all cases and advanced cases, but no association with heterocyclic amines and PCa.

Table 3.9: Summary of results from epidemiological studies of meat products and PCa

Study, year, location	Subjects	Food Item	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Case-Control Studies				
Talamini et al[161] 1992 Italy	271 Cases 685 Hospital Controls	Meat		Men aged 45 - 79 yrs. Stratified by age. ORs adjusted for age, residence, education and BMI.
		All	1.4 (0.97-2.0)	
		<70yrs	1.3 (0.8-2.0)	
		≥70yrs	2.1 (1.04-4.0)	
		Fish		
		All	0.8 (0.5-1.2)	
		<70yrs	0.6 (0.4-1.01)	
		≥70yrs	1.5 (0.7-2.9)	
		Liver		
		All	1.3 (0.8-2.1)	
		<70yrs	0.8 (0.4-1.5)	
		≥70yrs	6.9 (2.1-22.0)	
		Ham / Salami		
		All	1.2 (0.8-1.8)	
		<70yrs	0.8 (0.5-1.4)	
		≥70yrs	1.5 (0.8-3.0)	
Ewings et al[170] 1996 UK	159 Cases 161 BEP Controls 164 Hospital Controls	Meat	2.7 (0.5-15.8)	Adjusted ORs not presented as similar to crude ORs. Age matched.
		Meat Products	0.7 (0.3-1.3)	
		Liver	0.6 (0.3-1.2)	
Gronberg et al[176] 1996 Sweden	406 Cases 1218 Population Controls	Beef	0.6 (0.3-1.3)	ORs adjusted for age. Age matched. Data collected prospectively.
		Pork	1.2 (0.7-2.0)	
		Sausage	0.8 (0.5-1.5)	
		Fish	0.99 (0.6-1.7)	
Key et al[132] 1997 England	328 Cases 328 Population Controls	Meat	0.6 (0.4-1.1)	Men aged <75 yrs. ORs adjusted for EI & SES. Age frequency matched.
		Roasted / Grilled Meat	1.1 (0.5-2.5)	
Chan et al[171] 1998 Sweden	526 Cases 536 Population Controls	Meat		Men aged < 80 yrs. ORs adjusted for EI, age, FHPCa & smoking. Age frequency matched.
		All	1.4 (1.0-2.0)	
		Adv	1.6 (1.0-2.5)	
Deneo-Pellegrini et al[130] 1999 Uruguay	175 Cases 233 Hospital Controls	Total Meat	1.6 (0.8-3.4)	Men aged 40-89 yrs. ORs adjusted for age, EI, BMI, education, residence & FHPCa. ORs became n/s when controlled for EI.
		Red Meat	1.7 (0.8-3.4)	
		White Meat	0.9 (0.5-1.8)	
		Poultry	1.3 (0.7-2.4)	
		Fish	0.9 (0.5-1.8)	
		Processed Meat	0.8 (0.4-1.4)	
		Offal	1.1 (0.6-1.9)	
Hayes et al[128] 1999 USA	932 Cases 1201 Population Controls	Meat		Men aged 40-79 yrs. ORs adjusted for age & race, EI adjusted ORs not presented. Age frequency & race & region matched.
		All	1.4 (p< 0.05)	
		Adv	1.8 (p<0.05)	
		Red Meat		
		All	1.4 (p<0.05)	
		Adv	2.0 (p<0.05)	
		Poultry & Fish		
		All	1.1 (n/s)	
		Adv	1.0 (n/s)	
Jain et al[174] 1999 Canada	617 Cases 636 Population Controls	Red Meat	1.02 (0.7-1.4)	ORs adjusted for age & EI. Age frequency matched.
		Chicken	0.98 (0.7-1.4)	
		Fish	0.7 (0.5-1.00)	

Cont.

Table 3.9, cont.: Summary of results from epidemiological studies of meat products and PCa

Study, year, location	Subjects	Food Item	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Norrish et al[175] 1999 New Zealand	317 Cases 480 Population Controls	Meat Doneness All Adv Total Heterocyclic Amines All Adv	 0.8 (0.6-1.1) 0.8 (0.5-1.2) 1.1 (0.7-1.7) 1.2 (0.7-1.8)	Men aged 40-80 yrs. ORs adjusted for age, EI & SES. Age frequency matched. Doneness = well-done meat Vs meat never eaten / other cooking method.
Tzonou et al[142] 1999 Greece	320 Cases 246 Hospital Controls	Meat	0.97 (0.9-1.1)[#]	ORs adjusted for EI & age. Age frequency matched.
Villeneuve et al[134] 1999 Canada	1623 Cases 1623 Pop Ctrls	Meat	1.0 (0.7-1.3)	Men aged 50-74 yrs. ORs adjusted for age, residence, smoking, BMI, other food grps, income & FHPCa. Age frequency matched.
Hodge et al[141] 2004 Austrailia	858 Cases 905 Pop Ctrls Cases ≥ gleason score 5	Meat	1.0 (0.8-1.4)	Men aged < 70 yrs ORs adjusted for: EI (residual), age, study centre, year, FHPCa, SES Age frequency matched
Nested Case-Control Studies				
Schuurman et al[94] 1999 Netherlands	642 Cases 1525 Controls from 58,279 Men	Fresh Meat & Poultry Fish Cured Meat	1.1 (0.8-1.5) 1.0 (0.8-1.3) 1.4 (1.0-1.9)	ORs adjusted for age, FHPCa & SES. Case - Cohort approach. Netherlands Cohort Study.
Cohort Studies				
Chan et al[82] 2000 Finland	27,062 Men 184 Clinically Apparent Cases	Red Meat	0.7 (0.5-1.1)	Men aged 50-69 yrs at baseline. RRs adjusted for age, EI, intervention arm, smoking, education & BMI. Cohort study from the ATBC RCT study.
Michaud et al[173] 2001 USA	47,780 Men 1897 Non Stage A_1 Cases	Total Meat All Adv Red Meat All Adv	 0.9 (0.8-1.1) 0.96 (0.7-1.3) 0.9 (0.8-1.1) 1.2 (0.9-1.6)	Men aged 40-75 yrs. RRs adjusted for age. Health Professional Follow-up Study.
Berndt et al[172] 2002 USA	454 Men 69 Cases	Animal Protein	1.1 (0.6-2.0)	Men aged 46 - 92 yrs. RRs adjusted for age & EI. Baltimore Longitudinal Study of Aging.
Augustsson et al[177] 2003 USA	47,882 men 2482 Non Stage A_1 cases	Fish All Adv	 0.9 (0.8-1.1) 0.8 (0.6-1.1)	Men aged 40-75 yrs RRs adjusted for age, EI, fat, lycopene, retinol, Vit D & physical activity Health Professionals Follow-up Study.

N.B
[$] Odds / Risk ratio for highest relative to lowest percentile, except where stated
[@] Odds / Risk ratios based on all PCa cases, except where stated
Hosp Ctrls = hospital controls, Pop Ctrls = population controls
EI = Energy Intake, PCa = prostate cancer, OR = Odds Ratio, RR = Rate Ratio, SES = Socio-economic status, FHPCa = Family history of PCa, All = All PCa, Adv = Advanced PCa only, Agg = Aggressive PCa only, Local = Localised PCa only.

3.3.6 Dairy products

Total Dairy products

The majority of the five case-control studies and four cohort studies that examined the association between total dairy product consumption and PCa reported no association[82;128;141;142;169;173], see Table 3.10. However, two studies by Chan et al[83;171] reported borderline significant positive associations between dairy products and PCa risk (OR 1.5, 95%C.I. 1.01-2.2[171] and OR 1.3, 95%C.I. 1.04-1.7[83]).

Four studies also examined the relationship between dairy product consumption and advanced PCa [128;169;171;173], two of which reported borderline significant positive associations (OR 1.6, 95%C.I. 1.0-2.6[171] and OR 1.4, 95%C.I. 1.0-1.8[173]).

Milk

Most of the five case-control studies, one nested case-control study and two cohort studies that examined the association between milk consumption and PCa reported a significant / borderline significant association (OR 2.5, 95%CI 1.3-4.9[178], OR 1.6, 95%C.I. 1.1-2.4[161], OR 1.4, 95%CI 1.0-1.9[174] and OR 1.6, 95%C.I. 1.2-2.1[96]), see Table 3.10. Mettlin et al[178] also examined semi-skimmed milk and skimmed milk consumption, a non-significant positive association and no association was observed respectively. Talamini et al[161] also reported borderline significant positive associations in younger (OR 1.7, 95%CI 1.0-2.8) and older men (OR 1.9, 95%CI 1.0-3.8), whereas Giovannucci et al[96] reported a significant positive association between milk consumption and advanced PCa (OR 1.8, 95%C.I. 1.2-2.8).

Other individual dairy items

The majority of the six case-control studies, one nested case-control study and four cohort studies reported no significant association between individual dairy items and PCa risk, with the exception of Jain et al[174] who reported a borderline significant negative association between cream and PCa risk (OR 0.8, 95%CI 0.7-1.0) and Hodge et al[141] who reported significant positive associations between PCa risk and eggs (OR 1.2, 95%CI 1.0-1.6) and margarine (OR 1.3, 95%CI 1.0-1.7). No studies investigated the association between individual dairy items and advanced PCa.

Table 3.10: Summary of results from epidemiological studies of dairy products and PCa

Study, year, location	Subjects	Food Items	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Case-Control Studies				
Mettlin et al[178] 1989 USA	371 Cases 371 Hospital Controls	Whole Milk 2% Fat Milk Skimmed Milk	2.5 (1.3-4.9) 1.5 (0.4-1.2) 0.9 (0.4-2.2)	ORs adjusted for age & residence.
Talamini et al[161] 1992 Italy	271 Cases 685 Hospital Controls	Milk All <70yrs ≥70yrs Cheese All <70yrs ≥70yrs Butter All <70yrs ≥70yrs Margarine All <70yrs ≥70yrs Eggs All <70yrs ≥70yrs	 1.6 (1.1-2.4) 1.7 (1.0-2.8) 1.9 (1.0-3.8) 1.1 (0.7-1.7) 0.8 (0.5-1.3) 0.9 (0.4-1.8) 0.9 (0.6-1.5) 0.7 (0.4-1.5) 1.7 (0.7-4.0) 1.1 (0.7-1.9) 1.0 (0.5-1.9) 1.1 (0.4-2.8) 1.1 (0.8-1.6) 1.3 (0.8-2.0) 0.8 (0.4-1.6)	Men aged 45 - 79 yrs. Stratified by age. ORs adjusted for age, residence, education and BMI.
Ewings et al[170] 1996 UK	159 Cases 161 BEP Controls 164 Hospital Controls	Total Milk Type of Milk: Skimmed Half Fat Full Fat Fresh Cream Eggs	0.95 (0.5-1.8) 1.0 (ref) 0.3 (0.1-0.7) 0.7 (0.4-1.2) 0.6 (0.2-1.8) 0.6 (0.2-1.8)	Adjusted ORs not presented as similar to crude ORs. Age matched.
Gronberg et al[176] 1996 Sweden	406 Cases 1218 Population Controls	Milk Eggs	0.8 (0.5-1.6) 0.9 (0.5-1.5)	ORs adjusted for age. Age matched. Data collected prospectively.
Chan et al[171] 1998 Sweden	526 Cases 536 Population Controls	Dairy All Adv	 1.5 (1.0-2.2) 1.6 (1.0-2.6)	Men aged < 80 yrs. ORs adjusted for EI, age, FHPCa & smoking. Age frequency matched.
Deneo-Pellegrini et al[130] 1999 Uruguay	175 Cases 233 Hospital Controls	Dairy Foods Eggs	0.8 (0.4-1.6) 1.4 (0.7-2.6)	Men aged 40-89 yrs. ORs adjusted for age, EI, BMI, education, residence & FHPCa.
Hayes et al[128] 1999 USA	932 Cases 1201 Population Controls	Dairy Foods All Adv	 1.2 (n/s) 1.4 (n/s)	Men aged 40-79 yrs. ORs adjusted for age & race, EI adjusted ORs not presented. Age frequency & race & region matched.

Cont.

Table 3.10, cont.: Summary of results from epidemiological studies of dairy products and PCa

Study, year, location	Subjects	Food Items	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Jain et al[174] 1999 Canada	617 Cases 636 Population Controls	Milk Cream Cheese Yoghurt Eggs	1.4 (1.0-1.9) 0.8 (0.7-1.0) 1.0 (0.7-1.4) 1.1 (0.8-1.3) 1.2 (0.9-1.7)	ORs adjusted for age & EI. Age frequency matched.
Tzonou et al[142] 1999 Greece	320 Cases 246 Hospital Controls	Dairy Products	1.1 (1.0-1.3)	ORs adjusted for EI & age. Age frequency matched.
Hodge et al[141] 2004 Austrailia	858 Cases 905 Pop Ctrls Cases ≥ gleason score 5	Dairy Butter Margarine Eggs	1.0 (0.8-1.3) 1.0 (0.7-1.2) 1.3 (1.0-1.7) 1.2 (1.0-1.6)	Men aged < 70 yrs ORs adjusted for: EI (residual), age, study centre, year, FHPCa, SES Age frequency matched
Nested Case-Control Studies				
Schuurman et al[94] 1999 Netherlands	642 Cases 1525 Controls from 58,279 Men	Milk Products Cheese Eggs	1.1 (0.8-1.6) 1.2 (0.9-1.7) 1.0 (0.8-1.2)	ORs adjusted for age, FHPCa & SES. Case - Cohort approach. Netherlands Cohort Study.
Cohort Studies				
Mills et al[165] 1989 USA	14,000 Men 180 Cases	Whole Milk Eggs	0.8 (0.5-1.2) 0.8 (0.5-1.2)	Men aged ≥ 25 yrs at baseline. RRs adjusted for age. 7th Day Adventist Men.
Severson et al[166] 1989 Hawaii	7,999 Men 174 Cases	Milk Butter & Cheese Eggs	1.0 (0.7-1.4) 1.5 (0.97-2.3) 1.6 (0.97-2.5)	RRs adjusted for age. Analysis omitting latent PCa not reported as similar to all cases.
Hsing et al[167] 1990 USA	17,633 Men 149 Fatal Cases	Dairy Products Eggs	1.0 (0.6-1.7) 0.9 (0.5-1.5)	RRs adjusted for age & tobacco use. Lutheran Brotherhood Cohort. PCa Mortality.
Le Marchand et al[168] 1994 Hawaii	20,316 Men 198 Cases	Milk Eggs	1.4 (1.0-2.1) 1.1 (0.7-1.6)	RRs adjusted for age, ethnicity & income.
Giovannucci et al[96] 1998 USA	47,781 Men 1414 Non Stage A_1 Cases	Milk All Adv	 1.6 (1.2-2.1) 1.8 (1.2-2.8)	Men aged 40-75 yrs at baseline. RRs adjusted for age, EI & BMI. Health Professional Follow-up Study.
Chan et al[82] 2000 Finland	27,062 Men 184 Clinically Apparent Cases	Dairy Products	1.1 (0.7-1.7)	Men aged 50-69 yrs at baseline. RRs adjusted for age, EI, intervention arm, smoking, education & BMI. Cohort study from the ATBC RCT study.

Cont.

Table 3.10, cont.: Summary of results from epidemiological studies of dairy products and PCa

Study, year, location	Subjects	Food Items	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Chan et al[83] 2001 USA	20,885 Men 1012 Cases	Dairy Products	1.3 (1.0-1.7)	Men aged 50-69 yrs at baseline. RRs adjusted for age, intervention arm, smoking, exercise & BMI. Cohort study from the Physicians Health study.
Michaud et al[173] 2001 USA	47,780 Men 1897 Non Stage A_1 Cases	Dairy Products All Adv	 1.0 (0.9-1.2) 1.4 (1.0-1.8)	Men aged 40-75 yrs. RRs adjusted for age. Health Professional Follow-up Study.
Berndt et al[172] 2002 USA	454 Men 69 Cases	Milk Only Milk, Cheese & Yogurt	1.2 (0.6-2.5) 1.3 (0.6-2.8)	Men aged 46 - 92 yrs. RRs adjusted for age & EI. Baltimore Longitudinal Study of Aging.
Rodrigugez et al[169] 2003 USA	65,321 men 3811 cases	Dairy All Adv	 1.1 (0.9-1.3) 0.9 (0.5-1.4)	Men aged 50-74 yrs RRs adjusted for EI, education, FHPCa & fat CPS-II Nutrition Cohort

N.B
[$] Odds / Risk ratio for highest relative to lowest percentile, except where stated
[@] Odds / Risk ratios based on all PCa cases, except where stated
Hosp Ctrls = hospital controls, Pop Ctrls = population controls, n/s = non-significant,
EI = Energy Intake, PCa = prostate cancer, OR = Odds Ratio, RR = Rate Ratio, SES = Socio-economic status, FHPCa = Family history of PCa, All = All PCa, Adv = Advanced PCa only, Agg = Aggressive PCa only, Local = Localised PCa only.

3.3.7 Calcium intake

All of the five case-control studies, one nested case-control study and three cohort studies that examined the association between calcium intake and PCa found no significant association, see Table 3.11, with the exception of Chan et al[171] and Giovannucci et al[96] who reported significant positive associations between calcium and PCa risk (OR 1.9, 95%C.I. 1.2-3.0[171] and OR 1.7, 95%C.I. 1.2-2.5[96]).

Five studies also examined the relationship between calcium intake and advanced PCa. The majority of these studies observed significant / borderline significant positive associations (OR 2.1, 95%C.I. 1.3-3.6[171], OR 2.1, 95%C.I. 1.0-4.4[136] and OR 3.0, 95%C.I. 1.6-5.5[96]).

Table 3.11: Summary of results from epidemiological studies of calcium intake and PCa

Study, year, location	Subjects	Intake Variable	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Case-Control Studies				
Chan et al[171] 1998 Sweden	526 Cases 536 Population Controls	Calcium All Adv	 1.9 (1.2-3.0) 2.1 (1.3-3.6)	Men aged < 80 yrs. ORs adjusted for EI, age, FHPCa & smoking. Age frequency matched.
Hayes et al[128] 1999 USA	932 Cases 1201 Population Controls	Calcium All Adv	 0.9 (n/s) 0.9 (n/s)	Men aged 40-79 yrs. ORs adjusted for age & race, EI adjusted ORs not presented. Age frequency & race & region matched.
Tzonou et al[142] 1999 Greece	320 Cases 246 Hospital Controls	Calcium	1.2 (0.9-1.7)	ORs adjusted for EI & age. Age frequency matched.
Ramon et al[135] 2000 Spain	217 Cases 434 Hospital & Population Controls	Calcium	0.7 (0.5-1.1)	Men aged ≤ 80 yrs. ORs adjusted for age, EI, BMI, FHPCa & residence. Age frequency & region matched.
Tavani et al[164] 2001 Italy	288 Cases 762 Hospital Controls	Calcium	1.2 (0.8-1.9)	Men aged < 79yrs. ORs adjusted for age, BMI, education & meat intake.
Kristal et al[136] 2002 USA	605 Cases 592 Population Controls	Calcium Local Adv	 1.1 (0.6-1.8) 2.1 (1.0-4.4)	Men aged 40-64yrs. ORs adjusted for EI, age race FHPCa, education, BMI, PSA testing. Age frequency matched.
Nested Case-Control Studies				
Schuurman et al[94] 1999 Netherlands	642 Cases 1525 Controls from 58,279 Men	Calcium All Adv	 1.1 (0.8-1.5) 0.8 (0.5-1.3)	ORs adjusted for age, FHPCa & SES. Case - Cohort approach. Netherlands Cohort Study.

Cont.

Table 3.11, cont. : Summary of results from epidemiological studies of calcium intake and PCa

Study, year, location	Subjects	Intake Variable	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Cohort Studies				
Giovannucci et al[96]	47,781 Men	Calcium All	1.7 (1.2-2.5)	Men aged 40-75 yrs at baseline. RRs adjusted for age, EI & BMI.
1998	1414 Non Stage	Adv	3.0 (1.6-5.5)	Health Professional Follow-up
USA	A_1 Cases			Study.
Chan et al[82]	27,062 Men	Calcium	1.1 (0.7-1.8)	Men aged 50-69 yrs at baseline.
2000		Calcium	1.6 (0.8-3.0)	RRs adjusted for age, EI,
Finland	184 Clinically Apparent Cases	(controlling for Phosphorus)		intervention arm, smoking, education & BMI. Cohort study from the ATBC RCT study.
Chan et al[83]	20,885 Men	Calcium	1.3 (1.1-1.6)	Men aged 50-69 yrs at baseline.
2001				RRs adjusted for age,
USA	1012 Cases			intervention arm, smoking, exercise & BMI. Cohort study from the Physicians Health study.
Berndt et al[172]	454 Men	Calcium	0.9 (0.5-1.8)	Men aged 46 - 92 yrs.
2002				RRs adjusted for age & EI.
USA	69 Cases			Baltimore Longitudinal Study of Aging.
Rodrigugez et al[169]	65,321 men	Calcium All	1.4 (1.1-2.0)	Men aged 50-74 yrs RRs adjusted for age, EI,
2003	3811 cases	Adv	1.7 (0.8-3.5)	education, FHPCa, race & fat
USA				CPS-II Nutrition Cohort

N.B
[$] Odds / Risk ratio for highest relative to lowest percentile, except where stated
[@] Odds / Risk ratios based on all PCa cases, except where stated
Hosp Ctrls = hospital controls, Pop Ctrls = population controls, n/s = non significant
EI = Energy Intake, PCa = prostate cancer, OR = Odds Ratio, RR = Rate Ratio, SES = Socio-economic status, FHPCa = Family history of PCa, All = All PCa, Adv = Advanced PCa only, Agg = Aggressive PCa only, Local = Localised PCa only.

3.3.8 Retinol

All of the seven case-control studies, one nested case-control study and one cohort study that examined the association between retinol intake and PCa reported no significant association, with the exception of Giovannucci et al[8] who reported a significant positive association (OR 1.3, 95%C.I. 1.0-1.7), see Table 3.12. Three case-controls studies also examined vitamin A intake (i.e. the combined intake of retinol and pro-vitamin β-carotene) all of which reported no significant associations[131;133;137].

Andersson et al[131] and Schuurman et al[95] also examined the relationship between retinol / vitamin A intake and advanced PCa, as with the findings for the total PCa cases, no significant associations were observed.

Table 3.12: Summary of results from epidemiological studies of vitamin A and retinol intake and PCa

Study, year, location	Subjects	Intake Variable	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Case-Control Studies				
Rohan et al[137] 1995 Canada	207 Cases 207 Pop Controls	Retinol Vitamin A	0.7 (0.4-1.2) 0.7 (0.4-1.3)	ORs adjusted for age, EI & FHPCa. Age frequency matched.
Andersson et al[131] 1996 Sweden	526 Cases 536 Pop Controls	Retinol All Adv Vitamin A All Adv	 1.3 (0.9-1.8) 1.3 (0.9-1.9) 1.3 (0.9-1.8) 1.4 (0.9-2.0)	Men aged < 80 yrs. ORs adjusted for age & EI. Age frequency matched.
Ghadirian et al[138] 1996 Canada	232 Cases 231 Pop Controls	Vitamin A Retinol	0.9 (0.5-1.6) 0.8 (0.5-1.3)	Men aged 35-84 yrs. ORs adjusted for age, EI & FHPCa. Age frequency & residence matched.
Key et al[132] 1997 England	328 Cases 328 Pop Controls	Retinol	0.9 (0.6-1.3)	Men aged <75 yrs. ORs adjusted for SES. Age frequency matched.
Meyer et al[133] 1997 Canada	215 Incidental Cases 593 Hosp Controls	Vitamin A	1.0 (0.5-2.0)	Men aged ≥ 45 yrs. ORs adjusted for age, EI, study group, FHPCa & education.
Jain et al[174] 1999 Canada	617 Cases 636 Pop Controls	Retinol	1.0 (0.8-1.4)	ORs adjusted for age, EI, smoking, vasectomy, BMI, education & other nutrients. Age frequency matched.
Ramon et al[135] 2000 Spain	217 Cases 434 Hosp / Pop Controls	Retinol	1.2 (0.9-1.6)	Men aged ≤ 80 yrs. ORs adjusted for age, EI, BMI, FHPCa, residence & fat intake. Age frequency & region matched
Hodge et al[141] 2004 Austrailia	858 Cases (≥ gleason score 5) 905 Pop Ctrls Cases	Retinol	1.1 (0.8-1.5)	Men aged < 70 yrs ORs adjusted for: EI (residual), age, study centre, year, FHPCa, SES Age frequency matched

Cont.

Table 3.12, cont. : Summary of results from epidemiological studies of vitamin A and retinol intake and PCa

Study, year, location	Subjects	Intake Variable	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Nested Case-Control Studies				
Schuurman et al[95] 2002 Netherlands	642 Cases 1525 Controls from 58,279 Men	Retinol All Adv	 1.0 (0.7-1.3) 0.9 (0.5-1.4)	Men aged 55-69 yrs at baseline. RRs adjusted for age, SES, FHPCa & alcohol. EI & fat adjusted RRs not reported as EI & fat was shown not to be associated with PCa. Nested case-cohort study from Netherlands Cohort Study.
Cohort Studies				
Giovannucci et al[8] 1995 USA	47894 men 773 Non Stage A_1 Cases	Retinol	1.3 (1.0-1.7)	Men aged 40-75 yrs at baseline. RRs adjusted for age & EI. Adv PCa analysis: results not reported as similar to all cases. Health Professionals Follow-up study.

N.B
[$] Odds / Risk ratio for highest relative to lowest percentile, except where stated
[@] Odds / Risk ratios based on all PCa cases, except where stated
Hosp Ctrls = hospital controls, Pop Ctrls = population controls
EI = Energy Intake, PCa = prostate cancer, OR = Odds Ratio, RR = Rate Ratio, SES = Socio-economic status, FHPCa = Family history of PCa, All = All PCa, Adv = Advanced PCa only, Agg = Aggressive PCa only, Local = Localised PCa only.

3.3.9 Discussion

The evidence gathered from this systematic literature review is consistent with previous reviews and suggests that some animal products, in particular meat, red meat and milk play important roles in the aetiology of PCa. However, no strong evidence for an affect of either of the reported associated nutrients or cooking methods and heterocyclic amines on PCa risk was found, although the evidence does suggest that high calcium intake is associated with advanced PCa. Furthermore, several possible biological mechanisms that demonstrate a carcinogenic effect of meat and dairy product constituents other than animal fat have been proposed.

With the exception of calcium and retinol, the compounds in animal products, other than animal fat, that are responsible for this association remain largely unknown. It is therefore important that further study of these animal products and their components, including the covariance with other dietary factors such as vegetables and plant-based nutrient, is done. This should not only be in the form of epidemiological studies, but also laboratory and animal model studies that will allow us greater understanding of the components and biological mechanisms involved, in particular the suggested role of heterocyclic amines and polycyclic aromatic hydrocarbons and the vitamin D metabolic pathway.

3.4 Fruits and vegetables and their associated nutrients

3.4.1 Introduction

The consumption of fruit and vegetables is generally seen as health promoting and has been recommended over the years in the prevention of many diseases including cancer. There are many biologically plausible reasons for the suggested protective role that fruit and vegetable intake plays in the aetiology of cancer. These include the presence in such foods of potentially active anticarcinogenic nutrients, antioxidants and phytochemicals such as the carotenoids, vitamin E, vitamin C, phyto-oestrogens and selenium. However, despite many recent studies, their specific role and that of their components in PCa aetiology still remains unclear. As fruit and vegetable consumption has been discussed previously in Chapter 2, this section will concentrate on the background of the types of vegetables and the nutrients found in fruit and vegetables, including their role in PCa aetiology in addition to a systematic review of the literature.

3.4.2 Types of vegetables and fruits

Vegetables can be grouped into several categories, including cruciferous vegetables (also known as brassicas and include broccoli, cauliflower and Brussels sprouts), Allium vegetables (onions, garlic, chives and leeks) and leafy green vegetables (spinach and lettuce). Whereas fruits tend to be grouped together, with the exception of citrus fruits (oranges, grapefruits and lemons). The role that fruit and vegetables play in the aetiology of PCa has been suggested to vary according to type, as the kind and amount of individual plant-based nutrients tend to vary across these fruit and vegetable types.

3.4.3 Soy Foods

Soy / soya foods, although not exactly a vegetable or fruit have been included in this section for simplicity. Soy foods, as the name suggests, are made from soya beans that are the seeds of the leguminous soya bean plant. Soy foods include tofu, tempeh, textured vegetable protein, miso, soya sauces, soya oil and margarine, and soya dairy alternatives. They are a source of non-animal protein, making them a suitable

alternative to animal products, and contain phyto-oestrogens which are bio-active compounds that may have possible anti-carcinogenic activity, see section 3.4.8.

3.4.4 Carotenoids

Carotenoids are fat-soluble pigments synthesised by plants and are widespread in nature, with over 600 different types of carotenoids have been identified. They can be classified into two main groups: Carotenes, which include α-carotene, β-carotene and lycopene; and Xanthophylls, which include lutein, zeaxanthin and β-cryptoxanthin[179]. The specific carotenoids mentioned above account for the majority of carotenoid dietary intake and are found in detectable concentrations in human blood and tissues[180].

β-carotene is the most abundant carotenoid and is found in orange vegetables and fruits, such as carrots, pumpkins and melons, and in dark green leafy vegetables. Carrots are also a rich source of α-carotene, along with avocados, whereas lycopene is found in tomatoes and tomato products. The predominant carotenoids in spinach, kale and other greens are the xanthophylls, especially lutein, whilst cryptoxanthin is found in large amounts in red peppers and pumpkins.

As summarised in Table 3.13, the average daily intake of carotenes (from food sources only, β-carotene equivalents) in the UK is 2041μg and 2128μg for men aged 19-64 years in the UK and Scotland respectively[47], whereas daily carotene intake in men aged ≥ 65 years is 1951μg and 1948μg in the UK and Scotland respectively[105]. In the USA mean daily carotene intakes (expressed as retinol equivalents) were estimated at 544μg and 632μg for men aged ≥ 20 years and ≥ 70 years respectively[106]. In China, mean daily intake of carotenoids in men was estimated to be 1600μg[107], whilst in other parts of Asia, the average daily consumption of β-carotene is estimated to be about 3300μg/day[42].

Unlike other carotenes, β-carotene is a precursor to vitamin A known as pro-vitamin A. Along with pre-formed retinol, it is metabolised by the body to form retinol / vitamin A, due to this β-carotene is sometimes measured in retinol equivalents (the sum of vitamin A provided by preformed retinol and carotenoids[1]). Evidence from

the early epidemiological studies investigating an inverse association between vitamin A intake and cancer including PCa reported this association to be stronger for dietary carotenoids than for preformed retinol[98;154]. This gave rise to the hypothesis that β-carotene, along with the other carotenoids, may be a protective dietary factor in its own right, and not simply as a precursor of retinol (a nutrient essential for normal growth of the prostate)[181].

Carotenoids act as antioxidants in tissues by deactivating free radicals and protecting cells from oxidative damage[42]. Other possible anti-carcinogenic effects of carotenoids may derive from their influence on immune function and growth regulation mediated by gap-junction communication[179].

In recent years, research has begun to focus on other carotenoids, especially lycopene which has been specifically hypothesed to be protective against PCa[8]. As more accurate and complete data on the content of carotenoids in foods has become available over recent years, epidemiologists have been able to examine the relationship between these individual carotenoids and the risk of PCa.

Table 3.13: Average daily nutrient intakes, from various dietary consumption data:

Nutrient	Gregory et al, 1990[53] men only (16-64 yrs)		Henderson et al, 2003[47] men only (19-64 yrs)		Finch et al, 1998[105] men only (≥ 65yrs)		MAFF Nation Food Survey, 2000[48] men & women, all ages		USDA, 1997[106] men only		Chen et al, 1993[107] men only (18-45 yrs)
	UK (low – high 2.5%)	Scotland (SE)	UK (low – high 2.5%)	Scotland & North (SD)	UK (low – high 2.5%)	Scotland & North (SD)	UK	Scotland	≥20yrs	≥ 70 yrs	
Carotenes (μg)	2414 (247-7563)	2146 (220)	2041 [1] (322-5750)	2128[1] (2041)	1951 [1] (222-5760)	1948 [1] (1289)	n/a	n/a	544[2]	632[2]	n/a
β-carotene (μg)	n/a	n/a	1858 (301-5031)	n/a	1753 (221-5004)	n/a	1690	1490	n/a	n/a	n/a
Vitamin E (mg)	9.9 (3.5-19.5)	10.0 (1.15)	10.6 [3] (4.0-21.8)	11.4 [3] (7.04)	9.0 (2.7-22.0)	9.4 (5.7)	9.98	8.87	9.9[2]	8.6[2]	8.9
Vitamin C (mg)	66.5 (19.1-170.9)	64.9 (5.0)	83.4 (20.8-216.8)	86.4 (54.11)	66.9 (12.1-176.9)	60.3 (36.4)	59	49	109	101	n/a
Selenium (μg)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	129.6	100.9	42.3

N.B.
[1] β-carotene equivalent
[2] retinol equivalents
[3] α-tocopherol equivalents
n/a = not available

3.4.5 Vitamin E

Vitamin E is a fat-soluble vitamin, which occurs naturally in the form of several compounds including α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol and the tocotrienols. α-tocopherol is the most biologically active of these components and is also the most common source of vitamin E in food[182]. The major dietary source of vitamin E are vegetable oils and margarines, other sources include nuts, whole grains, seeds and green vegetables, such as asparagus and lettuce. As summarised in Table 3.13, the average daily intake of vitamin E (from food sources only) in the UK is 10.6mg and 9.0mg for men aged 19-64 years[47] and ≥ 65 years[105] respectively, where as in Scotland the average daily intake of vitamin E is slightly higher at 11.4mg and 9.4mg for men aged 19-64 years[47] and ≥ 65 years[105] respectively. This is similar to that observed in other Western Countries, especially the US[106] and also Far Eastern countries such as China, although intake is reported to vary widely by region[107].

Vitamin E has been hypothesised to protect against chronic disease, including cancer, due to its strong antioxidant properties and positive effects on immune function. A major function of vitamin E involves its role as an intracellular antioxidant, preventing oxidative damage to cell membrane lipids and also DNA damage[42].

Interest in the potential protective effects of vitamin E first arose from the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study[183]. This RCT, although designed primarily to test the hypothesis that vitamin E and β-carotene would reduce lung cancer risk, reported a negative association between the risk of PCa and the intake of vitamin E, thereby generating the hypothesis that vitamin E is protective against PCa[183]. Recently, γ-tocopherol has been suggested to have a similar if not stronger protective effect against PCa as α-tocopherol[85].

3.4.6 Vitamin C

Vitamin C, also known as ascorbic acid, is a water soluble vitamin found in vegetables, such as broccoli, cabbage, potatoes and fruits, especially citrus fruits. As summarised in Table 3.13, the average daily intake of vitamin C (from food sources

only) in the UK is 83.4mg and 66.9mg for men aged 19-64 years[47] and ≥ 65 years[105] respectively, where as in Scotland the average daily intake of vitamin E is 86.4mg and 60.3mg for men aged 19-64 years[47] and ≥ 65 years[105] respectively. These intakes are far smaller than in the US where mean daily vitamin C intakes were estimated at 109mg and 101mg for men aged ≥ 20 years and ≥ 70 years respectively[106].Vitamin C is a strong anti-oxidant and protects against damage from free radicals. It has also been observed to inhibit the growth of PCa cells *in vitro* by creating reactive oxygen species that kill these tumor cells[184].

3.4.7 Selenium

Selenium is an essential non-metal trace element that occurs in foods such as grains, fish, meat and dairy products, mainly as organic compounds having entered the food-chain through plants. Selenium levels in foods are largely dependent on the soil content in the region in which the original plant foods were grown. Hence dietary selenium intake varies substantially across populations. In Southern England, the average daily intake of selenium in a group of elderly men and women was reported as being approximately 65μg[185]. N.B. The National Diet and Nutrition Surveys [47;105;145] did not estimate selenium intake. In the US, the average daily intake of selenium is 129.6μg and 100.9μg for men aged ≥ 20 years and ≥ 70 years respectively[106], whilst in China the average daily intake of selenium is only 42.3μg[107], see Table 3.13. UK selenium intake has declined by about 50% since the UK joined the EU in the 1970s which caused imports of high-selenium North American wheat to be replaced with low-selenium European Union (EU) wheat[186].

Selenium has antioxidant properties and has been demonstrated to inhibit proliferation of malignant cells and tumour growth in *in-vitro* and *in-vivo* studies[187]. Selenium is a cofactor for the antioxidant enzyme glutathione peroxidase, which protects DNA and cell membranes from peroxide damage[187]. Selenium is also needed for normal testosterone metabolism[186].

Until recently, there had been only sparse data on selenium intake and risk of PCa. Current interest in the protective effect of selenium on PCa arose from the findings

of the National Prevention of Cancer Trial[188]. This RCT, although primarily designed to examine the affect of selenium on the re-occurrence of non-melanoma skin cancer, reported an inverse association between selenium supplementation and PCa risk, thereby generating the hypothesis that selenium is protective against PCa.

3.4.8 Phyto-oestrogens

Foods of plant origin contain many bioactive compounds in addition to those micronutrients and minerals discussed above. These include a group of polyphenolic, phytochemical compounds called the phyto-oestrogens. As the name suggests these are chemicals found in plants that possess a oestrogenic affect (albeit a weak one). There are two main groups of phyto-oestrogens: The isoflavones, which include daidzein and genistein and their respective metabolites, equol and p-ethylphenol; and the lignans, the plant precursors of which, matairesinol (MAT) and secoisolariciresinol (SECO) are metabolised after ingestion by intestinal bacteria into the lignan mammalian forms of enterolactone and enterodiol respectively.

Isoflavones are found mainly in soya beans in the form of glycoside conjugates, the content of which varies depending on the time and location of the harvest, as well as the variety of the soya bean itself[73;189;190]. Lignans, in the form of their precursors, are found in a wide variety of plant foods, including cereals, grains, fruits and vegetables, the richest source being linseed[191;192].

Phyto-oestrogens have numerous biological properties including antiviral, anti-angiogenic and antioxidant properties. As reviewed by Griffiths et al[193], phyto-oestrogens possess weak oestrogenic activity, in which they compete with oestradiol for binding to the nuclear oestrogen receptor and also stimulate the synthesis of sex hormone binding globulin (SHGB) which in turn mediates the plasma levels of testosterone for which the growth, development, maintenance and function of the prostate gland is dependant on. Phyto-oestrogens can also inhibit steroid metabolising enzymes, including: 5α-reductase, Aromatase and also Tyrosine-specific protein kinases, which are necessary for the function of several growth factor receptors.

The observation that Chinese and Japanese populations, that consume relatively large amounts of soya, have relatively low rates of clinical PCa compared to western countries has led to the generation of the hypothesis that phyto-oestrogens are protective against PCa[194]. However, up until recently relatively few studies have examined this association. Although new developments in high-performance liquid chromatography (HPLC), allowing greater accuracy in the determination of phyto-oestrogen levels in both food and body fluids such as blood and urine, has allowed for more studies to be undertaken to test this hypothesis.

At present, several published food composition tables for phyto-oestrogens are available [71;189;190;192;195-197], however these tables are far from complete, in particular for the lignan precursors, and have the additional caveats of variations of phyto-oestrogen levels in foods not only due to the variation of soya content in soya-based foods (which is often hidden) and processing methods, but also due to variety and location of soya bean harvests[73;74].

3.4.9 Literature review

The following section will discuss the findings of recent studies investigating the effect of fruit and vegetables and their associated nutrients on PCa risk.

Review papers and meta-analyses

Several recent papers have reviewed the association between PCa and fruit and vegetable consumption and the intake of associated nutrients[184;198;199]. Although the majority of these reviews discussed in depth the available evidence, not one of them gave a systematic and complete review of all studies. The consensus among these reviews was that there is reasonable, though inconsistent, evidence for a protective effect of vegetables and some of its associated nutrients, such as lycopene, vitamin E, selenium and phyto-oestrogens, whereas fruit consumption and vitamin C is not substantially related to PCa risk. To date, only one meta-analysis has been undertaken to examine the effect of tomato product and lycopene intake on PCa risk[104], for which combined relative risks of eleven case-control studies and ten cohort studies / nested case-control studies were 0.89 (95%CI 0.80-1.00) and 0.81 (95%CI 0.71-0.92) for raw and cooked tomato products respectively; whereas the combined relative risk for lycopene intake was 0.89 (95%CI 0.81-0.98).

A total of forty-nine analytical epidemiological studies have been identified that examine the association between fruit and vegetables and plant-based nutrients and PCa. Of these, twenty were omitted from the literature review for not fulfilling the methodology criteria, see Table 3.14. An additional two studies that examined both fruit and vegetables and their associated nutrients, were omitted from the review of the plant-based nutrients, but were included in the food group review due to not fulfilling the diet assessment and food table criteria which is an important criteria for nutrient analyses but not so for food group analyses. The remaining studies included nineteen case-control studies, two nested case-control studies and seven cohort studies.

Table 3.14: Methodology criteria and omitted studies

	Criteria	Studies not fulfilling criteria and which were subsequently omitted from review
1.	Study size appropriate for study design, statistical power and/or diet assessment method.	Ohno et al, 1988[119] Oishi et al, 1988[154] Bravo et al, 1991[120] Negri et al, 1991[200] Vlajinac et al, 1997[122] Lee et al, 1998[123] Rao et al, 1999[201] Lu et al, 2001[162] Daviglus et al, 1996[202] Parker et al, 1999[203]
2.	PCa cases histologically or pathologically confirmed.	Ross et al, 1987[124] Knekt et al, 1990[204] Shibata et al, 1992[205] Daviglus et al, 1996[202]
3.	Use of validated dietary assessment method.	Kolonel et al, 1987[163] Ross et al, 1987[124] Kolonel et al, 1988[126] Ohno et al, 1988[119] Oishi et al, 1988[154] Mettlin et al, 1989[178] Bravo et al, 1991[120] Le Marchand et al, 1991[206] Negri et al, 1991[200] West et al, 1991[98] Vlajinac et al, 1997[122] Lee et al, 1998[123] Hayes et al, 1999[128] (carotenoid intake only) Lu et al, 2001[162] Mills et al, 1989[165] Severson et al, 1989[166] Hsing et al, 1990[167] Shibata et al, 1992[205] Le Marchand et al, 1994[168] Parker et al, 1999[203]
4.	Dietary assessment method contains an appropriate number of food items to estimate nutrient intake accurately.	Ross et al, 1987[124] Ohno et al, 1988[119] Oishi et al, 1988[154] Mettlin et al, 1989[178] Bravo et al, 1991[120] Le Marchand et al, 1991[206] Negri et al, 1991[200] Deneo-Pellegrini et al, 1999[130] (carotenoid intake only) Hayes et al, 1999[128] (carotenoid intake only) Lu et al, 2001[162] Mills et al, 1989[165] Severson et al, 1989[166] Hsing et al, 1990[167] Shibata et al, 1992[205] Le Marchand et al, 1994[168] Parker et al, 1999[203]

Cont.

Table 3.14, cont.: Methodology criteria and omitted studies

	Criteria	Studies not fulfilling criteria and which were subsequently omitted from review
5.	Nutrient intake individually calculated using accurate, complete and internationally recognised food composition tables.	Kolonel et al, 1987[163] Ross et al, 1987[124] Mettlin et al, 1989[178] Bravo et al, 1991[120] Le Marchand et al, 1991[206] Negri et al, 1991[200] Deneo-Pellegrini et al, 1999[130] (carotenoid intake only) Mills et al, 1989[165] Severson et al, 1989[166] Shibata et al, 1992[205] Le Marchand et al, 1994[168] Daviglus et al, 1996[202] Parker et al, 1999[203]
6.	ORs / RRs adjusted for energy intake (or an equivalent judgement of energy intake, i.e. BMI, height, weight).	Kolonel et al, 1987[163] Ross et al, 1987[124] Kolonel et al, 1988[126] Ohno et al, 1988[119] Oishi et al, 1988[154] Mettlin et al, 1989[178] Bravo et al, 1991[120] Le Marchand et al, 1991[206] Negri et al, 1991[200] Mills et al, 1989[165] Severson et al, 1989[166] Hsing et al, 1990[167] Shibata et al, 1992[205] Le Marchand et al, 1994[168]
8.	ORs / RRs adjusted for age.	Ross et al, 1987[124] Oishi et al, 1988[154] Bravo et al, 1991[120] Vlajinac et al, 1997[122] Lee et al, 1998[123] Knekt et al, 1990[204]

Fruit and vegetable consumption

A total of twenty studies have examined the association between the intake of plant-based foods and PCa, see Table 3.15.

The majority of the seven case-control studies, one nested case-control study and two cohort studies that examined the effect of total vegetables on PCa risk reported inverse associations, of which three were shown to be significant / borderline significant (OR 0.9, 95%CI 0.5-0.9[207], OR 0.7, 95%CI 0.6-1.0[208] and OR 0.7, 95%CI 0.5-1.0[141]). Whereas for fruit consumption, including citrus fruit, most of the eight case-control studies, one nested case-control studies and two cohort studies reported positive associations including four shown to be significant the ORs of which ranged from 1.3 (95%CI 1.0-1.8)[92] and 1.5 (95%CI 1.1-2.0)[174]. It is therefore hardly surprising that two studies examining combined fruit and vegetable consumption reported no association[209;210]. Two studies also examined the association between vegetable and fruit consumption and advanced PCa, Hayes et al[128] continued to report no association, whereas Kolonel et al[208] reported a borderline significant inverse association for total vegetables (OR 0.7, 95%CI 0.5-1.0), but no association with total fruits.

Cruciferous / brassica vegetables

Six studies also investigated the association between cruciferous / brassica vegetables and PCa risk, two of which reported a significant inverse association (OR 0.5, 95%CI 0.4-0.8[207] and OR 0.8, 95%CI 0.6-1.0[208]). Kolonel et al[208] also reported a significant association with advanced PCa (OR 0.6, 95%CI 0.4-0.8), whereas Giovannucci et al[209] reported no association.

Allium vegetables

Four case-control studies investigated the association between allium vegetables and PCa risk, the majority of which reported significant inverse associations, two of which were significant (ORs 0.5, 95%CI 0.3-0.8)[211] and 0.7, 95%CI 0.5-0.9[141]). Hsing et al[211] also examined individual types of alliums, significant inverse associations were reported for garlic (OR 0.5, 95%CI 0.3-0.7) and scallions (OR 0.3,

95%CI 0.2-0.5), significant inverse associations were also reported for advanced PCa.

Leafy green / green vegetables

The most of the eight studies that examined leafy green / green vegetables reported no significant associations, with the exception of Jain et al[174] and Key et al[132] who reported significant inverse associations with green vegetables (OR 0.5, 95%CI 0.4-0.7) and peas (OR 0.4, 95%CI 0.1-0.9) respectively.

Tomatoes and tomato products

Many of the eight case-control studies and two cohort studies reported significant inverse associations with both tomatoes and tomato products, RRs of which ranged from 0.6 (95%CI 0.5-0.9)[174] to 0.8 (95%CI 0.6-0.9)[97]. These associations were also reported in advanced PCa (ORs 0.5, $p<0.05$[128], 0.5, 95%CI 0.2-1.0[8] and 0.7, 95%CI 0.4-1.0[97]).

Soy foods

Inverse associations were reported in all four studies that examined soy products, the majority of which were significant (OR range: 0.3, 95%CI 0.1-0.9[212] to 0.6, 95%CI 0.4-0.9[208])

Other individual vegetable items

Significant inverse associations were also reported for baked beans (OR 0.5, 95%CI 0.3-0.8[132]), legumes (OR 0.7, 95%CI 0.5-0.9[174]) and carrots (OR 0.7, 95%CI 0.5-1.0[207] and OR 0.6, 95%CI 0.5-0.8[208]).

Table 3.15: Summary of results from epidemiological studies of fruits and vegetables and PCa

Study, year, location	Subjects	Food Group	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Case-Control Studies				
Talamini et al[161] 1992 Italy	271 Cases 685 Hosp Controls	Total Vegetables Total Fruit	1.4 (0.9-2.2) 1.4 (1.0-2.1)	Men aged 45-79 yrs. ORs adjusted for age, education, residence & BMI.
Ewings et al[170] 1996 UK	159 Cases 161 BEP Controls 164 Hosp Controls	Carrots Leafy Green Veg Peas & Beans	1.2 (0.3-4.5) 0.4 (0.1-1.5) 1.1 (0.2-7.5)	Adjusted ORs not presented as similar to crude ORs. Age matched.
Key et al[132] 1997 England	328 Cases 328 Pop Controls	Carrots Leafy Green Veg Onions Garlic Raw Tomatoes Cooked Tomatoes Green Beans Peas Baked Beans Citrus Fruit	0.8 (0.4-1.4) 1.2 (0.8-1.9) 0.9 (0.5-1.5) 0.6 (0.4-1.1) 1.1 (0.6-1.6) 0.9 (0.6-1.4) 0.7 (0.4-1.1) 0.4 (0.1-0.9) 0.5 (0.3-0.8) 1.5 (0.8-2.5)	Men aged <75 yrs ORs adjusted for SES. Age frequency matched.
Deneo-Pellegrini et al[130] 1999 Uruguay	175 Cases 233 Hosp Controls	Fruit & Vegetables Vegetables Fruit Legumes Tubers	0.5 (0.3-0.9) 0.6 (0.3-1.1) 0.8 (0.4-1.4) 1.1 (0.6-1.9) 1.6 (0.8-3.1)	Men aged 40-89 yrs. ORs adjusted for age, EI, residence, FHPCa & BMI.
Hayes et al[128] 1999 USA	932 Cases 1201 Pop Controls	Vegetables All Adv Fruit All Adv Raw Tomatoes All Adv Cooked Tomatoes All Adv	 1.0 1.1 1.1 1.0 0.8 0.5 (p<0.05) 1.3 1.6	Men aged 40-79 yrs. ORs adjusted for age & race. Age frequency, race & region matched. 95% C.I.s not reported, ORs non significant unless stated.
Jain et al[174] 1999 Canada	617 Cases 636 Pop Controls	Total Vegetables Total Fruit Green Vegetables Cruciferous Tomatoes Legumes Citrus Fruit	1.0 (0.7-1.3) 1.5 (1.1-2.0) 0.5 (0.4-0.7) 0.9 (0.6-1.1) 0.6 (0.5-0.9) 0.7 (0.5-0.9) 1.5 (1.1-2.0)	ORs adjusted for age, EI, smoking, vasectomy, BMI & education. Age frequency matched.
Villeneuve et al[134] 1999 Canada	1623 Cases 1623 Pop Ctrls	Total Fruit Total Vegetables Yellow Green Veg Cruciferous Tomatoes Lentils & baked beans Tofu or Soybean	1.5 (1.1-1.9) 1.0 (0.8-1.3) 1.1 (0.7-1.6) 0.9 (0.7-1.1) 1.0 (0.7-1.3) 1.0 90.7-1.4) 0.8 (0.6-1.1)	Men aged 50-74 yrs. ORs adjusted for age, residence, smoking, BMI, other food grps, income & FHPCa. Age frequency matched.

Cont.

Table 3.15, cont.: Summary of results from epidemiological studies of fruits and vegetables and PCa

Study, year, location	Subjects	Food Group	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Cohen et al [207]	628 Cases	Tot Vegetables	0.7 (0.45-0.9)	Men aged 40-64 yrs.
	602 Pop	Tot Fruit	1.1 (0.7-1.6)	ORs adjusted for age, EI, race,
2000	Controls	Green Leafy Veg	0.8 (0.4-1.7)	PSA screening, FHPCa, BMI &
USA		Cruciferous	0.5 (0.4-0.8)	education.
		Carrots	0.7 (0.5-0.96)	Age frequency matched.
		Beans	0.7 (0.4-1.2)	
		Raw Tomatoes	0.9 (0.9-1.3)	
		Cooked Tomatoes	0.7 (0.5-1.1)	
		Citrus Fruit	0.9 (0.7-1.3)	
Kolonel et al [208]	1619 Cases	Total Vegetables		Men aged < 84 yrs.
	1618 Pop	All	0.7 (0.6-0.96)	ORs adjusted for age, EI, region,
2000	Controls	Adv	0.7 (0.5-0.96)	education & ethnicity.
Canada		Total Fruits		
Hawaii		All	1.0 (0.8-1.3)	
		Adv	1.1 (0.8-1.6)	
		Cruciferous		
		All	0.8 (0.6-1.0)	
		Adv	0.6 (0.4-0.8)	
		Yellow-orange Veg		
		All	0.8 (0.6-1.0)	
		Adv	0.7 (0.5-0.9)	
		Carrots		
		All	0.6 (0.5-0.8)	
		Adv	0.5 (0.4-0.7)	
		Tomatoes		
		All	1.1 (0.8-1.4)	
		Adv	1.1 (0.8-1.6)	
		Total Legumes		
		All	0.6 (0.5-0.8)	
		Adv	0.7 (0.5-1.1)	
		Soya Foods		
		All	0.6 (0.44-0.9)	
		Adv	0.6 (0.4-1.0)	
Norrish et al [213]	317 Cases	Leafy Green Veg	0.9 (0.6-1.3)	Men aged 40-80 yrs.
	480 Pop	Carrots	1.1 (0.7-1.7)	ORs adjusted for age & EI.
2000	Controls	Raw Tomatoes	1.0 (0.6-1.5)	Age frequency matched.
New		Tomato Based Foods	0.8 (0.5-1.2)	
Zealand				Adv PCa analysis: results not reported as similar to all cases.
Hsing et al [211]	238 Cases	Allium vegetables		Men aged ≥ 16 yrs
	471 Pop Ctrls	All	0.5 (0.3-0.8)	ORs adjusted for EI & age
2002		Adv	0.6 (0.4-1.0)	Age frequency matched
China		Garlic		
		All	0.5 (0.3-0.7)	
		Adv	0.5 (0.3-0.9)	
		Scallions		
		All	0.3 (0.2-0.5)	
		Adv	0.4 (0.2-0.7)	
		Chinese chives		
		All	0.8 (0.5-1.3)	
		Adv	0.9 (0.5-1.5)	
		Leeks		
		All	1.1 (0.7-1.8)	
		Adv	1.5 (0.9-2.6)	
		Onion		
		All	0.7 (0.5-1.1)	
		Adv	0.9 (0.5-1.4)	

Cont.

Table 3.15, cont. : Summary of results from epidemiological studies of fruits and vegetables and PCa

Study, year, location	Subjects	Food Group	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Lee at al[214] 2003 China	133 Cases 265 Pop Ctrls	Tofu Combined soy foods	0.6 (0.4-1.0) 0.5 (0.3-0.9)	Men aged 50-89 yrs ORs adjusted for EI & age Age frequency & community matched
Hodge et al[141] 2004 Austrailia	858 Cases (≥ gleason score 5) 905 Pop Ctrls	Vegetables Alliums Legumes Fruit Tomato Foods	0.7 (0.5-1.0) 0.7 (0.5-0.9) 0.8 (0.6-1.0) 1.1 (0.9-1.5) 0.8 (0.6-1.0)	Men aged < 70 yrs ORs adjusted for: EI (residual), age, study centre, year, FHPCa, SES Age frequency matched
Nested Case-Control Studies				
Schuurman et al[92] 1998 Netherlands	642 Cases 1525 Subcohort Controls	Total Vegetables Total Fruit Leafy Vegetables Brassicas Alliums Citrus Fruit Pulses	0.8 (0.6-1.1) 1.3 (1.0-1.8) 1.0 (0.7-1.3) 0.8 (0.6-1.1) 0.9 (0.7-1.3) 1.3 (0.9-1.7) 0.7 (0.5-1.0)	Men aged 55-69 yrs at baseline. ORs adjusted for age, SES & FHPCa. Adv PCa analysis: results not reported as similar to all cases. Nested case-cohort study from Netherlands Cohort Study.
Cohort Studies				
Mills et al[165] 1989 USA	14,000 Men 180 Cases	Tomatoes Dried / Canned Beans, Lentils, & Peas Citrus Fruit Dried Fruit Vegetarian Protein Products (soy rich)	0.6 (0.4-0.9) 0.5 (0.3-0.8) 0.5 (0.3-0.9) 0.5 (0.3-0.9) 0.7 (0.4-1.1)	Men aged ≥ 25 yrs at baseline. RRs adjusted for age. 7th Day Adventist Men.
Severson et al[166] 1989 Hawaii	7,999 men 174 Cases	Total Fruit Tofu	1.6 (0.95-2.6) 0.4 (0.1-1.4)	RRs adjusted for age.
Hsing et al[167] 1990 USA	17,633 men 149 fatal Cases	Vegetables Fruit Cruciferous	0.7 (0.4-1.2) 0.9 (0.6-1.4) 1.3 (0.8-2.0)	RRs adjusted for age & tobacco. Lutheran Brotherhood Cohort. PCa Mortality.
Giovannucci et al[8] 1995 USA	47894 men 773 non stage A1 Cases	Carrots Spinach Broccoli Tomato Sauce Tomatoes Tomato based products All Adv	1.1 (0.7-1.6) 1.2 (0.9-1.7) 1.1 (0.8-1.3) 0.7 (0.5-0.9) 0.7 (0.6-0.9) 0.7 (0.4-1.0) 0.5 (0.2-1.0)	Men aged 40-75 yrs at baseline. RRs adjusted for age & EI. Adv PCa analysis: most results not reported as similar to all cases. Health Professionals Follow-up study.
Jacobsen et al[212] 1998 US	12,395 men 225 Cases	Soya milk	0.3 (0.1-0.9)	Men aged > 25yrs at baseline RRs adjusted for: age, BMI, coffee, milk, eggs & citrus fruit consumption & age at 1st marriage. Adventist Health Study

Cont.

Table 3.15, cont. : Summary of results from epidemiological studies of fruits and vegetables and PCa

Study, year, location	Subjects	Food Group	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Chan et al[82] 2000 Finland	27,062 Men 184 clinically apparent Cases	Vegetables Fruit	0.8 (0.5-1.3) 1.3 (0.8-2.2)	Men aged 50-69 yrs at baseline. RRs adjusted for age, EI, RCT arm, smoking, education & BMI. Cohort study from the ATBC RCT study.
Giovannucci et al[97] 2002 USA	47,365 Men 2481 Cases	Tomato Sauce All Adv	 0.8 (0.6-0.9) 0.7 (0.4-1.0)	Men aged 40-75 yrs at baseline. RRs adjusted for age & EI. Health Professional Follow-up Study.
Giovannucci et al[209] 2003 USA	47,365 men 2969 Non Stage A_1 cases	Total Fruit & Vegetables Cruciferous All Adv	1.1 (0.9-1.2) 0.9 (0.8-1.1) 1.1 (0.8-1.5)	Men aged 40-75 yrs RRs adjusted for age, EI, BMI, height, smoking, FHPCa, diabetes, activity, meat, α-linolenic acid, Ca, tomato sauce. Health Professionals Follow-up Study.
Key et al[210] 2004 UK & Europe	130, 544 men from 7 countries 1,104 cases	Total fruit & vegetables Total Vegetables Total Fruit Cruciferous	1.0 (0.8-1.3) 1.0 (0.8-1.2) 1.1 (0.8-1.3) 1.0 (0.8-1.2)	RRs adjusted for EI, height, and weight. Stratified by centre EPIC study

N.B
[$] Odds / Risk ratio for highest relative to lowest percentile, except where stated
[@] Odds / Risk ratios based on all PCa cases, except where stated
Hosp Ctrls = hospital controls, Pop Ctrls = population controls
EI = Energy Intake, PCa = prostate cancer, OR = Odds Ratio, RR = Rate Ratio, SES = Socio-economic status, FHPCa = Family history of PCa, All = All PCa, Adv = Advanced PCa only, Agg = Aggressive PCa only, Local = Localised PCa only.

Carotenoids

Total carotenoids and carotenes

Inverse associations were reported in the majority of the four case-control studies that investigated the association between total carotenoid and carotene intake and PCa risk, see Table 3.16, one of which was borderline significant (carotenes OR 0.7, 95%CI 0.4-1.0[135]).

β-Carotene

No significant association was observed in the eight case-control studies, one nested case-control study and two cohort studies that investigated the association between β-carotene intake and PCa, see Table 3.16, with the exception of Wu et al[215] who reported a borderline significant association with β-carotene intake in younger men. Two studies also examined the association between β-carotene intake and advanced PCa[95;131], no significant associations were reported.

Lycopene

No significant associations were reported in the five case-control studies and one nested case-control study that examined the association between lycopene intake and PCa, see Table 3.16. However, the two cohort studies that examined this association reported borderline significant inverse associations (RRs 0.8, 95%CI 0.6-1.0[8] and 0.8, 95%CI 0.7-1.0[97]). Schuurman et al[95] also examined the association between lycopene intake and advanced PCa, no association was reported.

Other carotenoids

No significant associations were reported for other carotenoids, with the exception of Schuurman et al[95] who reported a borderline significant positive association between β-cryptoxanthin and PCa / advanced PCa (ORs 1.4, 95%CI 1.0-1.9 and 1.6, 95%CI 1.0-2.4, resectively) and Cohen et al[207] who reported a borderline significant inverse association with lutein + zeaxanthin (OR 0.7, 95%CI 0.5-1.0).

Table 3.16: Summary of results from epidemiological studies of carotenoid intake and PCa

Study, Year, Location	Subjects	Intake Variable	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Case-Control Studies				
Rohan et al[137] 1995 Canada	207 Cases 207 Pop Controls	β-carotene Other Carotenes	0.9 (0.5-1.7) 0.7 (0.4-1.2)	ORs adjusted for age, EI & FHPCa. Age frequency matched.
Andersson et al[131] 1996 Sweden	526 Cases 536 Pop Controls	β-carotene All Adv	 0.9 (0.6-1.3) 0.8 (0.6-1.2)	Men aged < 80 yrs. ORs adjusted for age & EI. Age frequency matched.
Ghadirian et al[138] 1996 Canada	232 Cases 231 Pop Controls	β-carotene Other Carotenes	1.0 (0.6-1.8) 1.1 (0.6-1.8)	Men aged 35-84 yrs. ORs adjusted for age, EI & FHPCa. Age frequency & residence matched.
Key et al[132] 1997 England	328 Cases 328 Pop Controls	Carotene Lycopene	0.8 (0.6-1.2) 1.0 (0.7-1.5)	Men aged <75 yrs. ORs adjusted for SES. Age frequency matched.
Meyer et al[133] 1997 Canada	215 Incidental Cases 593 Hosp Controls	β-carotene α-carotene Lycopene Lutein	1.0 (0.5-1.8) 1.0 (0.5-1.9) 1.7 (0.9-3.3) 0.9 (0.4-1.7)	Men aged ≥ 45 yrs. ORs adjusted for age, EI, study group, FHPCa & education.
Jain et al[174] 1999 Canada	617 Cases 636 Pop Controls	All Carotenoids β-carotene α-carotene Lycopene Lutein Cryptoxanthin	1.1 (0.8-1.5) 1.1 (0.7-1.4) 1.1 (0.8-1.4) 1.0 (0.8-1.4) 0.8 (0.7-1.2) 1.4 (1.1-1.9)	ORs adjusted for age, EI, smoking, vasectomy, BMI, education & other nutrients. Age frequency matched.
Cohen et al[207] 2000 USA	628 Cases 602 Pop Controls	Tot Carotenoids β-carotene α-carotene Lycopene Lutein+Zeaxanthin β-cryptoxanthin	0.8 (0.6-1.2) 0.7 (0.5-1.1) 0.8 (0.5-1.1) 0.9 (0.6-1.3) 0.7 (0.5-1.0) 0.9 (0.6-1.4)	Men aged 40-64 yrs. ORs adjusted for age, EI, race, PSA screening, FHPCa, BMI, education & fat intake. Age frequency matched.
Norrish et al[213] 2000 New Zealand	317 Cases 480 Pop Controls	β-carotene Lycopene	1.1 (0.7-1.6) 0.8 (0.5-1.2)	Men aged 40-80 yrs. ORs adjusted for age, EI, height & SES. Age frequency matched. Adv PCa analysis: results not reported as similar to all cases.
Ramon et al[135] 2000 Spain	217 Cases 434 Hosp / Pop Controls	Carotenes	0.7 (0.4-1.0)	Men aged ≤ 80 yrs. ORs adjusted for age, EI, BMI, FHPCa, residence & fat intake. Age frequency & region matched.
Hodge et al[141] 2004 Austrailia	858 Cases 905 Pop Ctrls Cases ≥ gleason score 5	β-carotene α-carotene Lycopene Lutein+Zeaxanthin β-cryptoxanthin	0.8 (0.6-1.1) 0.8 (0.6-1.1) 0.8 (0.6-1.2) 0.9 (0.7-1.3) 0.9 (0.7-1.3)	Men aged < 70 yrs ORs adjusted for: EI (residual), age, study centre, year, FHPCa, SES Age frequency matched

Cont.

Table 3.16, cont.: Summary of results from epidemiological studies of carotenoid intake and PCa

Study, year, location	Subjects	Intake Variable	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Nested Case-Control Studies				
Schuurman et al[95] 2002 Netherlands	642 Cases 1525 Controls from 58,279 Men	β-carotene All Adv α-carotene All Adv Lycopene All Adv Lutein+Zeaxanthin All Adv β-Cryptoxanthin All Adv	 1.1 (0.8-1.5) 1.0 (0.6-1.6) 0.9 (0.6-1.2) 0.6 (0.4-1.1) 1.0 (0.7-1.3) 0.9 (0.6-1.5) 0.9 (0.7-1.2) 1.2 (0.7-1.9) 1.4 (1.0-1.9) 1.6 (1.0-2.4)	Men aged 55-69 yrs at baseline. RRs adjusted for age, SES, FHPCa & alcohol. EI & fat adjusted RRs not reported as EI & fat was not shown to be associated with PCa. Nested case-cohort study from Netherlands Cohort Study.
Wu et al[215] 2004 US	450 Cases 450 Ctrls from 51,529 men	β-carotene < 65 yrs ≥ 65 yrs α-carotene < 65 yrs ≥ 65 yrs Lycopene < 65 yrs ≥ 65 yrs Lutein+Zeaxanthin < 65 yrs ≥ 65 yrs β-cryptoxanthin < 65 yrs ≥ 65 yrs	 0.3 (0.1-1.0) 1.4 (0.6-3.4) 0.5 (0.2-1.5) 0.6 (0.3-1.3) 2.0 (0.7-5.7) 1.4 (0.6-3.4) 0.9 (0.3-2.5) 0.7 (0.3-1.6) 1.6 (0.4-6.5) 1.1 (0.5-2.4)	Men aged 40-75 yrs at baseline. RRs adjusted for age, cholesterol, selenium, vit E, FHPCa, BMI, height, exercise, smoking & vasectomy. Age & time matched. Stratified by age group
Cohort Studies				
Giovannucci et al[8] 1995 USA	47894 men 773 Non Stage A_1 Cases	β-carotene α-carotene Lycopene Lutein β-Cryptoxanthin	1.1 (0.8-1.3) 1.1 (0.9-1.4) 0.8 (0.6-1.0) 1.1 (0.9-1.4) 0.9 (0.8-1.2)	Men aged 40-75 yrs at baseline. RRs adjusted for age & EI. Adv PCa analysis: results not reported as similar to all cases. Health Professionals Follow-up study.
Giovannucci et al[97] 2002 USA	47,365 Men 2481 Non Stage A_1 Cases	Lycopene	0.8 (0.7-1.0)	RRs adjusted for age, EI, BMI & other nutrients. Adv PCa analysis: results not reported as similar to all cases. Health Professional Follow-up Study.

N.B
[$] Odds / Risk ratio for highest relative to lowest percentile, except where stated
[@] Odds / Risk ratios based on all PCa cases, except where stated
Hosp Ctrls = hospital controls, Pop Ctrls = population controls
EI = Energy Intake, PCa = prostate cancer, OR = Odds Ratio, RR = Rate Ratio, SES = Socio-economic status, FHPCa = Family history of PCa, All = All PCa, Adv = Advanced PCa only, Agg = Aggressive PCa only, Local = Localised PCa only.

Vitamin E and tocopherol

No significant association was observed between vitamin E / tocopherol and PCa risk, see Table 3.17, with the exception of Tzonou et al[142] who reported a significant inverse association with PCa risk (OR 0.5, 95%CI 0.3-0.9), no association was also reported between vitamin E and advanced PCa[95;131]. Hartman et al[81] also examined the association between baseline vitamin E and tocopherol intake and PCa risk straitified by α-tocopherol intervention arm within the ATBC RCT. Borderline significant inverse associations were reported within the α-tocopherol arm for vitamin E (OR 0.5, 95%CI 0.3-1.0) and γ-tocopherol (OR 0.6, 95%CI 0.3-1.0), whilst a borderline significant positive association was reported within the non-α-tocopherol arm for δ-tocopherol (OR 1.5, 95%CI 1.0-2.2).

Vitamin C

No association between vitamin C and PCa risk was reported by the majority of the nine case-control studies, one nested case-control study and one cohort study that examined vitamin C, see Table 3.18. However, Ramon et al[135] did report a significant inverse association with PCa (OR 0.6, 95%CI 0.4-0.9). No association between vitamin C and advanced PCa risk was also reported[95;131].

Table 3.17: Summary of results from epidemiological studies of tocopherol & vitamin E intake and PCa

Study, year, location	Subjects	Intake Variable	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Case-Control Studies				
Rohan et al[137] 1995 Canada	207 Cases 207 Pop Controls	Vitamin E	No association	ORs not reported ORs adjusted for age, EI & FHPCa. Age frequency matched.
Andersson et al[131] 1996 Sweden	526 Cases 536 Pop Controls	Tocopherol All Adv	 0.9 (0.6-1.3) 0.9 (0.6-1.3)	Men aged < 80 yrs. ORs adjusted for age & EI. Age frequency matched.
Key et al[132] 1997 England	328 Cases 328 Pop Controls	Vitamin E	0.9 (0.6-1.4)	Men aged <75 yrs. ORs adjusted for SES. Age frequency matched.
Meyer et al[133] 1997 Canada	215 Incidental Cases 593 Hosp Controls	Vitamin E	1.5 (0.8-2.8)	Men aged ≥ 45 yrs. ORs adjusted for age, EI, study group, FHPCa & education.
Jain et al[174] 1999 Canada	617 Cases 636 Pop Controls	Vitamin E	1.1 (0.8-1.6)	ORs adjusted for age, EI, smoking, vasectomy, BMI,education & other nutrients. Age frequency matched.
Tzonou et al[142] 1999 Greece	320 Cases 246 Hosp Controls	Vitamin E	0.5 (0.3-0.9)	ORs adjusted for age, EI, height, BMI & education. OR = per increment of 1 SD of daily intake. Age frequency matched
Ramon et al[135] 2000 Spain	217 Cases 434 Hosp / Pop Controls	Vitamin E	1.3 (0.9-2.0)	Men aged ≤ 80 yrs. ORs adjusted for age, EI, BMI, FHPCa, residence & fat intake. Age frequency & region matched.
Hodge et al[141] 2004 Austrailia	858 Cases 905 Pop Ctrls Cases ≥ gleason score 5	Vitamin E	1.0 (0.8-1.4)	Men aged < 70 yrs ORs adjusted for: EI (residual), age, study centre, year, FHPCa, SES Age frequency matched
Nested Case-Control Studies				
Schuurman et al[95] 2002 Netherlands	642 Cases 1525 Controls from 58,279 Men	Vitamin E All Adv	 0.9 (0.7-1.3) 1.0 (0.6-1.5)	Men aged 55-69 yrs at baseline. RRs adjusted for age, SES, FHPCa & alcohol. EI & fat adjusted RRs not reported as EI & fat not associated with PCa. Nested case-cohort study from Netherlands Cohort Study.

Cont.

Table 3.17, cont.: Summary of results from epidemiological studies of tocopherol & vitamin E intake and PCa

Study, year, location	Subjects	Intake Variable	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Cohort Studies				
Giovannucci et al[8] 1995 USA	47894 men 773 Non Stage A_1 Cases	Vitamin E	0.9 (0.8-1.2)	Men aged 40-75 yrs at baseline. RRs adjusted for age & EI. Adv PCa analysis: results not reported as similar to all cases. Health Professionals Follow-up study.
Hartman et al[81] 1998 Finland	29,133 Men 317 Cases	Vitamin E (inc. supp.s) Non-AT AT α-tocopherol Non-AT AT β-tocopherol Non-AT AT δ-tocopherol Non-AT AT γ-tocopherol Non-AT AT	 1.2 (0.8-1.9) 0.5 (0.3-1.0) 1.3 (0.8-2.1) 0.7 (0.4-1.3) 1.4 (0.9-2.3) 0.8 (0.5-1.4) 1.5 (1.0-2.2) 0.7 (0.4-1.3) 1.3 (0.9-2.0) 0.6 (0.3-1.0)	Men aged 50-69 yrs at baseline. RRs adjusted for age, EI, intervention arm & BPH. Straitified by α-tocopherol intervention arm, as significant effect modification by α-tocopherol intervention was reported. Cohort study from the ATBC RCT study.

N.B
[$] Odds / Risk ratio for highest relative to lowest percentile, except where stated.
[@] Odds / Risk ratios based on all PCa cases, except where stated.
All = All Cancers, Adv = Advanced cancers only, Agg = Aggressive cancers only.
OR = Odds Ratio, RR = Rate Ratio, EI = Energy Intake, PCa = PCa, AT: α-tocopherol arm of ATBC Study, Non-AT: Placebo arm for ATBC Study, SES = Socio-economic status, FHPCa = Family history of PCa, PSA = Prostate-specific antigen.

Table 3.18: Summary of results from epidemiological studies of vitamin C intake and PCa

Study, Year, Location	Subjects	Intake Variable	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Case-Control Studies				
Rohan et al[137] 1995 Canada	207 Cases 207 Pop Controls	Vitamin C	n/s	ORs adjusted for age, EI & FHPCa. Age frequency matched. ORs for vitamin C not reported
Andersson et al[131] 1996 Sweden	526 Cases 536 Pop Controls	Vitamin C All Adv	1.2 (0.8-1.6) 1.0 (0.7-1.5)	Men aged < 80 yrs. ORs adjusted for age & EI. Age frequency matched.
Ghadirian et al[138] 1996 Canada	232 Cases 231 Pop Controls	Vitamin C	n/s	Men aged 35-84 yrs. ORs adjusted for age, EI & FHPCa. Age frequency & residence matched. ORs for vitamin C not reported
Key et al[132] 1997 England	328 Cases 328 Pop Controls	Vitamin C	1.2 (0.8-1.8)	Men aged <75 yrs. ORs adjusted for SES. Age frequency matched.
Meyer et al[133] 1997 Canada	215 Incidental Cases 593 Hosp Controls	Vitamin C	1.1 (0.6-2.2)	Men aged ≥ 45 yrs. ORs adjusted for age, EI, study group, FHPCa & education.
Jain et al[174] 1999 Canada	617 Cases 636 Pop Controls	Vitamin C	0.8 (0.5-1.2)	ORs adjusted for age, EI, smoking, vasectomy, BMI, education & other nutrients. Age frequency matched.
Cohen et al[207] 2000 USA	628 Cases 602 Pop Controls	Vitamin C	0.8 (0.5-1.1)	Men aged 40-64 yrs. ORs adjusted for age, EI, race, PSA screening, FHPCa, BMI, education & fat intake. Age frequency matched.
Ramon et al[135] 2000 Spain	217 Cases 434 Hosp / Pop Controls	Vitamin C	0.6 (0.4-0.9)	Men aged ≤ 80 yrs. ORs adjusted for age, EI, BMI, FHPCa, residence & fat intake. Age frequency & region matched.
Hodge et al[141] 2004 Austrailia	858 Cases (≥ gleason score 5) 905 Pop Ctrls Cases	Vitamin C	1.2 (0.9-1.7)	Men aged < 70 yrs ORs adjusted for: EI (residual), age, study centre, year, FHPCa, SES Age frequency matched

Cont.

Table 3.18, cont.: Summary of results from epidemiological studies of vitamin C intake and PCa

Study, Year, Location	Subjects	Intake Variable	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Nested Case-Control Studies				
Schuurman et al[95] 2002 Netherlands	642 Cases 1525 Controls from 58,279 Men	Vitamin C All Adv	 1.2 (0.9-1.5) 1.2 (0.8-1.9)	Men aged 55-69 yrs at baseline. RRs adjusted for age, SES, FHPCa & alcohol. EI adjusted RRs not reported as EI was not shown to be associated with PCa. Nested case-cohort study from Netherlands Cohort Study.
Cohort Studies				
Giovannucci et al[8] 1995 USA	47894 men 773 Non Stage A_1 Cases	Vitamin C	1.1 (0.9-1.4)	Men aged 40-75 yrs at baseline. RRs adjusted for age & EI. Adv PCa analysis: results not reported as similar to all cases. Health Professionals Follow-up study.

N.B
[$] Odds / Risk ratio for highest relative to lowest percentile, except where stated
[@] Odds / Risk ratios based on all PCa cases, except where stated
Hosp Ctrls = hospital controls, Pop Ctrls = population controls, n/s = no significant association
EI = Energy Intake, PCa = prostate cancer, OR = Odds Ratio, RR = Rate Ratio, SES = Socio-economic status, FHPCa = Family history of PCa, All = All PCa, Adv = Advanced PCa only, Agg = Aggressive PCa only, Local = Localised PCa only.

Selenium and phyto-oestrogens

Few epidemiological studies have investigated the effect of both selenium and phyto-oestrogen intake on PCa risk. No significant associations between selenium intake and PCa were reported by the one case-control study[174] and one cohort study[81] examined this association, see Table 3.19. Whereas the two case-control studies examining phyto-oestrogen intake, reported significant / borderline significant inverse associations for the isoflavone coumesterol (OR 0.5, 95%CI 0.3-0.9[216], genistein (OR 0.5, 95%CI 0.3-1.0[214] and Daidzein (OR 0.6, 95%CI 0.3-1.0[214]), see Table 3.20.

Table 3.19: Summary of results from epidemiological studies of selenium intake and PCa

Study, year, location	Subjects	Intake Variable	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Case-Control Study				
Jain et al[174] 1999 Canada	617 Cases 636 Pop Controls	Selenium	0.9 (0.7-1.3)	ORs adjusted for age, EI, smoking, vasectomy, BMI, education & other nutrients. Age frequency matched.
Cohort Study				
Hartman et al[81] 1998 Finland	29,133 Men 317 Cases	Selenium Non-AT arm AT arm	1.3 (0.7-2.5) 0.7 (0.3-1.5)	Men aged 50-69 yrs at baseline. RRs adjusted for age, EI, intervention arm & BPH. Straitified by α-tocopherol intervention arm, as significant effect modification by α-tocopherol intervention was reported. Cohort study from the ATBC RCT study.

N.B
[$] Odds / Risk ratio for highest relative to lowest percentile, except where stated
[@] Odds / Risk ratios based on all PCa cases, except where stated
EI = Energy Intake, PCa = PCa, OR = Odds Ratio, RR = Rate Ratio, AT: α-tocopherol arm of ATBC Study, Non-AT: Placebo arm for ATBC Study, SES = Socio-economic status,
FHPCa = Family history of PCa, PSA = Prostate-specific antigen,
All = All Cancers, Adv = Advanced cancers only, Agg = Aggressive cancers only.

Table 3.20: Summary of results from epidemiological studies of phyto-oestrogen intake and PCa

Study, year, location	Subjects	Intake Variable	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Case-Control Studies				
Strom et al[216] 1999 USA	83 Cases 107 Pop Controls	Isoflavones:		ORs adjusted for: age, EI, FHPCa, alcohol. Age frequency & race matched.
		Genistein	0.7 (0.4-1.3)	
		Daidzein	0.6 (0.3-1.1)	
		Formononetin	1.0 (0.5-1.8)	
		Biochanin A	0.9 (0.5-1.7)	
		Coumestrol	0.5 (0.3-0.9)	
		Flavonoids:		
		Quercetin	1.0 (0.5-1.8)	
		Kaempferol	0.8 (0.4-1.4)	
		Luteolin	0.8 (0.5-1.5)	
		Apigenin	0.8 (0.5-1.5)	
		Myricetin	1.1 (0.6-2.1)	
		Phytosterols:		
		β-Sitosterol	0.9 (0.5-1.7)	
		Campesterol	1.9 (0.9-4.0)	
		Stigmasterol	2.2 (1.1-4.4)	
		Total Phytosterols	1.0 (0.5-1.9)	
		Lignan precursors:		
		Secoisolariciresinol	1.2 (0.7-2.2)	
		Matairesinol	0.9 (0.5-1.7)	
Lee at al[214] 2003 China	133 Cases 265 Pop Ctrls	Genistein	0.5 (0.3-1.0)	Men aged 50-89 yrs ORs adjusted for EI & age Age frequency & community matched
		Daidzein	0.6 (0.3-1.0)	

N.B.
[$] Odds / Risk ratio for highest relative to lowest percentile, except where stated
[@] Odds / Risk ratios based on all PCa cases, except where stated
Hosp Ctrls = hospital controls, Pop Ctrls = population controls
EI = Energy Intake, PCa = prostate cancer, OR = Odds Ratio, RR = Rate Ratio, SES = Socio-economic status, FHPCa = Family history of PCa, All = All PCa, Adv = Advanced PCa only, Agg = Aggressive PCa only, Local = Localised PCa only.

3.4.10 Discussion

Evidence from this systematic literature review suggests that overall vegetable consumption is associated with a reduced risk in PCa, in particular allium, tomatoes and soy foods, thereby confirming the conclusions from previous reviews. The findings for fruit consumption is less consistent with the findings of some studies suggesting fruit consumption to be associated with increased risk of PCa. The evidence for a relation between nutrients associated with vegetables and fruit and PCa is even less consistent.

There is no clear evidence that carotenoids reduce PCa risk, with the possible exception of lycopene. This is confirmed by the inconclusive findings from several studies examining biomarkers of carotenoid intake such as carotenoid plasma / serum concentrations[86-88;162;217-219], although several invitro and animal studies, as reviewed by Chan et al[184], support the role of carotenoids to protect against PCa. However, there is some evidence for the protective effect of lycopene, with Giovannucci et al[8;97] estimating a 20% reduction in PCa risk with increased lycopene intake. This association has been confirmed in several studies examining serum / plasma lycopene concentrations[88;162] and also by the aforementioned studies that reported tomato consumption to be protective against PCa (as tomatoes are the major source of lycopene).

There is also little evidence from the literature review that vitamins C and E are associated with PCa risk. This is consistent with the findings of studies examining biomarkers of intake, with the exception of γ-tocopherol, which was reported to have a protective effect against PCa in several nested case-control studies, such as Helzlsouer et al[85] (OR 0.3,95%CI 0.1-0.7). Plasma vitamin E has also been suggested to have a protective effect against PCa in a sub-group of smokers (Low vitamin E OR 3.3, 95%CI 1.3-8.4[219]). The evidence of the protective effect of vitamin E is also supported by the findings of the ATBC Trial[183], in which α-tocopherol supplementation was found to significantly reduce both PCa incidence and mortality, and also in several experimental and animal studies as reviewed in Shklar et al[220].

The limited evidence on the association between selenium intake and PCa makes it impossible to make any judgements on the effect of selenium intake. However, evidence of a significant protective effect on PCa has been reported in several studies that have examined biomarkers for selenium intake (i.e. toenail and serum concentrations), the ORs of which ranged from 0.2 (95%CI 0.1-0.8)[221] to 0.7 (95%CI 0.5-1.00)[222].This association is also supported by the findings of the NTPC Trial[188] in which selenium supplementation was found to significantly reduce the incidence of PCa. Several *invitro* and experimental studies also support these findings, including Redman et al[223] and Menter et al[224].

As with selenium intake, very few studies to date have reported on the relation between phyto-oestrogen intake and PCa. Borderline significant inverse associations with these phytochemicals, especially daidzein and genistein, have been reported in Chinese men[214]. However, the findings of Strom et al[216]should be viewed with caution as it is doubtful that the food table used could accurately estimate intake for so many different types of phyto-oestrogens, most of which are found in such small quantities in foods, also the great number of phyto-oestrogens examined may have introduced the possibility of multiple testing . Nevertheless, the evidence is supported by several studies who have reported significant inverse associations between phyto-oestrogen serum / plasma concentrations and PCa, such as Ozasa et al[225] (equol OR 0.4, 95%CI 0.2-1.0, and equol / daidzein ratio OR 0.4, 95%CI 0.1-0.9) and also in the aforementioned vegetable consumption studies that reported significant protective effects of soyfood consumption[208;212]. Several experimental and animal studies have also presented evidence for the anti-carcinogenic abilities of phyto-oestrogens, such as the inhibition of PCa tumour growth, these studies have been reported in several reviews[226-228].

3.5 Alcohol

Alcohol consumption, including heavy use and abuse, has been reported to be associated with increased risk of some cancers, including cancers of the oral cavity and pharynx, oesophagus, larynx, breast and liver[229], but the findings for PCa are less conclusive. Alcohol has been assessed as a possible risk factor for PCa in a large number of studies. Although the majority of these studies have failed to show an association between alcohol and PCa, due to the fact that alcohol consumption is very common, any potential association may have a great impact on PCa incidence and its associated public health concerns.

3.5.1 Consumption

The world average for alcohol consumption is 9g of pure alcohol per day, however this average masks great regional and national variations, as well as cultural and religious variations. The lowest consumption is reported in the Middle East and North Africa where Islam, the predominant religion, bans the consumption of alcohol. Whereas the highest consumption occurs in European countries, such as the wine producing countries of France, Portugal and Italy, where consumption is around 27g of pure alcohol per day. Analysis of time trends shows increasing consumption of alcohol in most countries, especially those in transition to urban-industrial societies[42], and in any population, most alcohol is drunk by men.

Alcohol consumption in the UK has been examined in several surveys using different age groups, please see Table 3.21. Comparison between these surveys is difficult because of the variety of different measures used. The data suggest that there may be a time trend towards lower alcohol consumption; 21.9g/day in 2003[46] compared to 25.0g/day[145] in 1990, although this is more likely to be due to artefactual reasons, i.e. differences in alcohol measurements and study populations. The total alcohol consumption for Scottish men in the two surveys using age groups 16-64yrs[53] and 19-64yrs[46] were similar to that for UK men (24.8g/day[53] and 22.0g/day[46] respectively), the reported consumption in the most recent survey[46] also equates well to that reported by the Scottish Health Survey[44] (19.1 units/week which is approximately 21.8g/day), which reported 93% of men age 16-74yrs consumed

alcohol. Beer is by far the most popular alcohol type in Scotland, where average consumption is 12 units (6 pints) per week, compared to two and five units for wine and spirits respectively[44].

N.B. Alcohol consumption is expressed differently in different countries. In the US alcohol intake is usually expressed in terms of 'standard drinks' each of which contains approximately 12-14g of pure alcohol whereas in the UK alcohol intake is expressed in terms of 'units' where one unit contains 8 g of alcohol[230].

Table 3.21: Average alcohol consumption

Alcohol	Gregory et al, 1990[53] men only (16-64 yrs)		Finch et al, 1998[105] men only (≥65yrs)		Henderson et al, 2003[46] men only (19-64yrs)		MAFF Nation Food Survey, 2000[48] men & women (all ages)		Scottish Health Survey 1998[44] men only (16-74yrs)
	UK g/day (SE)	Scotland g/day (SE)	UK g/day (SD)	Scotland & North g/day (SD)	UK g/day (SD)	Scotland g/day (SD)	UK ml/week	Scotland ml/week	Units/week (SE)
Total alcohol	25.0 (0.95)	24.8 (3.66)	11.7 (19.6)	11.5 (20.2)	21.9 (24.7)	22.0 (20.8)	435	412	19.1 (0.38)
Beer	-	-	-	-	-	-	220	-	12 (-)
Wine	-	-	-	-	-	-	146	-	2 (-)
Spirits / Liquor	-	-	-	-	-	-	-	-	5 (-)

N.B.
- = data not available

3.5.2 Nutritional value and alcohol consumption guidelines

Alcohol is a source of energy, providing approximately 29kJ /g alcohol, many alcoholic drinks also contain sugars which increase the total energy content considerably. Alcohol is considered to be a low density food[230], meaning that it provides energy but few essential nutrients. Nevertheless some alcoholic drinks do have traces of vitamins and minerals, although these do not usually make a significant contribution to the diet, these nutrients include antioxidants found in wine and flavonoids which are found in beer, both of which may be associated with a protective effect against PCa. Alcohol may also contain potential carcinogens including nitrosamines and polycyclic hydrocarbons, particularly in locally prepared drinks, although the significance of these carcinogens, which are usually found in very small concentrations, is still speculative[231]. The Department of Health advises that alcohol consumption for men should be three to four units per day or less, consumption above this level may lead to significant health risks.

3.5.3 Biomechanisms

The biological pathway relating alcohol consumption to PCa risk is largely unknown, though some mechanisms have been proposed to both explain a protective as well as a positive association between alcohol consumption and PCa risk.

Alcohol consumption tends to result in greater oestrogen and lower androgen serum levels in both men and women[232]. As PCa appears to be closely linked to high levels of androgens[233;234], this suggests a protective biological mechanism against PCa.

The association with increased risk of PCa may be explained by biological pathways which include affects on the permeability of cell membranes to carcinogens, modification of carcinogen metabolising enzyme activity, and inhibition of DNA repair mechanisms[230;231;235]. Alcohol can also alter first-pass metabolism in the liver of carcinogens, including nitrosomines, and may modify DNA methylation affecting gene regulation[236]. Furthermore, alcohol contains possible carcinogens, including nitrosomines and acetaldehyde, a major metabolite of alcohol, is a recognised carcinogen and teratogen[237], please refer to Table 3.2.

Finally, as diet potentially plays an important role in PCa, alcohol consumption may be related to PCa indirectly though dietary effects, including malabsorption and the displacement of other nutrients[235]. For example, heavy drinkers who are in energy balance will have markedly lower intake of other nutrients as well as possibly having a diet that is poor in other respects such as a low intake of fruit and vegetables[230].

3.5.4 Literature review

Meta-analysis of PCa and alcohol

The findings of the meta-analysis by Dennis[102] of twenty-seven case-control studies and six cohort studies published prior to July 1998 showed no association between alcohol consumption and PCa (pooled RR estimate 1.05, 95%CI 0.98-1.11). Although small, though borderline significant, positive associations were observed for beer (pooled RR estimate 1.18, 95%CI 1.07-1.29), wine (pooled RR estimate 1.06, 95%CI 0.96-1.18) and liquor / spirits (pooled RR estimate 1.08, 95%CI 0.99-1.19). Denis[102] concluded that there was no relationship between moderate alcohol consumption and PCa, and that if any association between alcohol and PCa existed it appeared to be among heavy drinkers or alcohol abusers.

Review of recent studies since July 1998

Due to the thoroughness of the above meta-analysis in reviewing the association between alcohol consumption and PCa risk, this systematic literature review will concentrate on the studies that have examined alcohol consumption that were published after the meta-analysis. A total of four case-control studies and seven cohort studies published since Dennis[102] have examined the association between alcohol consumption and PCa.

All studies fulfilled the requirements of the methodological criteria, however, many did not adjust for energy intake[238-242] (mainly due to the lack of data on energy intake), but adjusted for BMI instead.

All studies were conducted in Western populations, especially the US, and reported present drinking habits, with four studies also reporting past drinking habits[238;239;241;243]. The majority studies examined the relationship between moderate

alcohol consumption and PCa, considering risks only up to consumption levels of about ≥ 4 drinks / day. Whereas Lumey et al[238] reported risks for subjects consuming ≥ 8 drinks /day, a level of consumption considered to be abusive[235].

Total alcohol

As found in the meta-analysis, no general pattern of association was observed, with the majority of studies reporting no association, see Table 3.22. However, two US studies observed significant associations, Sharpe et al[239] observed a significant positive association (OR =1.6, 95%CI 1.1-2.3) for those subjects reporting to drink daily, whereas Breslow et al[240] reported a significant negative association (OR = 0.23, 95%CI 0.06-0.95). Within those studies examining advanced PCa, Putnam et al[244] observed a strong significant positive association (OR = 6.4, 95%CI 1.4-29.7), whereas Schuurman et al[243] and Platz et al[245] continued to observe no association.

Alcohol types

Ten of the twelve studies also examined the association between PCa and alcohol type (beer, wine and spirits / liquor), see Table 3.22. Different patterns of association were observed with each alcohol type. Within beer drinkers, beer consumption was generally associated with decreased PCa risk, significant inverse associations were reported by Jain et al[246](OR = 0.68, 95%CI 0.49-0.94), Villeneuve et al[134] (OR = 0.5, 95%CI 0.2-1.0) and Breslow[240](OR = 0.34, 95%CI 0.12-0.92). However, Sharpe et al[239] reported a significant positive association (OR =1.6, 95%CI 1.1-2.3) for those subjects reporting to drink beer daily. An inverse non-significant association was also reported within advanced PCa[243].

For wine consumers, no association was reported by the majority of the ten studies examining the association between wine consumption and PCa risk, with the exception of two cohort studies which reported positive borderline significant associations (OR 1.41, 95%CI 1.01-1.96[247] and OR = 2.3, 95%CI 1.0-5.3[243]). This positive association continued to be significant with advanced PCa (OR = 2.9 95%CI 1.0-8.5)[243]. Schuurman et al[243] also categorised wine consumption by red, white and fortified wine, significant positive associations continued to be observed for white and fortified wines, ORs = 3.3 (95%CI 1.2-9.2) and 2.3 (95%CI 1.2-4.7)

respectively, whereas a non-significant negative association was reported for red wine.

No significant associations between spirit / liquor consumption and PCa risk were reported.

Past intake

The evidence for past intake is less consistent, within the four studies that examining past intake Sharpe et al[239] reported a significant positive association with increasing cumulative consumption of total alcohol, OR 2.1 (95%CI 1.3-3.3). Whereas Breslow et al[240] consistently reported significant negative associations with heavy alcohol consumption at ages 25years (OR 0.20, 95%CI 0.06-0.63), 35years (OR 0.30, 95%CI 0.12-0.77) and 45years (OR 0.39, 95%CI 0.17-0.93).

Table 3.22: Findings from recent epidemiological studies of alcohol and PCa

Study, year, location	Subjects	Food Item	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Case-Control Studies				
Jain et al[246]	617 Cases	Total alcohol	0.9 (0.6-1.3)	ORs adjusted for age & EI
1998	637 Pop Ctrls	Beer	0.7 (0.5-1.0)	Age frequency matched
Canada		Wine	1.1 (0.8-1.6)	
		Liquor	0.9 (0.6-1.2)	
Lumey et al[238]	699 Cases	Never/ any alcohol	1.2 (0.9-1.5)	ORs adjusted for age,
1998	2041 Hosp Ctrls	Drinks per week	1.1 (0.7-1.5)	education, occupation, smoking,
US		Current Drinker	1.3 (0.8-2.0)	religion & marital status
		Former Drinker	0.7 (0.3-1.4)	Age frequency, hospital & race matched
Villeneuve et al[134]	1623 Cases	Total alcohol	1.1 (0.8-1.6)	Men aged 50-74 yrs.
	1623 Pop Ctrls	Beer	0.5 (0.2-1.0)	ORs adjusted for age,
1999		Wine	0.9 (0.7-1.5)	residence, smoking, BMI, other
Canada		Liquor	1.8 (0.9-3.8)	food grps, income & FHPCa. Age frequency matched.
Sharpe et al[239]	399 Cases	Total Alcohol:		Men aged 45-70 yrs.
	476 Pop Ctrls	Drank daily	1.6 (1.1-2.3)	ORs adjusted for age, ethnicity,
2001		C. Consumption	2.1 (1.3-3.3)	smoking, BMI & income
US		Beer:		
		Drank daily	1.6 (1.1-2.3)	
		C. Consumption	1.7 (1.0-2.9)	
		Wine:		
		Drank daily	0.8 (0.5-1.3)	
		C. Consumption	1.0 (0.5-2.1)	
		Spirits:		
		Drank daily	1.4 (0.9-2.2)	
		C. Consumption	1.7 (0.9-3.1)	
Cohort Studies				
Breslow et al[240]	5,766 men	Total Alcohol	0.2 (0.1-1.0)	Men aged 25-74yrs
		Beer	0.3 (0.1-0.9)	RRs adjusted for race & Design
1999	299 cases	Wine	1.2 (0.4-3.9)	RRs reported for NHANES II
US		Liquor	1.0 (0.5-2.0)	cohort only
		Heavy drinker at 25yrs	0.2 (0.1-0.6)	
		Heavy drinker at 35yrs	0.3 (0.1-0.8)	
		Heavy drinker at 45yrs	0.4 (0.2-0.9)	
		Heavy drinker at 55yrs	0.4 (0.2-1.1)	
Schuurman et al[243]	58,279 Men	Total alcohol		Men aged 55-69 yrs at baseline.
		All	1.1 (0.8-1.6)	RRs adjusted for age, SES,
1999	680 cases	Adv	1.1 (0.7-1.8)	FHPCa & total alcohol (for
Netherlands		Beer		alcohol types only)
		All	0.5 (0.2-1.3)	
		Adv	0.7 (0.3-1.9)	Netherlands Cohort Study
		Wine		
		All	2.3 (1.0-5.3)	
		Adv	2.9 (1.0-8.5)	
		Liquors		
		All	1.1 (0.6-2.0)	
		Adv	1.2 (0.5-3.0)	

Cont.

Table 3.22, cont.: Findings from recent epidemiological studies of alcohol and PCa

Study, year, location	Subjects	Food Item	Odds / Risk Ratio[$@] (95% C.I.)	Comments
Ellison et al[247]	3,400 Men	Total alcohol	0.9 (0.6-1.6)	Men aged 50-84 yrs at baseline.
2000		Beer	1.1 (0.8-1.5)	RRs adjusted for age, smoking,
Canada	145 cases	Wine	1.4 (1.0-2.0)	BMI, education, fat, fibre, EI.
		Spirits	0.9 (0.6-1.3)	Nutrition Canada Survey Cohort
Lund Nilsen et al[241]	22,895 Men	Total alcohol	0.9 (0.6-1.3)	Men aged 40+ yrs at baseline.
		Teetotaller	1.2 (1.0-1.6)	RRs adjusted for age.
2000	644 cases	Past excessive		
Norway		drinking	1.0 (0.9-1.3)	
Putnam et al[244]	1572 men	Total alcohol		Men aged 45-70 yrs at baseline.
		All	1.5 (0.8-2.7)	RRs adjusted for age (& EI,
2000	101 cases	Adv	6.4 (1.4-29.7)	BMI, Fhist & other nutrients -
US		Beer	1.7 (0.9-3.0)	total alcohol only)
		Wine	1.9 (0.9-3.7)	
		Liquor	1.7 (0.9-3.0)	
Sesso et al[248]	7612 Men	Total alcohol	1.3 (0.9-2.1)	RRs adjusted for age, BMI,
2001		Beer	0.7 (0.2-2.9)	activity, smoking & FHPCa.
US	366 cases	Wine	1.1 (0.5-2.3)	
		Liquor	1.1 (0.6-1.9)	
Albertsen et al[242]	12,989 Men	Total alcohol	0.7 (0.3-1.5)	Men aged 20-98 yrs at baseline.
		Beer	1.0 (0.6-1.5)	RRs adjusted for age,
2002	233 cases	Wine	0.9 (0.4-2.0)	education, activity, BMI,
Denmark		Spirits	1.0 (0.5-2.0)	smoking, study.
Platz et al[245]	47,843 men	Total alcohol		Men age 40-75 yrs @ baseline
2004		All	1.0 (0.8-1.3)	RRs adjusted for age, EI BMI,
USA	2479 non stage	Adv	1.0 (0.7-1.3)	height, smoking, FHPCa,
	A_1 cases	Wine	1.2 (0.9-1.2)	diabetes, vasectomy, activity,
		Beer	1.1 (1.0-1.3)	Ca, fructose, tomato sauce,
		Liquor	1.1 (0.9-1.2)	meat, vit E & α-linolenic acid

N.B
[$] Odds / Risk ratios for highest relative to lowest percentile, except where stated
[@] Odds / Risk ratios based on all PCa cases, except where stated
EI = Energy Intake, PCa = PCa, OR = Odds Ratio, RR = Rate Ratio,
SES = Socio-economic status, FHPCa = Family history of PCa, PSA = Prostate-specific antigen,
All = All Cancers, Adv = Advanced cancers only, Agg = Aggressive cancers only, C. Consumption = Cumulative consumption among daily drinkers.

3.5.5 Discussion

Evidence from studies reviewed in this literature review, although somewhat inconsistent, suggest that there is no association between alcohol consumption and PCa, thereby confirming the conclusion made by Dennis[102]. Nevertheless in recent studies examining alcohol type, beer consumption was reported to have a protective effect, whereas wine was reported to have a borderline significant positive association with PCa risk in several other studies. This suggests that the various types of alcohol may each have a different effect on PCa.

Evidence is even less consistent for past drinking habits, with one case-control study reporting a significant positive association between PCa risk and the cumulative consumption of total alcohol[239], whilst Breslow et al[240] reported a significant inverse association with heavy drinking at ages 25 to 45 years. This finding not only suggests that long-term consumption maybe aetiologically relevant but also that high consumption of alcohol maybe too. However, these findings should be interpreted with caution as they were based on small numbers of cases who were heavy drinkers.

Few other studies have examined the association between high / abusive alcohol consumption and PCa risk. This is probably due to difficulties in examining high alcohol consumption. Heavy alcohol consumers may tend to be under-represented among study participants, as they are more likely to refuse or not respond when asked to take part in a study. Study participants may also tend to under-report alcohol use, due to an unwillingness to confess true intake that they feel may be less socially acceptable. If this occurs differentially between cases and controls, substantial bias may result. Amongst the reviewed studies, where reported, average consumption of total alcohol ranged from 17.4g/day[243] to 19.6g/day[248], with the typical highest categories of alcohol consumption being ≥ 30g/day / ≥ 3 drinks/day. Only Lumey et al[238] attempted to examine heavy alcohol consumption (≥ 8 drinks per day), however only 8% of the total number of subjects fell within this category .

As reviewed by Dennis et al[235], the findings of several studies that examined abusive alcohol consumption reported a positive association between alcohol abuse and PCa risk[249-252], however, none of these studies provided quantitative information about the amount of alcohol consumed. In addition, autopsy studies[253;254] have reported a lower prevalence of PCa in cirrhotics than in controls, suggesting that physiological changes associated with cirrhosis may reduce PCa risk. However, both these autopsy studies had small study sizes, plus latent cancers were not distinguished from more aggressive tumours. No recent studies published since this review have examined the association between alcohol abusers and PCa.

3.6 General discussion

3.6.1 Introduction

Evidence gathered from this literature review suggests that several dietary factors may be associated with PCa risk. In particular, meat product consumption was observed to be associated with an increased risk in PCa in many studies, whereas vegetable and soy food consumption and to a lesser extent lycopene, selenium and phyto-oestrogens were observed to be associated with a protective association with PCa. Nevertheless, findings for other dietary factors have produced some contradictory and possibly inconclusive evidence, in particular for alcohol consumption and most plant-based nutrients.

3.6.2 Covariance of diet

The complex nature of diet, with its many inter-correlated components, makes the individual effect of different nutrients and foods on disease very difficult to study. For fat intake in particular, it is not just energy intake that is highly correlated with this nutrient, many other food components and nutrients are as well. Animal foods, including meat and dairy products, are a major fat source in western diets and are therefore also highly correlated with fat intake. In addition to fat, animal products also contain other components that have been suggested to play a role in PCa aetiology, such as calcium and retinol. A diet high in meat can also result in exposure to carcinogenic chemicals (such as aromatic hydrocarbons and heterocyclic amines) that are created when meats are cooked by grilling or frying at high temperatures[175]. High fat/high meat consumption is also generally associated with a lower consumption of plant foods, such as vegetables and fruit, that contain nutrients which have been suggested to have a protective effect against PCa[184;255;256]. It therefore makes it possible to conclude that it is not so much the high levels of fat / meat consumption that is a main factor of PCa, but rather the correlated low levels of fruit and vegetable consumption.

3.6.3 Methodological considerations

The wealth of epidemiological studies of all types of designs, methodologies and sizes that have examined dietary factors associated with PCa risk has made it increasingly difficult to allow for a definitive answer to be made about the effect of these factors on PCa risk. However, the systematic nature of this review has permitted for studies with dubious nutritional epidemiological methodologies and therefore possible spurious findings to be discarded, thereby allowing for a much clearer picture of the effect that these dietary factors have on PCa risk to be obtained.

As well as the use of a validated and comprehensive dietary assessment method, all studies included in this review reported ORs adjusted for EI, thereby allowing for the examination of the effect of each dietary factor whilst controlling for any potential effect that EI may have on PCa risk. It is interesting to note that the majority of studies examining fat intake which were omitted because they did not adjust for EI amongst other methodological reasons, reported significant positive associations between fat intake and PCa[98;120;124-126;128] . Also, studies included in the review which also reported crude relative risks, such as Andersson et al[131], reported crude significant associations between fat and PCa risk, which generally became non-significant when EI was adjusted for.

The large variation in the way food groups were classified could also explain discrepancies in the findings. For example, the lack of consistant evidence for individual vegetable categories, especially cruciferous vegetables, could have been due to the wide variation in the classifications and groupings used. Meat product classification also varied considerably, especially for total meat for which the inclusion criteria of fish and/or poultry differed from study to study. The range of countries and populations in which the reviewed studies were conducted also make comparisons difficult. For example, evidence that phyto-oestrogens are protective against PCa is mainly reported in studies from China and Japan, where soy is consumed on a regular basis, thus allowing for a large enough variation in soy consumption to enable any true association with PCa risk to be examined.

Another difficulty in data interpretation arises from the lack of reporting of null findings. Some studies that have reported results for only a few nutrients / food groups have probably also found null association for other dietary factors, but have not included these results in their publication. Furthermore some studies have analysed data for a large number of dietary factors, thus increasing the probability of finding a significant association for one or a few items due to chance alone.

With regards to alcohol consumption in particular, the inconsistent nature of the available evidence may, in part, be due to study design and methodological issues not accounted for in the methodology criteria. In particular, the methodology used to report alcohol consumption seemed to vary greatly. The type of alcohol assessment methods ranged from diet histories and FFQs in which usual alcohol consumption over the past year was reported[134;243;246], to interviews regarding current and/or past drinking habits[238;240;241]. Within the studies that reported g/day of alcohol, the calculation methods also varied, Jain et al[246] and Schuurman et al[243] used alcohol data from various food composition tables including the United States Department of Agriculture Food Composition Handbook No. 8[70], whereas Ellison et al[247] estimated the amount of pure alcohol based on set proportions of alcohol for different alcohol types (5% for beer, 13.5% for wine and 40% for spirits). Within alcohol types, the differences in the choice of reference category could also have caused such inconsistent findings. Most studies tended to use non-drinkers of each alcohol type as the reference category, whereas Schuurman et al[243], Putnam et al[244], Albertsen et al[242] and Platz et al[245] used non-drinkers of any alcohol as the reference category.

Another reason for the lack of a general pattern in reported risks for alcohol consumption (and also to a lesser extent for other dietary factors) may be the considerable variation in the potential confounding factors that were adjusted for. The extent to which potential confounding factors were controlled for ranged from age only[241] to multivariate models in which demographic, lifestyle, dietary intake and family history factors were adjusted for[134;247].

Energy intake was only adjusted for in a few of the studies examining alcohol consumption[244-248], this was mainly due to the lack of data on energy intake, instead

most studies adjusted for BMI. As mentioned previously, energy intake is an important potential confounder, especially as it is a large component of alcoholic beverages. Regular consumers of alcohol may obtain a substantial proportion of their total energy intake from alcohol[230] and in cases of chronic alcohol abuse, alcohol may account for as much as 50% of an individuals daily total energy intake[231].

Residual confounding by socio-economic status or other factors related to socio-economic status might explain the variation in the patterns of association between PCa and different types of alcohol. Beer consumption is more common in lower social classes[257], whereas consumption of wine is more associated with higher social classes. As socio-economic status may influence availability and access to health care, as well as attitudes and concerns over health in general thereby influencing PSA screening and stage of presentation[3]; it is therefore of utmost importance that socio-economic status is controlled for. With this regard, the stronger positive associations between wine consumption and localised PCa observed by Schuurman et al[243] (OR = 4.6, 95%CI 2.6-13.4) may suggest a socio-economic status effect related to increased use of medical services (including PSA screening) among men with a higher socio-economic status.

3.6.4 Conclusions

Evidence from this literature review suggests that several components of diet, in particular meat, vegetables and lycopene, may be associated with PCa risk. It is the aim of this thesis to examine these potential dietary factors within a population known for its 'unhealthy' diet and relatively high rate of PCa, using a study design and methodology based on the methodological considerations discussed in chapter 2. To my knowledge this is the first epidemiological study to examine the effect of diet on PCa in Scottish men alone. Further details of this aim and the hypotheses to be tested are discussed in the next chapter.

4 . Chapter 4: Methodology

This chapter describes the aims and objectives of the thesis and the methodology used, including subject recruitment, data collection and data analysis.

4.1 Aims and Objectives

4.1.1 Aim

The main aim of this study was to investigate the association between PCa and foods and nutrients commonly consumed by Scottish men (see Table 4.1) and which previous literature (as discussed in Chapter 3) suggest are associated with a protective effect against / increase of risk of PCa.

Table 4.1: List of the specified dietary factors

Nutrients and minerals

- Total energy (EI)
- Protein
- Total fat and its constituents
- Alcohol
- Calcium
- Selenium
- Retinol
- Carotenes
- Vitamin E
- Vitamin C
- Isoflavones

Food groups

- Alcohol Consumption
- Dairy products
- Meat products
- Soy products
- Fruit
- Vegetables

4.1.2 Main objectives

1. To assess the dietary intake of the above dietary factors, for all subjects and also by case / control status.

2. To examine the inter-association between the above dietary factors and also potential confounding factors (see Table 4.2).

3. To analyse the above dietary factors by case / control status in order to obtain crude ORs and 95%CIs.

4. To repeat the above objective, adjusting for potential confounders.

5. To test for interaction between the above dietary factors and potential confounders.

6. To examine the possible variation in the effect of dietary factors on PCa risk between younger and older subjects, by repeating steps 3 and 4, stratifying by age group.

Table 4.2: List of potential confounding factors

Potential confounding factors:

- Age
- Family History of PCa and BRCa
- Carstairs deprivation index
- Smoking status
- EI:BMR ratio
- BMI

N.B. EI was also included as a potential confounding factor.

4.1.3 Hypotheses

It was hypothesed that there would be an association between the below dietary factors and PCa:

- Protein *(hypothesed to increase risk of PCa)*
- Total fat and its constituents *(hypothesed to increase risk of PCa)*
- Calcium *(hypothesed to increase risk of PCa)*
- Selenium *(hypothesed as being protective against PCa)*
- Retinol *(hypothesed to increase risk of PCa)*
- Carotenes *(hypothesed as being protective against PCa)*
- Vitamin E *(hypothesed as being protective against PCa)*
- Vitamin C *(hypothesed as being protective against PCa)*
- Isoflavones *(hypothesed as being protective against PCa)*
- Alcohol *(hypothesed to increase risk of PCa)*
- Dairy products *(hypothesed to increase risk of PCa)*
- Meat products *(hypothesed to increase risk of PCa)*
- Soy products *(hypothesed as being protective against PCa)*
- Fruit *(hypothesed as being protective against PCa)*
- Vegetables *(hypothesed as being protective against PCa)*

N.B. Due to the lack of information regarding lycopene intake, unfortunately the hypothesis that lycopene in associated with a specific protective affect against PCa cannot be tested.

4.2 The PCANDIET Study

This thesis was based on PCANDIET: A population based epidemiological case-control study of PCa in relation to inherited susceptibility and diet, and focused mainly on the dietary side of this study. The PCANDIET study took place between 1998 and 2002 at the Department of Community Health Sciences, University of Edinburgh and was headed by Professor Freda Alexander. It was funded by Cancer Research UK (CRUK) and the Food Standards Agency (FSA) (as part of an ongoing group of projects investigating phyto-oestrogens).

The protocol was for a population based epidemiological case-control study of prostate cancer. The main aims of the study were:

1. To investigate dietary factors specified in advance as being protective against, or as increasing risk of, clinically important (or progressive) PCa.
2. To investigate polymorphisms of the androgen receptor (AR) gene as modulator of risk of clinically important (or progressive) PCa cancer.
3. To examine synergism between inherited susceptibility and dietary constituents.

The specified dietary factors were:

- Phyto-estrogens (hypothesised as being protective)
- Carotenes (hypothesised as being protective)
- Animal and total fat (hypothesised to increase risk)
- Red meat (hypothesised to increase risk)

It should be noted that the PCANDIET study also used blood samples to examine certain genetic polymorphisms and also to analyse phyto-oestrogen serum concentrations in order to validate the Scottish Collaborative Group - Food Frequency Questionnaire's (SCG-FFQ) ability to assess isoflavone intake accurately. The genetics part of the PCANDIET study was not included in this thesis.

N.B. Some of the work in this thesis will refer to work done by other collaborators of PCANDIET. Where the work was undertaken by others, this is explicitly noted in the text, otherwise the work was conducted by the author.

4.3 Ethical Approval

Ethical approval was obtained for this study from the Multi-centre Research Ethics committee for Scotland (MREC) and the appropriate Local Research Ethics Committees (LRECs). In addition, permission to contact potential subjects were obtained from the respective consultants / GPs and informed consent was obtained from each subject agreeing to take part in the study.

4.4 Study subjects

The study was made up of three subject groups (one case and two control groups):

- **Cases:** Subjects newly diagnosed with clinically important PCa, see below for more details (proposed n = 400).
- **Controls:**
  - **Benign Prostatic Hyperplasia (BPH) controls:** Subjects newly diagnosed with BPH but with no diagnosis of PCa. (proposed n = 200).
  - **Population controls:** Subjects randomly selected from the target population, who had no diagnosis of PCa. (proposed n= 335).

The recruitment of BPH controls ensured that a proportion of controls were histologically confirmed as not having PCa, thereby reducing the likelihood of selection bias, unlike the population controls for which there is a possiblity for the presence of undiagnosed asymptomatic PCa. A more detailed discussion can be found in Chapter 6, section 2.

At the start of the PCANDIET study, power calculations were undertaken to calculate the sample size required to give 80% power to detect ORs of 2.0 for comparison between dichotomous genetic polymorphism categories in addition to comparisons of highest versus lowest dietary intake categories. The formula for these power calculations is found in Bland, 1995[271]. The sample of size of 935 was found to be suitable for the above comparisons.

4.5 Subject recruitment

N.B. Please see appendix for copies of subject correspondence letters etc.

4.5.1 Recruitment of cases

Identification of potential cases

All cases of clinically important PCa (defined as grade > T1a and Gleason Score > 4) newly diagnosed between April 1998 and December 2001 at hospitals within the Lothian, Borders and Glasgow Health Boards, whilst resident in Greater Glasgow, Lothian and Borders and aged 50 - 74 years were eligible.

Monthly computer downloads of newly diagnosed cases from each hospital (including details of name, age and address and treating consultant and GP), were collected and checked to confirm diagnosis was 1st diagnosis of PCa, before being assigned an individual ID number and added to the PCANDIET database. Once on the database these potential cases were checked for eligibility (age and residence), any cases found to be ineligible due to age or residence were given a status of INELIGIBLE and were omitted from further recruitment stages.

The following recruitment procedure was then performed for each potential case. Please see Figure 4.1 for an overview of the subject recruitment strategy.

Approach of treating consultant

The treating consultant of each eligible potential case was approached by letter in order to obtain permission to approach the potential case and also to confirm that the potential case was diagnosed with PCa after 1st April 1998 and was mentally capable of completing the FFQ. The name and address of the GP, in addition to the potential case's address was also asked to be confirmed.

If the treating consultant indicated diagnosis was before 1st April 1998 or that the potential case was mentally incapable of completing the FFQ, the potential case was given the status of INELIGIBLE. If the treating consultant did not wish the otherwise eligible potential case to be approached, the potential case was given the status of

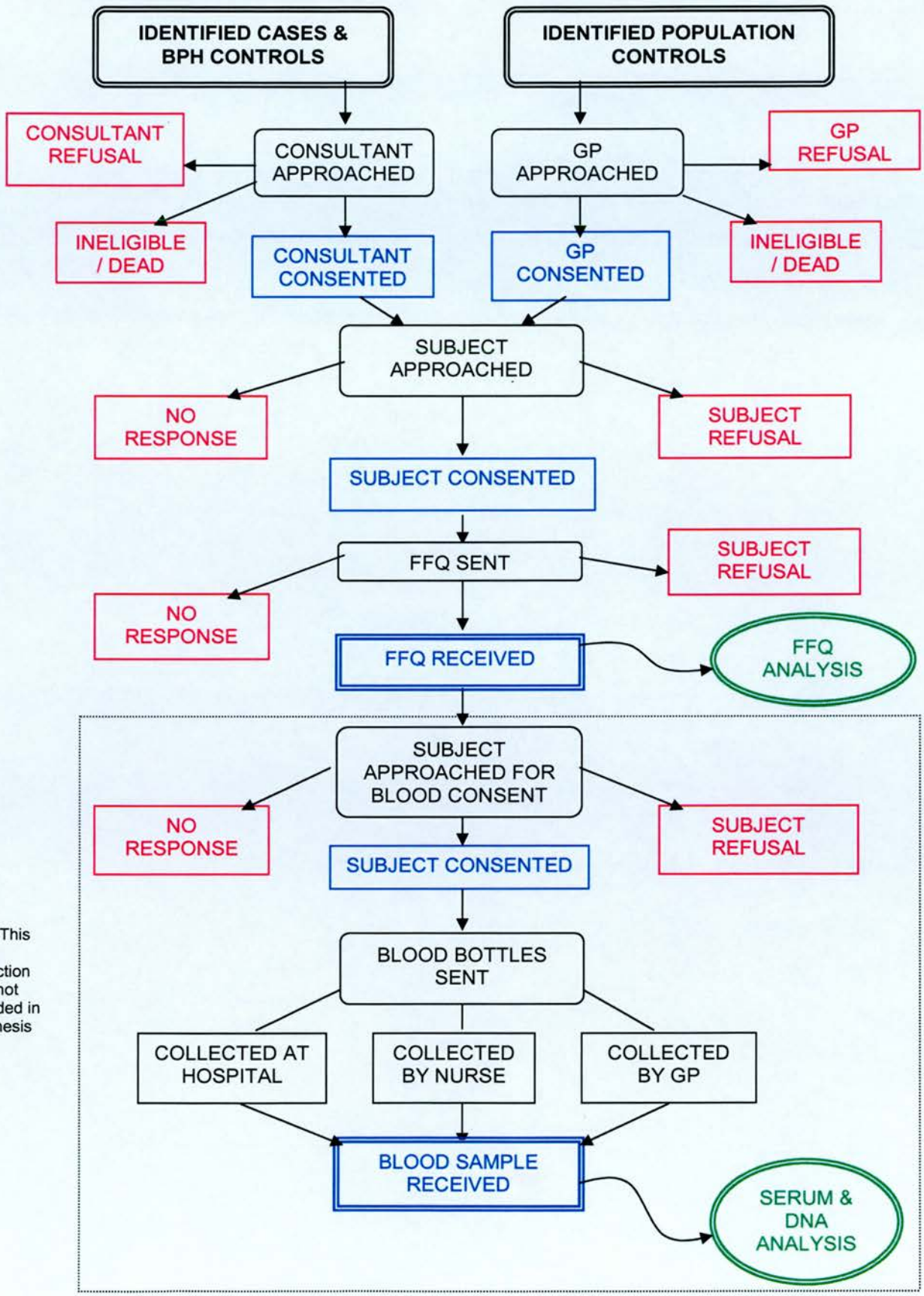
CONSULTANT REFUSAL. In both these cases, the potential case was omitted from further recruitment stages.

Approach of potential case

Having received permission from the treating consultant, each eligible potential case was approached by letter in order to invite them to take part in the study. The letter and enclosures included an outline of the study and what it would entail. Permission was also asked to check their medical records and also to inform their GP of their participation in the study.

If the potential case did not wish to take part, they were given the status of CASE REFUSAL and were omitted from the study. Otherwise they were given the status of CASE CONSENT and were recruited to the study.

Figure 4.1: Subject recruitment summary



N.B. This data collection was not included in the thesis

4.5.2 Recruitment of BPH Controls

Identification of potential BPH controls

All cases of benign prostatic hyperplasia (BPH) newly diagnosed between April 1998 and December 2001 at the Western General Hospital, Edinburgh and Borders General Hospital, Melrose, whilst resident in Greater Glasgow, Lothians and Borders and aged 50 - 74 years were eligible. Monthly downloads of newly diagnosed BPH cases from each hospital were collected and checked to confirm diagnosis (i.e. no evidence of PCa), before being assigned an individual ID number and added to the PCANDIET database. Once on the database these potential BPH controls were checked for eligibility (age and residence), any controls found to be ineligible due to age or residence were given a status of INELIGIBLE and were omitted from further recruitment stages.

The following recruitment procedure was then performed for each potential BPH control. Please see Figure 4.1 for an overview of the recruitment strategy.

Approach of treating consultant

The treating consultant of each eligible potential BPH control was approached by letter in order to obtain permission to approach the potential BPH control and also to confirm that the potential BPH control was diagnosed with BPH after Jan 1998 and was mentally capable of completing the FFQ.

If the treating consultant indicated diagnosis before Jan 1998 or that the potential BPH control was mentally incapable of completing the FFQ, the potential BPH control was given the status of INELIGIBLE. If the treating consultant did not wish the otherwise eligible potential BPH control to be approached, the potential BPH control was given the status of CONSULTANT REFUSAL. In both these cases, the potential BPH control was omitted from further recruitment stages.

Approach of potential BPH Control

Having received permission from the treating consultant, each eligible potential BPH control was approached by letter in order to invite them to take part in the study. The letter and enclosures included an outline of the study and what it would entail. Permission was also asked to inform their GP of their participation in the study.

If the potential BPH control did not wish to take part, they were given the status of CONTROL REFUSAL and were omitted from the study. Otherwise they were given the status of CONTROL CONSENT and were recruited into the study.

4.5.3 *Recruitment of Population controls*

Random selection of population controls by age distribution

Population controls were age-frequency matched to cases (five-year age groups) and by health board region. Table 4.3 shows the five-year age distribution of population controls requested.

Table 4.3: Distribution of population controls requested

Age group	Health Board		
	Borders	Greater Glasgow	Lothian
<55	0	7	6
55-59	2	11	13
60-64	6	31	33
65-69	12	60	70
70-74	2	38	43
Total	***22***	***147***	***165***

Identification and recruitment of potential population controls

Due to varying conditions imposed for ethical approval for control selection and recruitment across the Health Boards, different recruitment procedures were used.

Borders Health Board

Borders Health Board gave access to their Health Board lists in order to select potential controls. The request for twenty-two potential primary controls and four replacement controls for each control (in case the primary control was ineligible or did not wish to take part in the study), with a given birth month/year, was sent to the data department at Borders Health Board with instructions to use the same control selection methodology as used in a previous study (Scottish and Newcastle Epidemiological Study of Hodgkin's Disease).

Once the download of the potential primary and replacement controls (including details of name, date of birth, address and GP) were received, the potential primary controls were assigned an individual ID number and added to the PCANDIET database. Once on the database the potential controls' eligibility (age and residence in the Borders region) was confirmed, any primary controls found to be ineligible due to age or residence were given a status of INELIGIBLE and were omitted from further recruitment stages. Ineligible primary controls were replaced with a respective replacement control.

The following recruitment procedure was then performed for each potential Borders population control. Please see Figure 4.1 for an overview of the subject recruitment strategy.

Approach of Borders general practitioners

The named GP of each eligible potential Borders population control was approached by letter in order to obtain permission to approach the potential population control and also to confirm that the potential control was eligible to take part in the study (i.e. no previous diagnosis of PCa and mentally capable of completing the FFQ). The GP was also asked if the control was currently receiving therapy by finasteride or any other drug for BPH and to confirm the potential control's address.

If the GP indicated a previous diagnosis of PCa or that a potential population control was mentally incapable of completing the FFQ, the potential population control was given the status of INELIGIBLE. If the GP did not wish an otherwise eligible potential population control to be approached, the potential population control was given the status of GP REFUSAL. In both these cases, the potential population control was omitted from further recruitment stages, and a respective replacement control was selected.

Approach of potential Borders population control

Having received permission from the GP, each eligible potential Borders population control was approached by letter in order to invite them to take part in the study. The

letter and enclosures included an outline of the study and what it would entail. The control was also asked to confirm that they had never been given a diagnosis of PCa.

If the potential control did not wish to take part, they were given the status of CONTROL REFUSAL and were omitted from the study. As in the previous steps, a respective replacement control was then selected. Otherwise they were given the status of CONTROL CONSENT and were recruited to the study.

Lothian Health Board

Like Borders Health Board, Lothian Health gave us access to their Health Board lists in order to select potential controls. However, in order to protect patient identities under the Data Protection Act 1998, Lothian Health undertook to contact the selected potential Lothian population controls and their GPs, as outlined in Steps 1 and 2 above, themselves. The request for 165 population controls with a given birth month/year was sent to the data department at Lothian Health Board, with instructions to select at random potential controls who were born within the given birth month/year and who resided within the Lothian area. Once contacted by Lothian Health Board (after receiving permission from their GP), potential Lothian population controls would then send their reply to the PCANDIET Team.

If the potential Lothian population control did not wish to take part, they were given the status of CONTROL REFUSAL and were omitted from the study, otherwise they were given the status of CONTROL CONSENT and were recruited into the study. Recruitment updates were exchanged at fortnightly meetings.

Greater Glasgow Health Board

Unlike the other Health Boards, Greater Glasgow Health Board did not allow access to their health board lists. Instead, GP patient lists from individual GP practices allowing access to their patient lists were used as a sampling frame to select Glasgow population controls with the birth month/year as requested.

Selection of Greater Glasgow general practitioners

Using the Greater Glasgow GP practice list received from Information Services at Greater Glasgow Health Board, 115 Glasgow GP practices were selected at random, weighted according to the number of men aged 50-74 in each practice. The number of GP practices was chosen so as to allow for an average of two controls to be selected from each consenting GP practice and a refusal / non-response rate of approximately 40%. The first GP listed for each selected GP practice was chosen as primary contact.

Approach of Greater Glasgow general practitioner

The 115 selected GP practices were approached in three batches (West Glasgow (n=22), South Glasgow (n=48), North and East Glasgow (n=45)) by letter in order to ask permission to randomly select potential Glasgow population controls from their practice lists. If the GP practice agreed, they were also asked if they would be prepared to collect a blood sample from the controls agreeing to participate in the study. The name and telephone number of the appropriate contact (usually the practice manager) was also asked for.

If permission to access their patient lists was given, each GP practice was assigned Glasgow population control IDs with respective birth month/years and the GP practice was given the status of GP CONSENT. If the GP practice did not wish to participate or did not respond to the reminder letter (see Reminder Letters section below), the GP practice was given the status of GP REFUSAL or GP NON-RESPONSE respectively and were not contacted again.

Selection of potential Greater Glasgow control

Each consenting GP practice was visited, during which the required number of primary controls and their five replacements were selected at random according to the required birth month/year(s) using the procedure as described in the appendix (See Appendix - recruitment). The name, address and date of birth of each potential control were noted on the control selection form, and then given to the GP in order to confirm eligibility and to give permission to contact the control.

Approach of potential Greater Glasgow population control

Once each completed and signed control selection form was returned by the GP practice, the first potential Glasgow population control on each form was assigned an ID number and his details were entered into the PCANDIET database. If the GP indicated the potential control to be ineligible or did not wish him to be contacted, the potential population control was given the status of INELIGIBLE or GP REFUSAL respectively and was omitted from further recruitment stages. The next potential Glasgow population control was then selected from the respective control selection form. If the GP gave his permission to approach the potential control, the control was approached by letter in order to invite them to take part in the study.

If the potential Glasgow population control did not wish to take part, they were given the status of CONTROL REFUSAL and were omitted from the study. As in the previous steps, the next replacement control from the respective control selection form was then selected. Otherwise they were given the status of CONTROL CONSENT and were recruited into the study.

4.5.4 Mailing of the Scottish Collaborative Group - Food Frequency Questionnaire (SCG-FFQ)

Recruited subjects were sent an SCG-FFQ with an attached information sheet regarding completion guidelines and portion sizes and a cover letter (see appendix: FFQ and FFQ information sheet). A free phone number was also given for population controls to telephone if they had any queries about the FFQ and it's completion. If a subject still had difficulty in completing the FFQ, a research nurse would then be sent round to help them in person.

4.5.5 Case-note review

For those recruited cases that gave consent to check hospital records, research nurses visited the hospital where the appropriate case-notes were kept in order to review each cases' case-notes regarding the PCa diagnosis, prognosis and treatment.

4.5.6 Permission to give blood sample

Once the completed FFQ had been returned, subjects were also asked to give a blood sample for serum phyto-oestrogen and DNA analysis. This was not part of the present thesis, although the serum phyto-oestrogen data was used to validate the SCG-FFQ.

4.5.7 Reminder letters

Subjects who had still not replied to any of the recruitment / data collection steps after four weeks were re-sent the required letter and enclosures, along with a covering letter reminding them to reply. If after another four weeks the subject had still not replied, depending on the stage of recruitment reached, the subject was either deemed as a NON-RESPONDER and a replacement was selected or LOST TO FOLLOW-UP, their statuses were changed accordingly.

4.6 Subject response analysis

Subject response rates (proportion of subjects agreeing to participate within the total number of eligible subjects contacted) were examined across status, Health Board, Carstairs Deprivation Index and age group, in order to investigate the possibility of selection bias related to subject status and other characteristics being introduced into the study.

The overall response rate was observed to be 67%, please see Table 4.4. The response rate was also observed to differ significantly ($p < 0.001$) across status, with a higher number of cases agreeing to participate compared to controls. Subjects from the Borders Health Board were far more likely to participate than those from the Greater Glasgow Health Board, as were younger subjects and those with lower levels of deprivation.

N.B. The number of responding subjects differs from the study size used in the analysis (916) due to the inclusion of subjects who were later found to be ineligible (21 subjects) and those who failed to complete an SCG-FFQ.

Table 4.4: Subject response rates

		All subjects	Cases	BPH controls	Population controls (1st choice only)
Status		1016 / 1515 (67%)	481 / 604 (80%)	204 / 277 (74%)	140 / 268 (52%)
	Chi-square test			*p < 0.0001*	
Health Board	Borders	31 / 41 (76%)	10 / 10 (100%)	-	13 / 20 (65%)
	Lothians	660 / 944 (70%)	288 / 355 (81%)	204 / 277 (74%)	69 / 131 (53%)
	Greater Glasgow	325 / 530 (61%)	183 / 239 (77%)	-	58 / 117 (50%)
	Chi-square test	*p = 0.002*	*p = 0.109*	-	*p = 0.439*
Carstairs deprivation index	1	141 / 164 (86%)	73 / 82 (89%)	26 / 29 (90%)	16 / 22 (73%)
	2	149 / 184 (81%)	71 / 86 (83%)	26 / 31 (84%)	27 / 35 (77%)
	3	211 / 280 (75%)	101 / 117 (86%)	54 / 78 (69%)	26 / 40 (65%)
	4	192 / 258 (74%)	86 / 102 (84%)	45 / 59 (76%)	24 / 39 (62%)
	5	139 / 214 (65%)	62 / 86 (72%)	40 / 61 (66%)	14 / 28 (50%)
	6	73 / 116 (63%)	35 / 49 (71%)	8 / 8 (100%)	8 / 22 (36%)
	7	90 / 179 (50%)	45 / 70 (64%)	3 / 2 (40%)	19 / 36 (53%)
	Chi-square test	*p < 0.0001*	*p < 0.0001*	*p = 0.025*	*p = 0.038*
Age group	Younger (≤ 65 yrs)	352 / 494 (71%)	132 / 172 (77%)	108 / 131 (82%)	49 / 95 (52%)
	Older (> 65 yrs)	664 / 1021 (65%)	349 / 432 (81%)	96 / 146 (66%)	91 / 173 (53%)
	Chi-square test	*p = 0.016*	*p = 0.265*	*p = 0.002*	*p = 0.873*

4.7 Subject data processing and management

4.7.1 Assignment of ID numbers

Subjects were assigned ID numbers in order to protect the subjects' identity and also to ensure that the laboratory technicians were blinded to the status of each subject. The ID number consisted of three digits for cases, four digits for BPH controls and five digits for the population controls, the ID number range is summarised in Table 4.5.

For cases and BPH controls, ID numbers were assigned consecutively according to the order in which they were identified from the hospital files. For the population controls, the first four digits denoted the control number, whereas the fifth digit identified the control choice (primary or replacement control).

Table 4.5: ID distribution by status

Status	ID Range
Cases:	1 to 980
BPH Controls:	7000 to 7615
Population Controls:	
Borders:	20000 to 20201
Lothian:	10000 to 11970
Glasgow:	30000 to 31774

4.7.2 Subject recruitment spreadsheets

Recruitment and subject details were stored and managed in Microsoft Excel spreadsheets that made up the PCANDIET database. Each subject group had their own spreadsheet. The spreadsheets contained the information as listed in Table 4.6. In addition to storing recruitment information, the spreadsheets were used to mail-

merge recruitment and data collection correspondence in conjunction with Microsoft Word and also to create recruitment updates for the monthly team meetings.

Once all the recruitment and data collection stage was completed, time was taken to clean the recruitment data, checking dates and recruitment status and correcting incorrect date sequences.

Table 4.6: List of details included in recruitment spreadsheets

	Column Title	Data
1.	ID	Assigned ID number
2.	Ctrl Choice	Control choice number (population controls only)
3.	Status	Recruitment status
4.	Recruited	Subject recruited (yes/no/ineligible)
5.	Case Note Review	Case note review done (cases only)
6.	DT Target	Date consultant / GP contacted. (not used for Lothian population controls).
7.	DT Cons/ GP Resp	Date Consultant / GP responded.
8.	DT Subject Resp	Date Subject responded.
9.	Last Name	Subject's last name.
10.	First Name	Subject's first name.
11.	DOB	Subject's date of birth.
12.	DODIAG	Subject's date of diagnosis (Cases and BPH controls only).
13.	Ref Date	Reference date for calculation of age.
14.	Age	Subject's age (at time of recruitment)
15.	Treating Consultant	Subject's treating consultant (Cases and BPH controls only).
16.	Treating Hospital	Subject's treating hospital (Cases and BPH controls only).
17.	ConsAddress_1, _2, _3	Consultant's address and postcode (Cases and BPH controls only).
18.	Unit No	Unit Number.
19.	Address_1, _2, _3	Subject's address and postcode.
20.	FFQ Sent	Date FFQ sent.
21.	FFQ Recvd	Date FFQ received.
22.	GP	Subject's GP (not Lothian controls).
23.	GPAddress _1, _2, _3	GP's address and postcode (not Lothian controls).
24.	Blood App	Date of approach for consent to give blood sample.
25.	Blood Cons	Date of consent to give blood sample
26.	GP No	GP not willing to take blood (population controls only).
27.	ID_B	ID + control choice (population controls only)
28.	Blood WGH	Date of blood sample received at WGH Laboratories, Edinburgh
29.	Blood Cardiff	Date of blood sample received at Cardiff laboratories (Cases and population controls only).
30.	Comments	Additional subject details.

4.8 FFQ Data collection and collation

4.8.1 The Scottish Collaborative Group food frequency questionnaire

The FFQ used in this study was the validated Scottish Collaborative Group Food Frequency Questionnaire (SCG-FFQ), Version 6.31, previously known as the Aberdeen Food Frequency Questionnaire, see Appendix: FFQ. This FFQ, modified by Geraldine McNeil and colleagues at the University of Aberdeen, has been based on a FFQ that has been extensively used in Scottish populations[50] and has been validated against, 4-day weighed diet records[259]; and now also against serum phyto-oestrogen concentrations.

The SCG-FFQ consisted of a list of 150 foods, divided into 20 food groups (as described in Table 4.7). Subjects were asked to describe the amount and frequency of each food on the list they had eaten in the last 2-3 months. For those foods that were never or rarely eaten (< once a month), subjects were asked to circle 'R' (rarely / never). For foods that were eaten once a month or more, subjects were asked the amount of food eaten in one day (1 measure – 5+ measures), and the number of days in a week the food was usually eaten (once a month to 7 days per week). An FFQ information sheet, which included a colour picture showing examples of the size of measures, was enclosed with the FFQ. Subjects were also given the opportunity to add other foods that they ate regularly. The FFQ also contained questions on the type and amount of vitamins, minerals and food supplements taken, recent dietary change and special diets / dietary restrictions, general information questions (age at completion of FFQ, height, weight, smoking status) and family history of PCa / BrCa and other prostate / breast problems.

Table 4.7: FFQ food groups and other sections

FFQ Section	Food Group / Other questions
1. a – d	Bread
2. a – f	Breakfast Cereals
3. a – d	Milk
4. a – e	Cream and Yogurt
5. a – e	Cheese
6. a – c	Eggs
7. a – n	Meats
8. a – l	Fish
9. a – i	Potatoes, Rice and Pasta
10. a - s	Savoury Foods, Soups and Sauces
11. a – q	Vegetables
12. a - j	Fruit
13. a - f	Puddings
14. a - h	Chocolates, Sweets, Nuts and Crisps
15. a - g	Biscuits
16. a - e	Cakes
17. a - g	Sugar and Spreads
18. a - g	Beverages and Soft Drinks
19. a - i	Alcoholic Drinks
20. a - d	Other Foods
Other Sections	
21. a - b	Vitamin, Mineral and Food Supplements
22. a - g	Dietary Restrictions
23. a - b	Special Diets
24. a - g	General Information
24. h - s	Family History Information

4.8.2 Processing of the SCG-FFQ

Data from the SCG-FFQ was extracted using the scanning software package TELEForm (version 5.2, Cardiff Software, Inc., San Marcos, CA), set up by Sherry Patheal (database manager) and Alastair Murray (computing assistant).

A data entry clerk was employed to process, review and scan the FFQs. She was supervised by the author, who was also responsible for cleaning and processing the FFQ data ready for the nutrient calculation and in house analysis. The FFQ processing procedure was as follows:

FFQ receiving process and storage

Completed FFQs were grouped according the subject status and allocated a storage file, the number of which was written on the front of the FFQ. Each storage file held ten FFQs and was grouped together in sets of three storage folders.

Pre-scan review process

Before the scanning, the pre-scan review was done using the FFQ Review checklist (Table 4.8) to insure that the FFQ was complete and ready to scan. Once the FFQ had been reviewed, and if necessary referred to and returned by the supervisor (author), it was deemed ready to scan.

Table 4.8: FFQ checklist

1.	ID number	ID was written in the top right hand corner of each FFQ page.
2.	Removal of staples	The staples holding the FFQ together were removed to facilitate the scanning, afterwards FFQs were stored in plastic folders.
3.	Data checks	Each page of the FFQ was reviewed, where required the response was enhanced so that Teleform would identify the response, i.e. circles which were too light (pale pen or pencil) or too small, or if tick marks were used instead. The FFQ was referred to the supervisor if there was any question regarding the readability, if a frequency question had more than one response or if whole sections had not been completed by the subject.
4.	Coding	Questions 17e and 17g were open-ended questions relating to the spreads, fats and oils consumed. Codes were entered onto the FFQ according to the type of spread / fat / oil (see appendix: Data collection for code sheets).
5.	Other foods	Section 20 allowed subjects to record foods that were not included in the FFQ and that they regularly ate, if the subject had reported any 'other foods', the FFQ was referred to the supervisor.
6.	Comments	Any FFQ on which the subject had written comments were referred to the supervisor.

SCG-FFQ referral

Those FFQs referred to the supervisor (author) were dealt with according to the procedures summarised below:

Data Check Referrals

For Frequency questions in which there was more than one response, the lowest response was recorded.

For FFQs with incomplete sections that were deemed to have been skipped by mistake, a copy of the incomplete page was sent to the subject to fill in. Once returned, the section was added to the original FFQ.

Other Foods

Where the subject had reported 'other foods', a list of other foods devised by Geraldine McNeill and colleagues at the University of Aberdeen was used to add these foods to existing food group questions. If there was no suitable alternative, a note was made for reference in the analysis stage.

Comments

Any comments made by the subject were noted for future reference and acted upon if thought to be important.

Scanning process

FFQs noted as ready to scan, were scanned using a multi-page scanner and the software scanning package TELEForm. Once the FFQ had been scanned into the computer, it was then verified using the TELEForm Verifier. This process involved verifying and checking that the FFQ data had been scanned and read correctly, particularly that open answer questions were read and identified correctly and that the chosen value for multiple response answers was correctly identified. The FFQ data was then automatically saved and exported to an SPSS file. Once the FFQ had been scanned and verified, the FFQ was returned to its respective folder.

4.8.3 FFQ data preparation

The FFQ data was cleaned and processed to create FFQ datasets for food group / family history analysis and for the individual calculation of nutrient intakes. This process was done in batches of 100 – 250 FFQs.

Each batch was checked for odd ID numbers, date / weight / height values, missing variables and duplicate study numbers. Data for several FFQs picked at random were checked with the hard copy of the FFQ. The data file was then processed using an SPSS Macro devised by Sherry Patheal, database manager in which:

1. If the bread type (Qu. 1) was blank, a default value of all three bread types was assigned.

2. If a day-variable (number of days eaten per week) value was blank, a default value of 'B' was assigned as the day-value.

3. If a measure-variable (number of measures eaten in a day) value was blank, but the day-variable value was neither blank or 'R' (rarely or never), a default value of '1' was assigned as the measure-value.

4. If an food exclusion variable (Qu. 22) had a value of 'yes', but the subject had reported eating this food, a flag was created.

The fixed ascii file (DAT file) created was sent to Dr David Grubb at the Rowett Research Institute, Aberdeen for the nutrient intake calculations. The SPSS 'inhouse' file was processed and saved for food-group and family history analyses.

4.8.4 Nutrient intake calculations

The FFQ data were processed using software based on the Oracle Relational Database Management System (Version 7), which has been developed and routinely used at the University of Aberdeen. Intake estimates of 39 specific nutrients and minerals, in particular the isoflavones daidzein and genistein, were calculated using the UK National Nutrient Databank, based on McCance and Widdowson's The Composition of Foods (5th edition)[60] and related supplements[61-69], and also the new

validated Isoflavone Food Table[71;260], constructed by Margaret Ritchie at the University of St Andrews. A list of the specific nutrients is shown on Table 4.9.

4.8.5 Food group variables

FFQ food items for several á priori food groups (see Table 4.10) were used to calculate food group intake data, using the procedure below.

The consumption of each individual food item was computed using the formula:

Food item intake = (number of measures) x (number of days)

(N.B. the day responses 'Rarely' and 'Monthly' were recoded to 0 and 0.5 respectively.)

Food group intake was then computed using:

Food group intake = sum of food item intakes within the food group

Grilled meat score

The grilled meat score was calculated using the formula:

Grilled meat score = [qu.7m] x [qu.7n]

Where: qu.7m = number of measures grilled meat per week and qu.7n = meat doneness (1 = lightly browned, 2 = medium browned, 3 = well browned).

Table 4.9: List of Nutrients estimated from the SCG-FFQ

Nutrient	Units
Protein	(g/day)
Fat	(g/day)
Carbohydrate	(g/day)
Energy	(g/day)
Alcohol	(g/day)
Saturated fat	(g/day)
Monounsaturated fat	(g/day)
Polyunsaturated fat	(g/day)
Cholesterol	(mg/day)
Total sugar	(g/day)
Starch	(g/day)
Fibre	(g/day)
Sodium	(mg/day)
Potassium	(mg/day)
Calcium	(mg/day)
Magnesium	(mg/day)
Phosphorus	(mg/day)
Iron	(mg/day)
Copper	(mg/day)
Zinc	(mg/day)
Chloride	(mg/day)
Manganese	(mg/day)
Selenium	(μg/day)
Iodine	(mg/day)
Retinol	(μg/day)
Carotene equivalent	(μg/day)
Vitamin D	(μg/day)
Vitamin E (α tocopherol equivalent)	(mg/day)
Thiamine	(mg/day)
Riboflavin	(mg/day)
Niacin	(mg/day)
Potential niacin (from tryptophan)	(mg/day)
Vitamin B6	(mg/day)
Vitamin B12	(μg/day)
Folic acid	(μg/day)
Pantothenic acid	(mg/day)
Biotin	(μg/day)
Vitamin C	(mg/day)
Isoflavones	(mg/day)

Table 4.10: List of food groups

Food group	FFQ food items (FFQ question number)
Dairy products	
Total dairy	Milk (qu.3), Cream and Yoghurt (qu.4), Cheese (qu.5)
Milk	Milk (qu.3)
Cheese	Cheese (qu.5)
Eggs	Eggs (qu.6)
Meat products	
Total meat	Meats (qu.7: a - l)
Red meat	Meats (qu.7: a,b,c,d,e,g,h,i)
Processed meat	Meats (qu.7: b,c,l,,j,k,l)
Fish	Fish (qu.8)
Grilled meat	Meats (qu.7: m)
Grilled meat score	Meats ([qu.7: m] x [qu.7n])
Fruit & Vegetables	
Total whole fruit	Fruit (qu.12)
Total vegetables (excluding potatoes)	Vegetables (qu.11)
Soy products	Savoury foods, soups & sauces (qu.10: e & g)
Alcohol type	
Drinkers Vs non-drinkers	Alcoholic drinks (qu.19:a)
Beer & lager	Alcoholic drinks (qu.19:b,c,d)
Wine	Alcoholic drinks (qu.19:e)
Spirits	Alcoholic drinks (qu.19:g)

4.8.6 Alcohol intake variables

The consumption of each alcohol type was calculated using the FFQ alcohol items in which consumption of several types of alcohol was reported as the number of units per week across nine categories ranging from 0 units to 40+ units. These categories were recoded into five smaller ones for ease of analysis, as shown in Table 4.11. A category for no overall alcohol consumption, in addition to one for no consumption of each individual type, was also included. The top five original categories were originally recoded into two categories (10-19 & 20+), however these were combined into one large category due the small number of subjects reporting high consumption of each alcohol type.

Table 4.11: Recoding of alcohol categories

Original Alcohol Categories (units per week)	New Categories (units per week)
0	No alcohol consumed
	Consumption of other alcohol types
1-2	1-2
3-4	3-9
5-9	
10-14	10+
15-19	
20-29	
30-39	
40+	

As beer / lager was measured by three items (low alcohol beer / lager, beer and lager), overall beer consumption was calculated by recoding the three beer items to the appropriate category median (see Table 4.12), these recoded beer items were then added together and recoded using the categories as shown in Table 4.10.

Table 4.12: Recoding of beer items for the calculation of overall beer consumption

Original category	Category Median
0	0
1-2	1.5
3-4	3.5
5-9	7.5
10-14	12
15-19	17
20-29	24.5
30-39	34.5
40+	50

4.8.7 Smoking status variable

The smoking status variable was coded using Qu. 24 f in the general information section of the FFQ, as shown in Table 4.13.

Table 4.13: Smoking status coding

Smoking status response (Qu. 24 f)	Smoking status code (smoking)
Non-smoker	0
Ex-smoker	1
Smoker	2

4.8.8 Family history of PCa and BrCa variable

The family history variable was coded using the FFQ family history questions in which subjects were asked whether any male or female relatives had been diagnosed with prostate or breast cancer respectively as shown in Table 4.14.

Table 4.14: Family history of PCa / BrCa coding

FFQ family history response	Family history code (FHIST)
No family history of either PCa or BrCa reported	0
Family history of PCa reported	1
Family history of BrCa reported	2
Family history of both PCa and BrCa reported	3

N.B. It should be noted that the family history variable was based on the responses given in the FFQ and here not followed up for confirmation. Therefore, it is very likely that this variable is prone to recall bias.

4.8.9 Further FFQ data preparation

Calculation of additional anthropometric variables

Additional anthropometric characteristics including: Body Mass Index (BMI), Basal Metabolic Rate (BMR) and the energy intake:BMR ratio (EI:BMR) were calculated using the below formulas:

Body Mass Index (BMI)[261]

$$BMI = weight_{(kg)}/height_{(m)}^{2}$$

Estimated Basal Metabolic Mass (BMR):

Based on formula according to Schofield[262]

- *Men aged 30 to 60 years:*

$$BMR = (0.048 \times weight_{(kg)}) - (0.011 \times height_{(m)}) + 3.670$$

- *Men aged over 60 years:*

$$BMR = (0.038 \times weight_{(kg)}) + (4.068 \times height_{(m)}) - 3.491$$

EI : BMR Ratio (EI:BMR)

Based on formula according to Goldberg et al[263]

$$EI{:}BMR = EI / BMR$$

Low Energy Reporters (LERs)[264]

In order to control for the possible effect of under reporting, Low Energy Reporter status, i.e. those subjects who reported consuming less total energy than their estimated metabolic requirements were computed, using the cut-off point defined by Black et al[264]:

$$Subject\ is\ an\ LER\ when\ EI{:}BMR < 1.10$$

Computation of energy-adjusted nutrient and food group variables

In order to control for the potential confounding effect of total energy intake, the residual method, as determined by Willet and Stampfer[80], was used. This method estimates individual dietary intake when EI is constant. The procedure was as follows:

For each dietary intake variable:

1. Check the distribution of energy intake

Check the distribution of EI to identify any outliers and that the distribution is normally distributed.

2. Check the distribution of dietary intake

For each nutrient / food group check that the distribution is normally distributed. If it is not normally distributed then the data can be transformed.

3. Simple linear regression

Perform simple linear regression with dietary intake variable as response (Y variable) and EI as x variable:

$Y = a + bx$ Where a is the intercept and b the slope.

4. Record the residuals

Save the residuals from step 3. Record the intercept (a) and the slope (b).

5. Calculate mean EI

Calculate the mean EI ($\bar{x}$) i.e. mean of x.

6. Calculate expected nutrient intake, when EI is constant (i.e. equal to its mean)

Calculate the expected dietary intake (y variable) using the formula:

$y = a + (b \times \bar{x})$ Where values for a and b are from step 3. and $\bar{x}$ is mean EI (from step 5.).

Record the value for y for each dietary intake variable.

7. Calculate the energy adjusted dietary intake variable

To obtain the energy adjusted dietary intake value, add y to the residuals recorded in step 4.

8. For previously transformed variables

If the dietary intake in step 2 has been transformed these are to now be reversed. For example if the log transformation of a dietary intake variable has been used then the values obtained in step 7 are to be anti-logged.

9. Analyse the energy adjusted variables

Look at the mean, standard deviation, minimum and maximum of the energy adjusted variable.

Compare the mean of the energy adjusted variable to that of the original variable. The mean should be similar. The standard deviation should be lower for the energy adjusted variable.

There should be no negative values in the energy adjusted variable. If negative values are present go back to steps 1. and 2. to check for outliers and to ensure that the skewness of the data is between –1 and 1.

4.9 Deprivation category data

The Carstairs deprivation index (DEPCAT)[265], based on the 1991 Census data, was assigned to each subject at the postcode sector level. The index contained seven categories ranging from very low deprivation (DEPCAT = 1) to very high deprivation (DEPCAT = 7).

N.B. DEPCAT data was missing for several subjects, due to postcode changes and the exclusion of very small postcode sectors from the DEPCAT calculation.

4.10 Histo-pathological and case-note review

Pathology specimens from all cases were reviewed by Dr Ken Grigor at University of Edinburgh for which the stage and grade of each PCa case was classified and the eligibility confirmed.

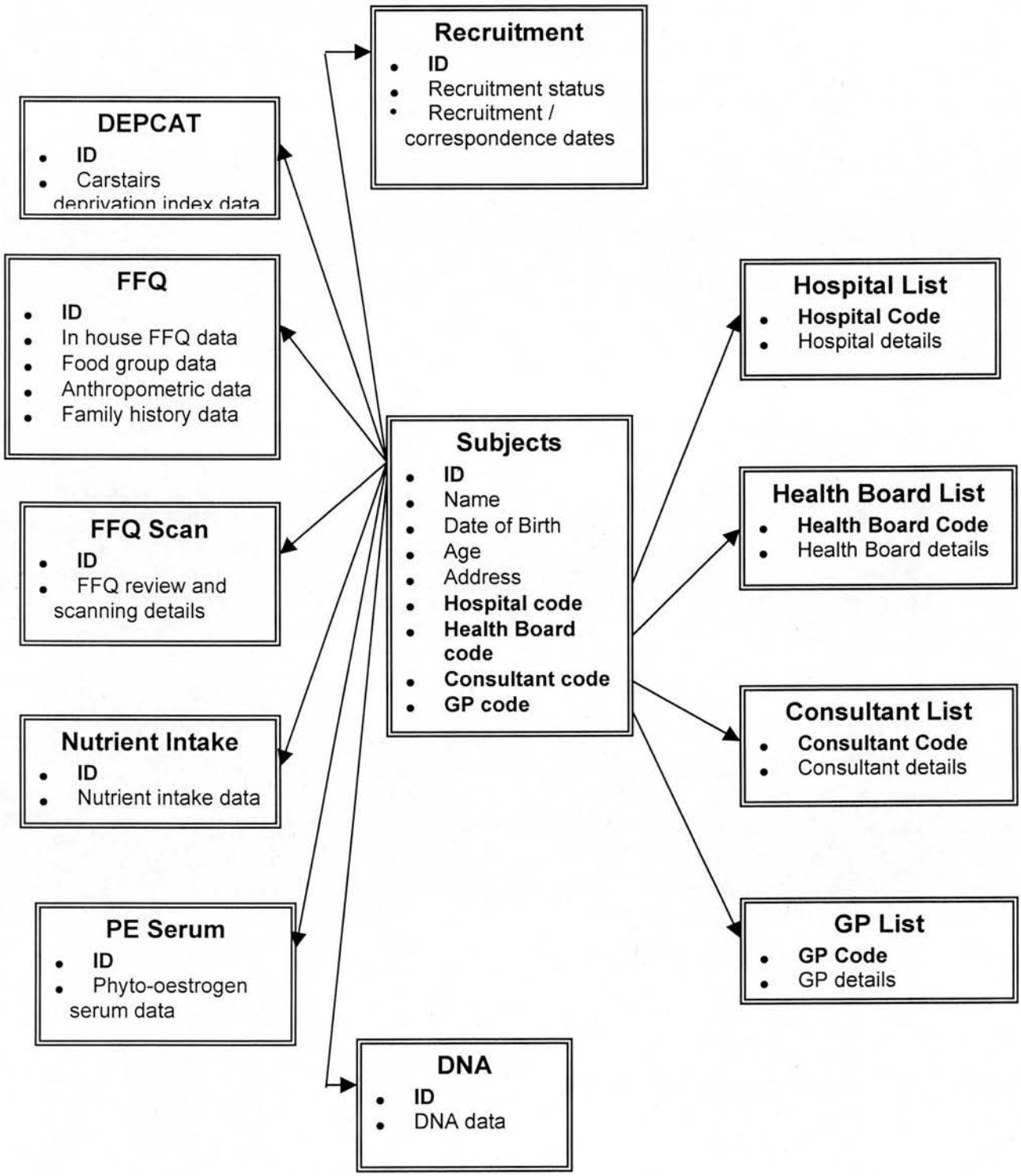
The case-notes were reviewed by the research nurses, supervised Professor Freda Alexander, in order to confirm stage and grade classification and to elucidate any other information regarding diagnosis and prognosis that may be important.

N.B. Stage and grading data was not available for the present analysis.

4.11 The PCANDIET Access Database

Once all the data for PCANDIET was collected and cleaned, it was collated together within one large Microsoft Access database. Each set of data was contained on a separate table, see Figure 4.2 for an overview of the PCANDIET database tables and relationships. The tables were linked together by a key variable (ID number). Although this database was primarily used to store the data in a convenient form, the query function was used to collate data for analysis when needed.

Figure 4.2: PCANDIET database relationship summary



4.12 Data analysis

4.12.1 List of dietary and confounding variables

To test the hypotheses as stated in the aims and objectives section of this chapter, the following nutrient intake and food group variables were included in the analysis:

Nutrients and minerals

1. EI
2. Protein
3. Total fat
4. Saturated fat
5. Mono-unsaturated fat
6. Poly-unsaturated fat
7. Cholesterol
8. Alcohol
9. Calcium
10. Selenium
11. Retinol
12. Carotenes (as carotenoid equivalents)
13. Vitamin E (as α-tocopherol equivalents)
14. Vitamin C
15. Isoflavones

Food groups

1. Total dairy products
2. Milk
3. Cheese
4. Eggs
5. Total meat products
6. Red meat
7. Processed meat
8. Fish
9. Grilled Meat
10. Grilled Meat Score
11. Soy products
12. Alcohol consumption
13. Beer
14. Wine
15. Spirits
16. Whole Fruit
17. Vegetables

The following potential confounding variables were also included in the analysis:

1. Age
2. Family history of PCa and BrCa
3. Carstairs deprivation index (DEPCAT)
4. Smoking
5. EI:BMR ratio
6. BMI (N.B. BMI was not included in the final model as it was shown not to be associated with any dietary factor nor PCa risk)

4.12.2 Statistical analysis

The statistical analyses were conducted using the statistical packages SPSS (version 11, SPSS Inc. USA) and STATA (Intercooled Stata, version 7.0, USA).

The analysis was divided into two main parts, the analysis of nutrient intake and the analysis of selected food groups, the analysis for both these parts followed the same method as follows:

Descriptive analysis

The distributions of each dietary and potential confounding variable were examined. Any extreme values / outliers were investigated with the view of omitting from subsequent analyses using continuous data. Any variable showing a skewed distribution was normalised using log transformation.

A correlation analysis, using Spearman's Rank Correlation was also performed on dietary and potential confounding variables in order to examine any associations between these variables.

The distributions of each dietary and potential confounding variable were then examined by:

- **BPH Vs population controls** (in order to confirm that dietary intake did not vary significantly between these two control groups, thereby allowing for the two control groups to be combined into one control group).
- **Cases Vs BPH and population controls**
- **Potential confounding variables (using categorical variables)**

Differences in dietary intake and confounding variables were tested for significance using both parametric (t-tests: for tests between two groups, and ANOVA: for tests between more than two groups) and non-parametric tests (Mann-Whitney U: for tests between two groups, and Kruskal-Wallis: for tests between more than two groups).

Data categorisation

Continuous dietary and confounding variables were grouped into four categories using quartiles (based on the distributions within the combined control group) as the cut-off points. Categories that had too few subjects in them were combined with the next lowest category.

Odds ratio (OR) analysis

Crude ORs

The association of case / control status with each dietary and confounding variable was examined using 2x4 tables. Each nutrient intake category was compared with the reference category (lowest category) in order to obtain crude ORs and 95% confidence intervals (95%CIs). The score test for a linear trend of the odds ratios was also conducted to examine any potential dose-response effects.

Mantel-Haeszel Test for Interaction

In order to test for any interaction between dietary variables and confounding variables, ORs and 95%CIs were estimated for each dietary variable stratified by each confounding variable using the Mantel-Haeszel method, so as to examine the OR within each individual confounding variable category. Interaction was examined using the Mantel-Haeszel test for homogeneity of ORs.

Log Likelihood Ratio test

The log likelihood ratio test was used to examine the effect of each dietary variable on PCa risk, with and without adjusting for confounding factors. The effect of each confounding variable was also examined.

Multiple logistic regression

Multiple logistic regression models were used to study the effect of each dietary variable adjusting for the confounding variables as listed previously. Adjusted ORs were calculated with 95%CIs.

N.B. Energy-adjusted dietary variables, calculated using the residual method, were included in the model instead of the original dietary variables, in order to control for EI.

Analysis omitting LERs

A descriptive analysis for all dietary and confounding variables by LER status was conducted to examine any variation in dietary intake and confounding between LERs and non-LERs.

The descriptive, crude OR and logistic multiple regression analysis was then repeated omitting LERs in order to examine whether potential misclassification due to under-reporting had effected the estimations of risk.

Analysis stratified by age group

As age is a known risk factor for PCa and that dietary intake has been observed to change with age, it is possible that there may be an interaction between age group and dietary intake, as has been noted by previous studies observing a variation in the effect of dietary factors on PCa between older and younger subjects[98]. The analysis was therefore repeated stratified by two age groups: younger (≤ 65 yrs) and older (>65 yrs).

5 . Chapter 5: Results

5.1 Dataset

The dataset used for analysis contained 916 subjects (after four subjects whose FFQs were found to be reviewed incorrectly and thirteen age ineligible subjects were omitted). Data were complete for all nutrient variables and for age. However data for weight and/or height, on which the variables BMI, EI / BMR ratio and LER status were based on, were missing for twenty nine subjects, and data for smoking status and the Carstairs deprivation index were missing for fifteen and seventeen subjects respectively.

5.2 Subject characteristics

The 916 subjects consisted of 433 cases and 483 controls, see Table 5.1. The majority of continuous general characteristics, including the potential confounding variables (see methods chapter for list of confounding variables) were normally distributed, see Figure 5.1. An exception was age which was skewed towards the older age groups, where the incidence of PCa increases. The distributions of categorical general characteristics are also shown in Figure 5.1. The majority of subjects reported no family history of either PCa or BrCa (74.8%) and were either non- or ex-smokers (81.4%). They also tended to be low to moderately deprived (Carstairs deprivation index 3 and 4), with relatively few subjects being highly deprived (Carstairs deprivation index 6 and 7).

Table 5.1: Study subjects

Subject Group	Number of eligible subjects (%)
Cases	433 (47)
Controls	
• BPH controls	178 (20)
• Population controls	305 (33)
Total	***916 (100)***

Figure 5.1: Distributions of general characteristics and potential confounders

Fig 5.1a: Age

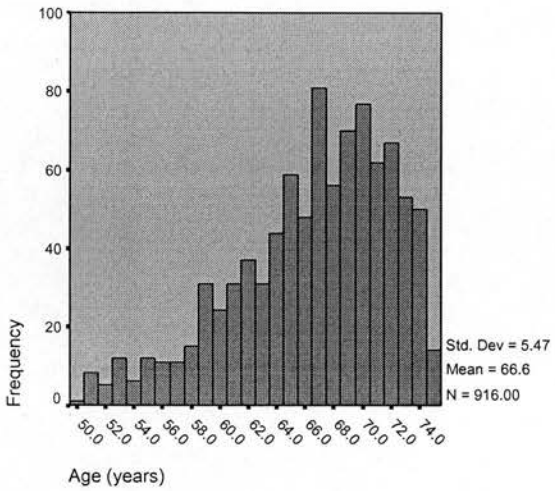


Fig 5.1b: Height

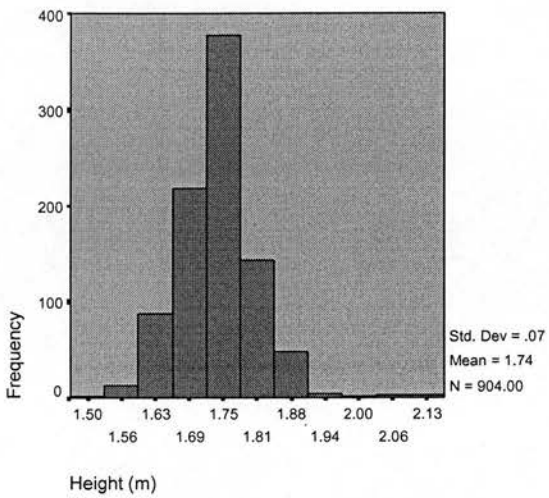


Fig 5.1c: Weight

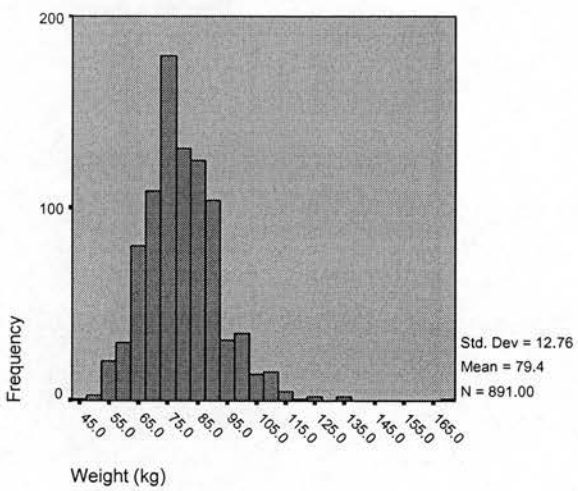


Fig 5.1d: BMI

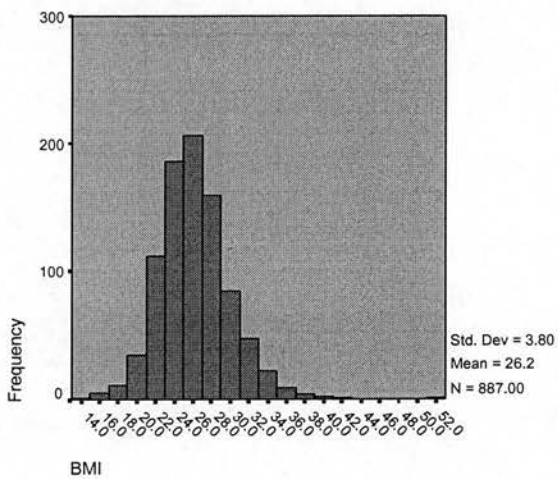


Fig 5.1e: EI / BMR ratio

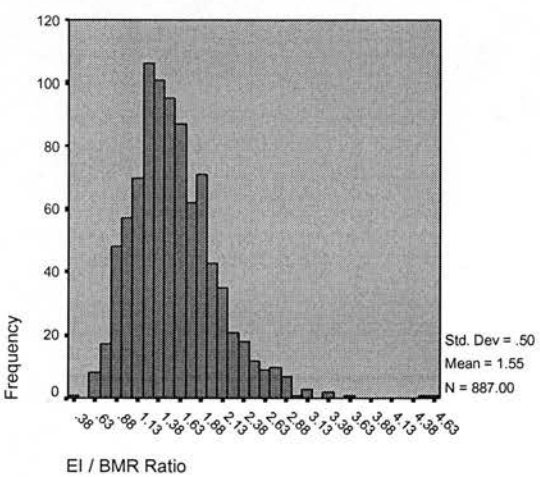


Fig 5.1, cont.: Distributions of general characteristics and potential confounders

Fig 5.1f: Family history

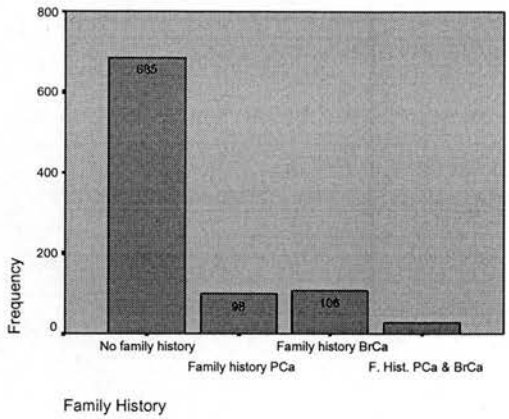


Fig 5.1g: Smoking status

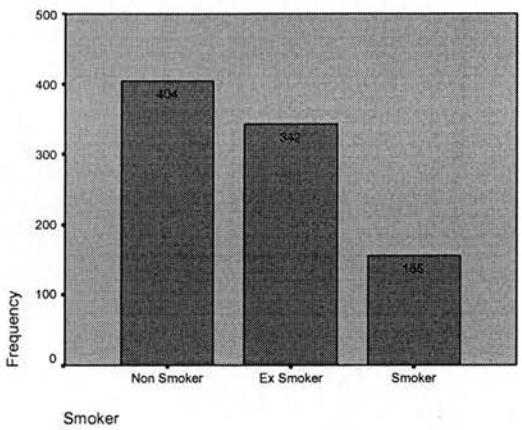


Fig 5.1h: Carstairs deprivation index

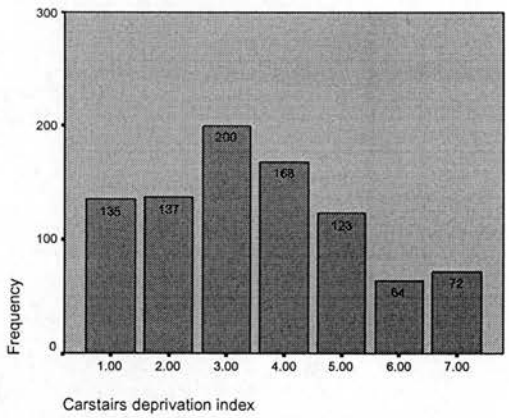
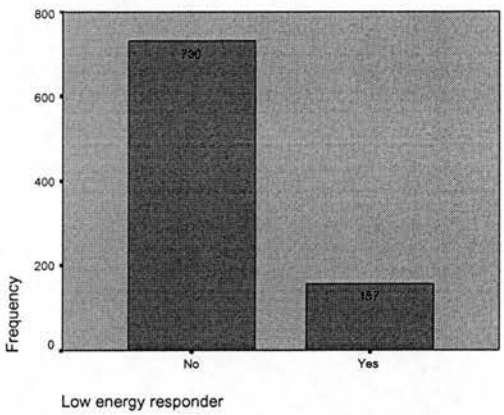


Fig 5.1i: Low energy responder (LER)



5.2.1 Distribution of general characteristics by case-control status

A summary of the distribution of general characteristics by subject status is shown in Tables 5.2 and 5.3. BPH and population controls were combined together, as no significant differences were observed between the BPH and population controls with the exception of age and the Carstairs deprivation index, see Tables 5.4 and 5.5.

Cases were significantly older than controls, the significant difference is probably due to the inclusion of BPH controls which were not frequency matched to cases unlike the population controls. The EI / BMR ratio was also significantly higher within the cases, suggesting either that cases consumed more food than necessary (thereby suggesting that over consumption is association with increased risk of PCa) or that controls were underreporting. As BMI did not differ significantly between cases and controls the latter seems more likely, this was confirmed by the proportion of LERs being significantly higher within the control group, see Table 5.3. Family history of PCa and/or BrCa was also observed to be significantly higher within the cases (Table 5.3).

Table 5.2: Distribution of general characteristics by status (continuous variables)

Continuous Variables	Cases (n=437)		Controls (Population and BPH controls) (n=483)		Test for difference between Cases and Controls	
	Mean (s.d.)	Median (I-QR)	Mean (s.d.)	Median (I-QR)	T-test (p-value)	Mann-Whitney U Test (p-value)
Age (years)	67.2 (5.5)	68.3 (64.5-71.4)	66.0 (5.4)	67.1 (62.7-69.8)	0.001	<0.001
Height (m)	1.74 (0.08)	1.73 (1.70-1.78)	1.74 (0.07)	1.73 (1.70-1.78)	0.91	0.70
Weight (Kg)	79.8 (13.4)	78.9 (70.8-88.0)	79.1 (12.1)	77.6 (71.2-85.9)	0.40	0.41
BMI	26.3 (4.0)	25.9 (23.7-28.6)	26.1 (3.6)	25.8 (23.7-28.1)	0.37	0.49
EI / BMR ratio	1.59 (0.50)	1.50 (1.25-1.87)	1.51 (0.50)	1.45 (1.17-1.78)	0.03	0.02

N.B.
BMI = Body mass index
EI / BMR ratio = Energy intake : basal metabolic rate ratio

Table 5.3: Distribution of general characteristics by status (categorical variables)

Confounding Variable		Frequencies (n)		
		Cases (%)	Controls (Population & BPH Controls) (%)	Total Subjects (%)
Family History of Cancer	No Family History of Prostate or Breast Cancer	298 (69)	387 (80)	685 (75)
	Family History of Prostate Cancer	60 (14)	38 (8)	98 (11)
	Family History of Breast Cancer	58 (13)	48 (10)	106 (12)
	Family History of Prostate and Breast Cancer	17 (4)	10 (2)	27 (3)
	Total	**433 (100)**	**483 (100)**	**916 (100)**
	Missing Values	0	0	0
		Chi-square test (p value) = 0.001		
Smoking	Non Smoker	175 (41)	229 (48)	404 (45)
	Ex Smoker	174 (41)	168 (35)	342 (38)
	Smoker	76 (18)	79 (17)	155 (17)
	Total	**425 (100)**	**476 (100)**	**901 (100)**
	Missing Values	8	7	15
		Chi-square test (p value) = 0.11		
LER	Yes	62 (15)	95 (20)	157
	No	359 (85)	371 (80)	730
	Total	**421 (100)**	**466 (100)**	**887**
	Missing Values	12	17	29
		Chi-square test (p value) = 0.03		
Carstairs deprivation index	1	69 (16)	66 (14)	135
	2	64 (15)	73 (15)	137
	3	97 (23)	103 (22)	200
	4	75 (18)	93 (20)	168
	5	54 (13)	69 (15)	123
	6	31 (7)	33 (7)	64
	7	37 (9)	35 (7)	72
	Total	**427 (100)**	**472 (100)**	**899**
	Missing Values	6	11	17
		Chi-square test (p value) = 0.87		

N.B percentages may not add up to 100% due to rounding.

Table 5.4: Distribution of general characteristics between population and BPH controls (continuous variables)

Continuous Variables	Population controls (n=305)		BPH Controls (n=178)		Test for difference between population and BPH controls	
	Mean (s.d.)	Median (I-QR)	Mean (s.d.)	Median (I-QR)	T-test (p-value)	Mann-Whitney U Test (p-value)
Age (years)	66.7 (4.9)	67.4 (63.8-69.9)	64.8 (6.0)	65.0 (60.7-69.6)	0.001	<0.001
Height (m)	1.75 (0.07)	1.75 (1.70-1.80)	1.74 (0.07)	1.73 (1.68-1.78)	0.14	0.14
Weight (m)	79.2 (12.3)	77.6 (71.2-85.7)	78.9 (11.9)	78.0 (71.2-86.6)	0.75	0.82
BMI	26.0 (3.5)	25.6 (23.7-27.7)	26.2 (3.7)	26.0 (23.6-28.7)	0.35	0.50
EI / BMR ratio	1.52 (0.52)	1.46	1.51 (0.48)	1.42 (1.20-1.76)	0.75	0.86

BMI = Body mass index
EI : BMR ratio = Energy intake : basal metabolic rate ratio

Table 5.5: Distribution of general characteristics between population and BPH controls (categorical variables)

Confounding Variables		Frequencies (n)		
		Population Controls (%)	BPH Controls (%)	Total Controls (%)
Family History of Cancer	No Family History of Prostate or Breast Cancer	250 (82)	137 (77)	387 (80)
	Family History of Prostate Cancer	18 (6)	20 (11)	38 (8)
	Family History of Breast Cancer	30 (10)	18 (10)	48 (10)
	Family History of Prostate and Breast Cancer	7 (2)	3 (2)	10 (2)
	Total	**305 (100)**	**178 (100)**	**483 (100)**
	Missing Values	0	0	0
		Chi-square test (p value) = 0.20		
Smoking	Non Smoker	135 (45)	94 (53)	229 (48)
	Ex Smoker	106 (36)	62 (35)	168 (35)
	Smoker	58 (19)	21 (12)	79 (17)
	Total	**299 (100)**	**177 (100)**	**476 (100)**
	Missing Values	6	1	7
		Chi-square test (p value) = 0.07		
LER	Yes	62 (21)	33 (19)	95 (20)
	No	233 (79)	138 (81)	371 (80)
	Total	**295 (100)**	**171 (100)**	**466 (100)**
	Missing Values	10	7	17
		Chi-square test (p value) = 0.66		
Carstairs Deprivation Index	1	40 (14)	26 (15)	66 (14)
	2	51 (17)	22 (13)	73 (16)
	3	55 (19)	48 (27)	103 (22)
	4	55 (19)	38 (22)	93 (20)
	5	35 (12)	34 (19)	69 (15)
	6	26 (9)	7 (4)	33 (7)
	7	34 (11)	1 (1)	35 (7)
	Total	**296 (100)**	**176**	**472 (100)**
	Missing Values	9	2	11
		Chi-square test (p value) <0.001		

N.B. percentages may not add up to 100% due to rounding

5.3 Nutrient analysis

The following section reports the results of the nutrient analysis part of the study.

5.3.1 Nutrient intake distribution

Distributions for the majority of nutrient intakes were shown to have some degree of skewedness towards lower intake, in particular alcohol, retinol, and the antioxidants (carotenes, vitamin E, vitamin C and the isoflavones) see Fig 5.2. Only EI and protein intake neared normality. Due to the nutrient intake being generally skewed, the nutrient intake variables were normalised by log transformation for the use in parametric tests, in addition to the use of non-parametric tests.

5.3.2 Outliers

Analysis of the nutrient intake distributions revealed outliers for many of the nutrient intakes. Several subjects were reported as having very high intakes of total energy and fats. These subjects also had very high EI/BMR ratios therefore suggesting that they were high-energy responders (HERs) (i.e. over-reported dietary intake). Due to this and the presence of LERs, the EI/BMR ratio was included in the final model in order to control for both over and under reporting.

Several subjects were reported to have very high intakes of antioxidants, in particular isoflavones and carotenes and selenium. The majority of these outliers were cases who had changed their diet after diagnosis to include food items known to contain high levels of antioxidants and isoflavones, i.e. soy products for isoflavones and tomatoes for lycopene (carotenes). This information was gained from notes written on the completed FFQs. Unfortunately there was no adequate FFQ question regarding change in diet over last three months (i.e. since diagnosis), which could have been used to control for this effect. The results for these nutrients should therefore be interpreted with caution.

For the present analysis no outliers where omitted, as the repeated checking of FFQs showed that subjects with very high intakes of these nutrients had indeed reported to consume high quantities of the respective food items. Also as categorical variables for nutrient intake were used in the odds ratio analysis, instead of the original

continuous variables, the potential effect that these outliers may have on the observed ORs would be reduced.

Figure 5.2: Distribution of nutrient intake

Fig 5.2a: EI

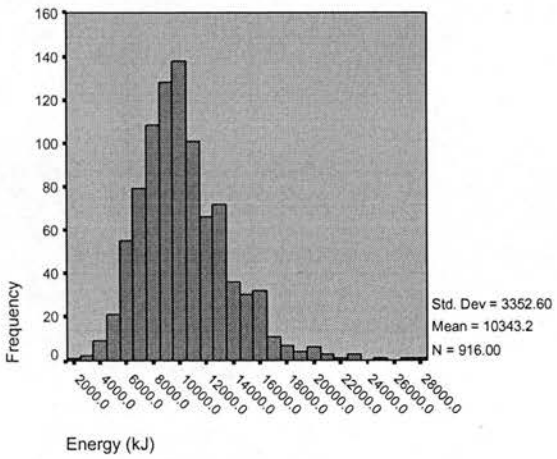


Fig 5.2b: Protein

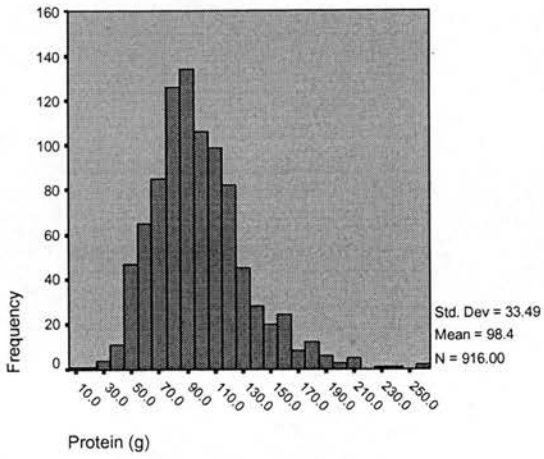


Fig 5.2c: Total fat

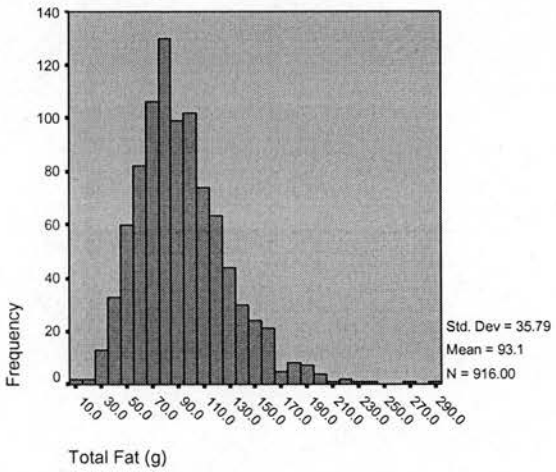


Fig 5.2d: Saturated fat

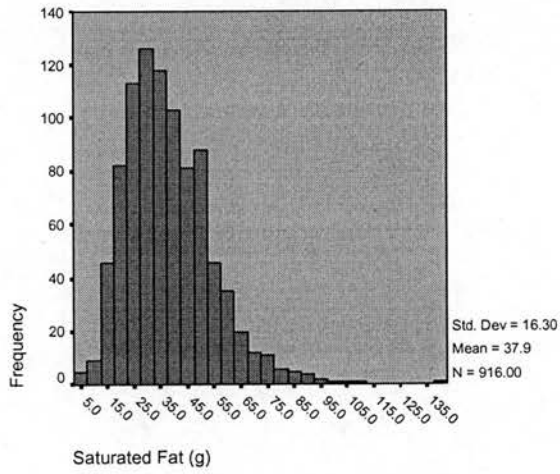


Fig 5.2e: Mono-unsaturated fat

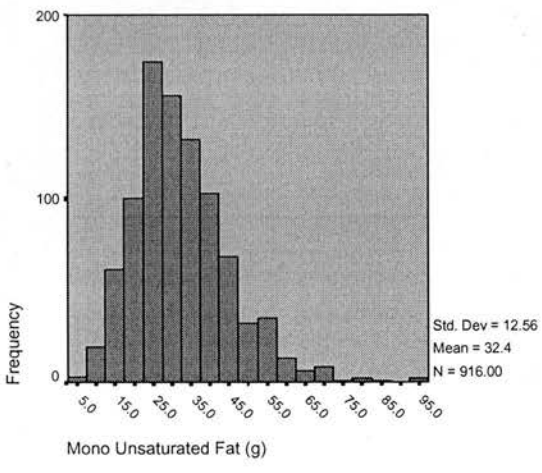


Fig 5.2f: Poly-unsaturated fat

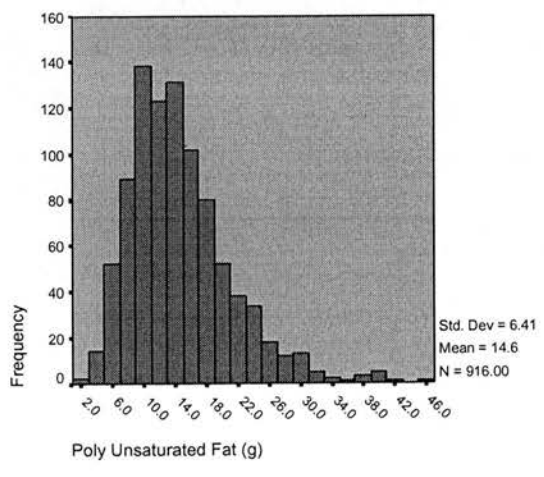


Fig 5.2, cont: Distribution of nutrient intake

Fig 5.2g Cholesterol

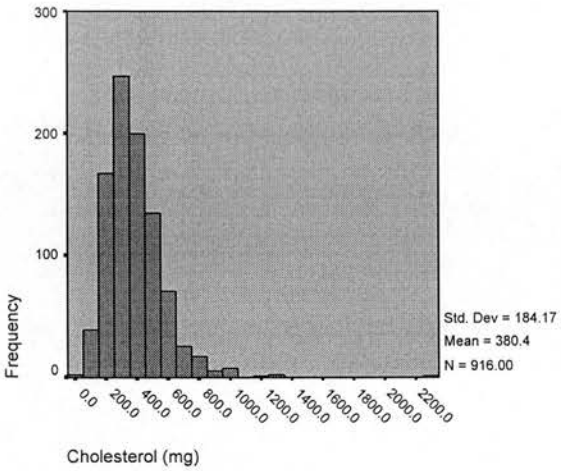


Fig 5.2h: Alcohol

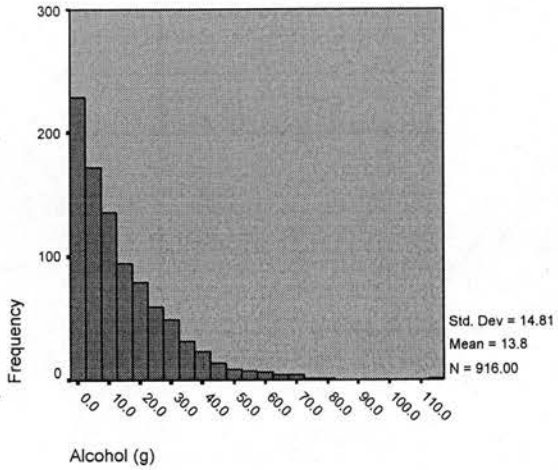


Fig 5.2i: Calcium

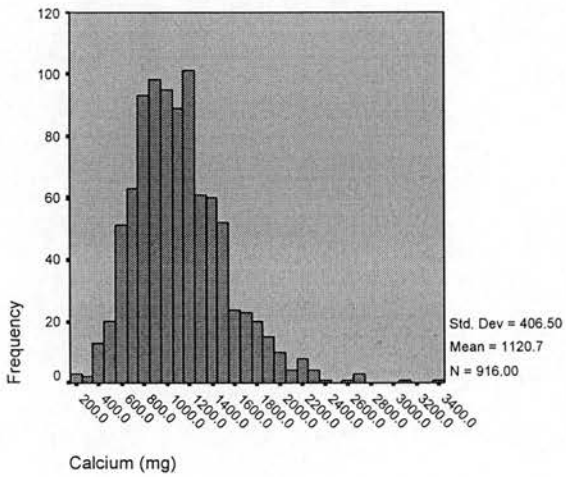


Fig 5.2j: Selenium

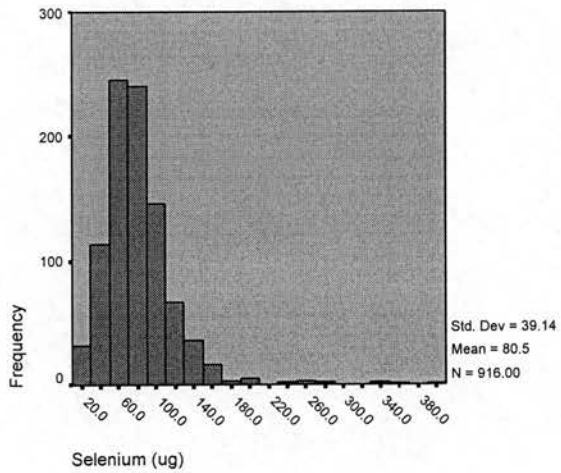


Fig 5.2k:Retinol

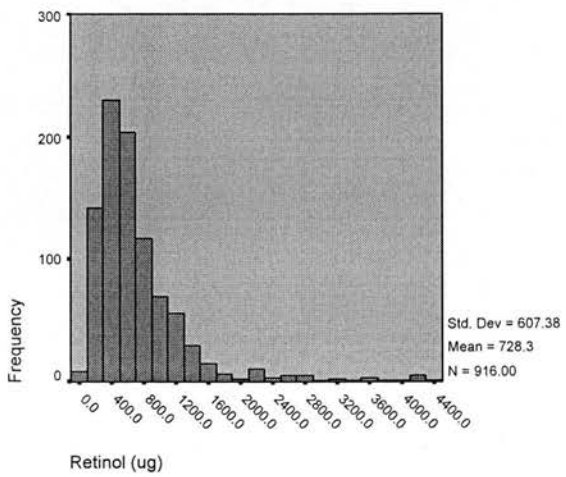


Fig 5.2l: Carotenes

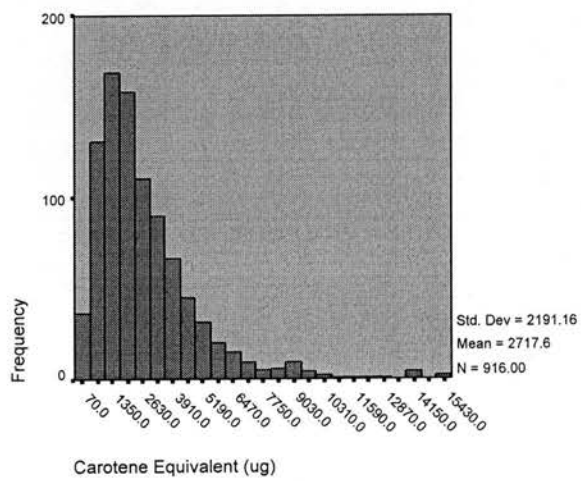


Fig 5.2, cont: Distribution of nutrient intake

Fig 5.2m: Vitamin C

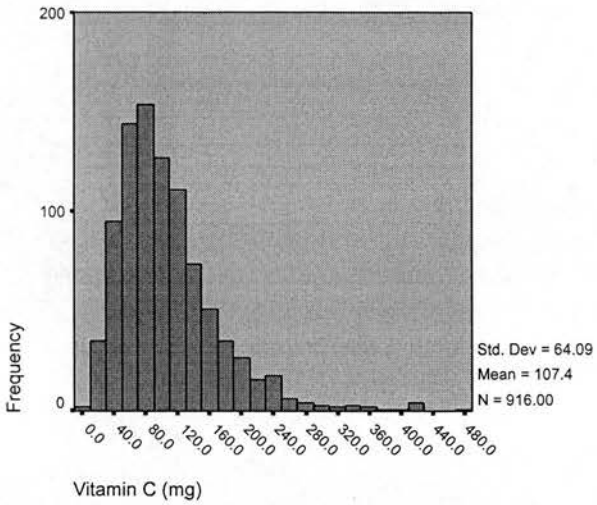


Fig 5.2n: Vitamin E

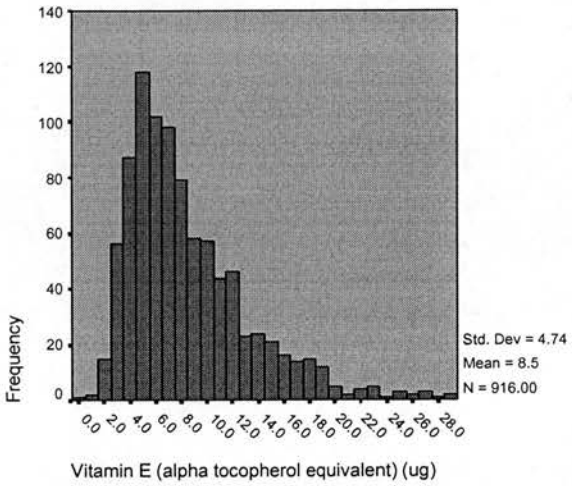
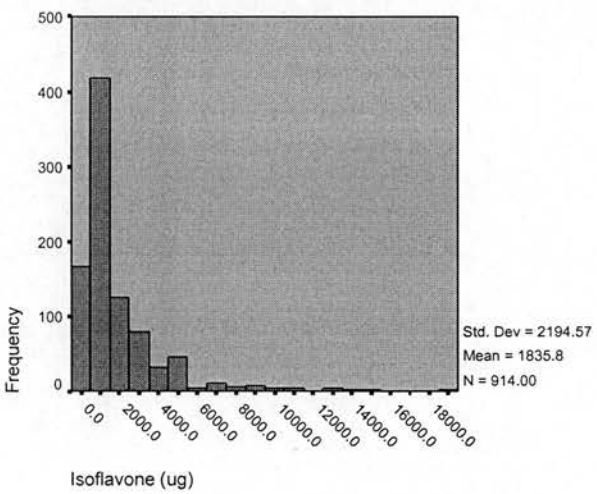


Fig 5.2o: Isoflavones



N.B. 2 outliers (> 20000 g) were omitted from the graph for clarifying purposes

5.3.3 *Nutrient Intake: by control status (BPH Vs population controls)*

In order to confirm that there were no major significant differences between the population and BPH controls, thereby justifying the combining of these two control groups into one control group, the distribution of nutrient intakes between population and BPH controls were examined, see Table 5.6.

No significant differences between population and BPH controls were reported, with the exception of vitamin E and alcohol (Mann-Whitney U test only), thereby confirming that there were no major significant differences between population and BPH controls.

Table 5.6: Distribution of nutrient variables between population and BPH controls

Nutrient Daily Intake Variables	Population Controls (n=305)		BPH Controls (n=178)		Test for difference between Population and BPH Controls	
	Mean (s.d.)	Median (I-QR)	Mean (s.d.)	Median (I-QR)	T-test * (p-value)	Mann-Whitney U Test (p-value)
Total Energy (kJ)	10113 (3423)	9657 (7705-11956)	10151 (3227)	9731 (8047-11375)	0.63	0.88
Protein (g)	96.46 (35.14)	93.10 (72.80-117.0)	96.14 (31.38)	91.20 (76.66-110.5)	0.68	0.99
Total Fat (g)	90.12 (36.48)	83.90 (63.3-110.2)	91.17 (34.28)	86.05 (67.30-108.6)	0.52	0.60
Saturated Fat (g)	36.46 (16.17)	33.20 (24.85-46.7)	37.04 (15.27)	35.00 (26.48-44.80)	0.46	0.57
MUFA (g)	31.37 (12.90)	29.50 (22.4-38.55)	31.74 (12.41)	30.15 (23.10-37.58)	0.54	0.69
PUFA (g)	14.31 (6.85)	13.10 (9.55-18.00)	14.52 (5.91)	13.65 (10.30-17.63)	0.39	0.29
Cholesterol (mg)	369.1 (185.7)	336.0 (240.5-457.5)	350.5 (150.1)	317.5 (248.8-446.0)	0.66	0.43
Alcohol (g)	15.5 (15.2)	11.4 (3.7-24.5)	12.5 (13.2)	7.8 (2.4-17.8)	0.19	0.03
Calcium (mg)	1096 (435)	1031 (789-1340)	1110 (367)	1070 (847-1284)	0.22	0.54
Selenium (μg)	77 (33)	73 (56-93)	80 (34)	74 (57-95)	0.27	0.42
Retinol (μg)	721 (604)	579 (343-884)	666 (501)	567 (395-813)	0.76	0.96
Carotenoids (μg)	2850 (2417)	2234 (1237-3480)	2559 (1837)	1992 (1376-3386)	0.82	0.60
Vitamin E (μg)	8.11 (4.82)	6.99 (4.53-10.24)	8.74 (4.27)	7.76 (5.46-11.00)	0.02	0.02
Vitamin C (mg)	103.5 (61.3)	87.5 (61.9-135.1)	106.8 (61.2)	95.1 (65.7-134.5)	0.24	0.38
Isoflavones (μg)	1747 (3105)	991 (577-1735)	1988 (2278)	1226 (594-2365)	0.05	0.06

N.B.
* using transformed data
s.d. = Standard Deviation
I-QR = Inter-quartile Range
MUFA = Mono unsaturated Fat
PUFA = Poly unsaturated Fat

5.3.4 Distribution of nutrient intake: by case-control status

Controls were observed to have lower intakes of all nutrients compared to cases, however these differences were observed to be significant for total energy, protein, total fat and its constituents (excluding poly-unsaturated fat), alcohol and calcium (Mann-Whitney U test only) only, see Table 5.7. Antioxidant intakes were observed to have no significant differences between cases and controls.

Please see Appendix: Table 8.1 for the distribution of all nutrients by case-control status.

Table 5.7: Descriptive Report of nutrient intake by status

Daily Nutrient Intake	Cases (n=437)		Controls (Population and BPH controls) (n=483)		Test for difference between Cases and Controls	
	Mean (s.d.)	Median (I-QR)	Mean (s.d.)	Median (I-QR)	T-test * (p-value)	Mann-Whitney U Test (p-value)
Total Energy (kJ)	10584 (3344)	10165 (8369-12370)	10127 (3349)	9684 (7874-11757)	0.02	0.02
Protein (g)	100.69 (33.07)	96.10 (78.15-118.85)	96.34 (33.77)	92.10 (74.70-112.70)	0.02	0.03
Total Fat (g)	95.95 (35.77)	91.30 (72.75-116.30)	90.51 (35.66)	84.90 (65.30-109.60)	0.01	0.01
Saturated Fat (g)	39.36 (16.71)	37.00 (27.55-48.15)	36.67 (15.83)	34.00 (25.30-46.30)	0.01	0.01
MUFA (g)	33.32 (12.34)	31.20 (25.50-40.60)	31.50 (12.71)	29.90 (22.80-38.30)	0.01	0.01
PUFA (g)	14.83 (6.29)	13.90 (10.50-17.90)	14.39 (6.51)	13.30 (9.70-17.80)	0.14	0.14
Cholesterol (mg)	401 (194)	368 (277-486)	362 (173)	326 (242-450)	0.001	<0.001
Alcohol (g)	13.2 (15.1)	7.9 (1.8-20.3)	14.4 (14.6)	9.9 (3.4-21.6)	0.03	0.06
Calcium (mg)	1143 (400)	1110 (859-1373)	1101 (411)	1039 (812-1321)	0.08	0.04
Selenium (μg)	83 (45)	75 (58-98)	78 (33)	73 (56-94)	0.15	0.25
Retinol (μg)	759 (647)	582 (390-910)	701 (568)	571 (348-838)	0.13	0.15
Carotene (μg)	2690 (2156)	2143 (1185-3614)	2742 (2224)	2187 (1308-3447)	0.49	0.75
Vitamin E (μg)	8.70 (4.86)	7.31 (5.35-10.97)	8.34 (4.63)	7.27 (4.89-10.56)	0.16	0.30
Vitamin C (mg)	110.4 (67.1)	97.2 (65.2-136.5)	104.7 (61.2)	90.5 (62.5-134.7)	0.25	0.19
Isoflavones (μg)	1975.9 (2455.1)	1143.2 (636.8-2444.5)	1835.7 (2828.2)	1050.9 (581.1-1982.8)	0.16	0.10

N.B.
* using transformed data
s.d. = Standard Deviation
I-QR = Inter-quartile Range
MUFA = Mono unsaturated Fat
PUFA = Poly unsaturated Fat

5.3.5 Correlation between individual nutrient intakes

As expected, crude correlation coefficients showed that the majority of nutrients were highly positively correlated with each other, see Appendix: Table 8.2. Therefore, the correlation analysis was repeated using EI-adjusted nutrient intakes.

Most nutrients remained associated with each other, though these correlations tended to be weaker, see Table 5.8. Total fat and its constituents continued to be strongly positively associated with each other, with the exception of PUFA and saturated fat / cholesterol for which significant negative associations were observed. Retinol was also highly positively associated with fats. Significant inverse associations were observed between fats and most antioxidants, especially total fat, saturated fat and cholesterol, whereas PUFA was shown to be positively associated with antioxidants, in particular vitamin E and selenium, as was selenium and protein. Antioxidants also continued to be associated with each other. Whereas alcohol was observed to be inversely associated with most nutrients, especially total fat and its constituents and calcium.

Table 5.8: Correlation coefficients for energy adjusted nutrient intakes

Correlations

		Energy (kJ)	Protein (Energy Adjusted)	Total Fat (Energy Adjusted)	Saturated Fat (Energy Adjusted)	MUFA (Energy Adjusted)	PUFA (Energy Adjusted)	Cholesterol (Energy Adjusted)	Alcohol (Energy Adjusted)	Calcium (Energy Adjusted)	Selenium (Energy Adjusted)	Retinol (Energy Adjusted)	Carotene (Energy Adjusted)	Vitamin C (Energy Adjusted)	Vitamin E (Energy Adjusted)	Isoflavone (Energy Adjusted)
Energy (kJ)	Correlation Coefficient	1.000	-.007	-.016	-.017	-.025	.008	.006	-.067*	-.006	-.035	.003	-.055	-.039	.001	-.010
	Sig. (2-tailed)	.	.831	.639	.617	.453	.801	.851	.043	.846	.297	.934	.095	.236	.978	.768
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Protein (Energy Adjusted)	Correlation Coefficient	-.007	1.000	.100**	-.063	.158**	.173**	.347**	-.104**	.278**	.417**	.021	.203**	.032	-.015	-.094**
	Sig. (2-tailed)	.831	.	.002	.058	.000	.000	.000	.002	.000	.000	.518	.000	.341	.651	.004
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Total Fat (Energy Adjusted)	Correlation Coefficient	-.016	.100**	1.000	.814**	.905**	.234**	.572**	-.213**	.039	.019	.505**	-.106**	-.421**	.027	.069*
	Sig. (2-tailed)	.639	.002	.	.000	.000	.000	.000	.000	.241	.558	.000	.001	.000	.410	.036
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Saturated Fat (Energy Adjusted)	Correlation Coefficient	-.017	-.063	.814**	1.000	.629**	-.262**	.539**	-.180**	.121**	-.175**	.529**	-.188**	-.393**	-.311**	-.011
	Sig. (2-tailed)	.617	.058	.000	.	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.745
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
MUFA (Energy Adjusted)	Correlation Coefficient	-.025	.158**	.905**	.629**	1.000	.300**	.569**	-.152**	-.024	.045	.407**	-.097**	-.404**	.033	.062
	Sig. (2-tailed)	.453	.000	.000	.000	.	.000	.000	.000	.466	.173	.000	.003	.000	.317	.062
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
PUFA (Energy Adjusted)	Correlation Coefficient	.008	.173**	.234**	-.262**	.300**	1.000	-.087**	-.045	-.121**	.311**	-.081*	.145**	.019	.706**	.143**
	Sig. (2-tailed)	.801	.000	.000	.000	.000	.	.008	.175	.000	.000	.014	.000	.573	.000	.000
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Cholesterol (Energy Adjusted)	Correlation Coefficient	.006	.347**	.572**	.539**	.569**	-.087**	1.000	-.040	.038	.052	.479**	-.072*	-.329**	-.226**	-.091**
	Sig. (2-tailed)	.851	.000	.000	.000	.000	.008	.	.225	.254	.113	.000	.030	.000	.000	.006
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Alcohol (Energy Adjusted)	Correlation Coefficient	-.067*	-.104**	-.213**	-.180**	-.152**	-.045	-.040	1.000	-.225**	-.007	-.017	.061	-.010	-.078*	-.157**
	Sig. (2-tailed)	.043	.002	.000	.000	.000	.175	.225	.	.000	.822	.606	.067	.754	.018	.000
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Calcium (Energy Adjusted)	Correlation Coefficient	-.006	.278**	.039	.121**	-.024	-.121**	.038	-.225**	1.000	-.010	.123**	.002	.010	-.045	.032
	Sig. (2-tailed)	.846	.000	.241	.000	.466	.000	.254	.000	.	.765	.000	.948	.756	.169	.339
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Selenium (Energy Adjusted)	Correlation Coefficient	-.035	.417**	.019	-.175**	.045	.311**	.052	-.007	-.010	1.000	-.034	.193**	.089**	.141**	.104**
	Sig. (2-tailed)	.297	.000	.558	.000	.173	.000	.113	.822	.765	.	.309	.000	.007	.000	.002
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Retinol (Energy Adjusted)	Correlation Coefficient	.003	.021	.505**	.529**	.407**	-.081*	.479**	-.017	.123**	-.034	1.000	.118**	-.234**	-.098**	.007
	Sig. (2-tailed)	.934	.518	.000	.000	.000	.014	.000	.606	.000	.309	.	.000	.000	.003	.842
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Carotene (Energy Adjusted)	Correlation Coefficient	-.055	.203**	-.106**	-.188**	-.097**	.145**	-.072*	.061	.002	.193**	.118**	1.000	.388**	.179**	-.030
	Sig. (2-tailed)	.095	.000	.001	.000	.003	.000	.030	.067	.948	.000	.000	.	.000	.000	.358
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Vitamin C (Energy Adjusted)	Correlation Coefficient	-.039	.032	-.421**	-.393**	-.404**	.019	-.329**	-.010	.010	.089**	-.234**	.388**	1.000	.264**	-.072*
	Sig. (2-tailed)	.236	.341	.000	.000	.000	.573	.000	.754	.756	.007	.000	.000	.	.000	.029
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Vitamin E (Energy Adjusted)	Correlation Coefficient	.001	-.015	.027	-.311**	.033	.706**	-.226**	-.078*	-.045	.141**	-.098**	.179**	.264**	1.000	.098**
	Sig. (2-tailed)	.978	.651	.410	.000	.317	.000	.000	.018	.169	.000	.003	.000	.000	.	.003
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Isoflavone (Energy Adjusted)	Correlation Coefficient	-.010	-.094**	.069*	-.011	.062	.143**	-.091**	-.157**	.032	.104**	.007	-.030	-.072*	.098**	1.000
	Sig. (2-tailed)	.768	.004	.036	.745	.062	.000	.006	.000	.339	.002	.842	.358	.029	.003	.
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916

*. Correlation is significant at the .05 level (2-tailed).

**. Correlation is significant at the .01 level (2-tailed).

5.3.6 Nutrient intake by confounding variables

The association between nutrient intake and confounding variables were examined using Spearman's rank correlation, see Table 5.9. The EI: BMR ratio was significantly positively correlated with all nutrients, and also age. Significant inverse correlations were observed between age and alcohol, and also family history, Carstairs deprivation index and BMI. Family history of PCa / BrCa was significantly positively correlated with total energy, protein, PUFA, selenium and vitamin E intake, but with no other confounding variables. Smoking status was significantly positively correlated with cholesterol and alcohol and significantly inversely correlated with PUFA, carotene, isoflavones and vitamins E and C. Whilst BMI was significantly positively correlated with protein, PUFA, cholesterol, selenium, carotene and vitamin C intakes.

To examine the association between nutrient intake and confounding variables further, mean nutrient intake (with 95%CIs) were compared across confounding variable categories. The associations that were observed to be significant are shown in Figures 5.3 to 5.9. As expected, intake for all nutrients increased significantly across total energy and the EI:BMR ratio categories (Figures 5.4 and 5.8). Most nutrients also varied significantly across the Carstairs deprivation index (Figure 5.6). In general, no clear linear trends were observed, with most nutrient intakes, especially fat and its constituents, remaining relatively homogeneous across most of the deprivation index categories except categories 5 and 6 for which intake tended to be relatively higher and lower respectively. However, intakes for calcium, retinol, carotene and vitamin C were shown to decrease with increasing deprivation, whereas cholesterol was shown to increase.

Nutrient intake also varied across smoking status, with cholesterol, alcohol and retinol intake being higher in ex-smokers and smokers, whilst for carotene, vitamins E and C, isoflavones and PUFA, intake was higher in non smokers (Figure 5.7). However, only alcohol and retinol varied significantly across age categories (Figure 5.3), which was surprising as there is general evidence that dietary intake decreases in old age[105]. In addition, only PUFA, selenium and vitamin E varied significantly

across family history categories (Figure 5.5), with intake increasing with increasing family history categories, and only carotene intake varied significantly across BMI categories (Figure 5.9).

Table 5.9: Correlation matrix for confounding variables Vs nutrient intake

		Age (years)	Family History	Carstairs deprivation index	Smoker	EI / BMR Ratio	BMI	Energy (kJ)	Protein (g)	Total Fat (g)	Saturate Fat (g)	MUFA (g)	PUFA (g)	Cholesterol (mg)	Alcohol (g)	Calcium (mg)	Selenium (ug)	Retinol (ug)	Carotene (ug)	Vitamin E (ug)	Vitamin C (mg)	Isoflavone (ug)
Age (years)	Rho	1.000	**-.067**	**-.090**	-.033	**.092**	**-.167**	-.020	-.026	.013	.033	-.006	-.035	-.006	**-.190**	.009	-.029	-.010	-.055	-.024	.013	-.023
	p value	.	.042	.007	.329	.006	.000	.536	.428	.695	.314	.867	.283	.866	.000	.792	.381	.766	.097	.470	.685	.486
	N	916	916	899	901	887	887	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Family History	Rho	**-.067**	1.000	-.049	-.058	.055	.052	**.069**	**.077**	.058	.030	.060	**.099**	.017	.038	.038	**.109**	.006	.042	**.117**	.065	.025
	p value	.042	.	.140	.082	.104	.122	.037	.020	.082	.366	.072	.003	.609	.249	.245	.001	.848	.200	.000	.050	.442
	N	916	916	899	901	887	887	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Carstairs deprivation index	Rho	**-.090**	-.049	1.000	**.221**	.024	**.082**	.008	.032	.046	.040	.058	-.012	**.134**	-.061	-.042	-.016	.002	**-.132**	**-.066**	**-.185**	-.020
	p value	.007	.140	.	.000	.474	.016	.805	.331	.173	.226	.080	.727	.000	.065	.204	.631	.956	.000	.047	.000	.546
	N	899	899	899	885	872	872	899	899	899	899	899	899	899	899	899	899	899	899	899	899	899
Smoker	Rho	-.033	-.058	**.221**	1.000	-.017	-.012	-.015	.014	-.001	.015	.011	**-.072**	**.119**	**.094**	-.039	-.033	.045	**-.118**	**-.134**	**-.176**	**-.141**
	p value	.329	.082	.000	.	.611	.716	.656	.673	.988	.646	.742	.031	.000	.005	.243	.324	.174	.000	.000	.000	.000
	N	901	901	885	901	877	877	901	901	901	901	901	901	901	901	901	901	901	901	901	901	901
EI / BMR Ratio	Rho	**.092**	.055	.024	-.017	1.000	**-.114**	**.937**	**.823**	**.861**	**.793**	**.843**	**.714**	**.683**	**.110**	**.716**	**.612**	**.494**	**.355**	**.575**	**.441**	**.361**
	p value	.006	.104	.474	.611	.	.001	.000	.000	.000	.000	.000	.000	.000	.001	.000	.000	.000	.000	.000	.000	.000
	N	887	887	872	877	887	887	887	887	887	887	887	887	887	887	887	887	887	887	887	887	887
BMI	Rho	**-.167**	.052	**.082**	-.012	**-.114**	1.000	.064	**.066**	.055	.027	.063	**.079**	**.090**	.055	-.016	**.081**	.030	**.071**	.065	**.095**	-.005
	p value	.000	.122	.016	.716	.001	.	.056	.050	.099	.422	.061	.019	.008	.101	.643	.016	.373	.035	.053	.005	.880
	N	887	887	872	877	887	887	887	887	887	887	887	887	887	887	887	887	887	887	887	887	887

N.B
Significant correlation coefficients ($p < 0.05$) are highlighted in **bold**

Figure 5.3: Nutrient intake across age categories

Fig 5.3a: Alcohol

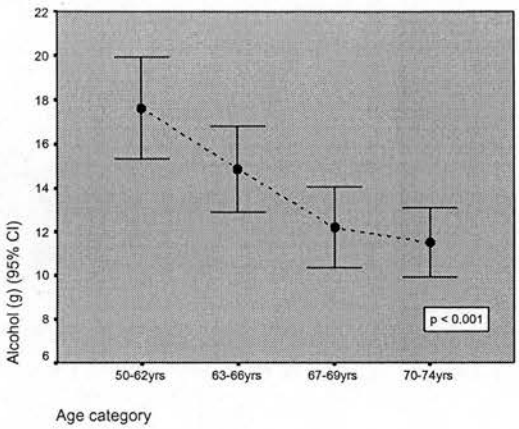


Fig 5.3b: Retinol

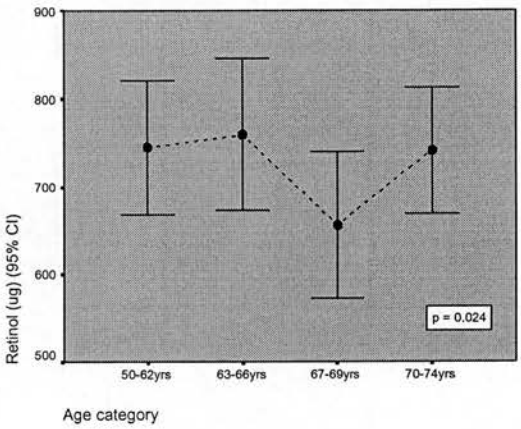


Figure 5.4: Nutrient intake across EI categories

Fig 5.4a: Protein

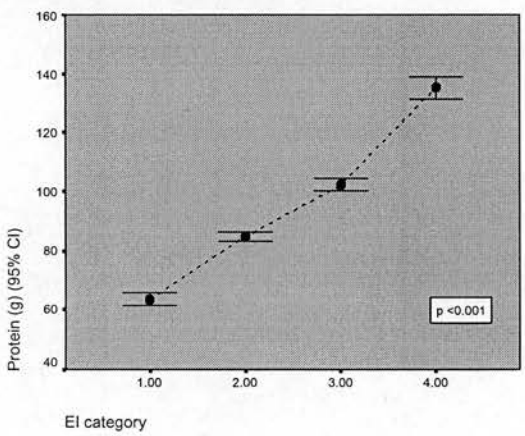


Fig 5.4b: Total fat

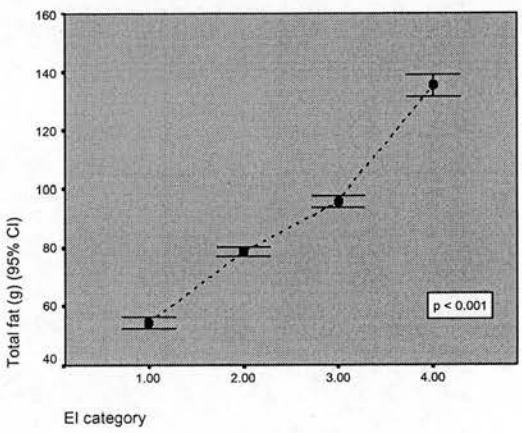


Fig 5.4c: Saturated fat

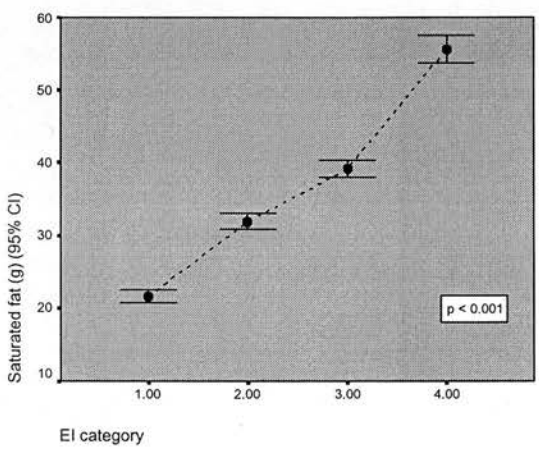


Fig 5.4d: MUFA

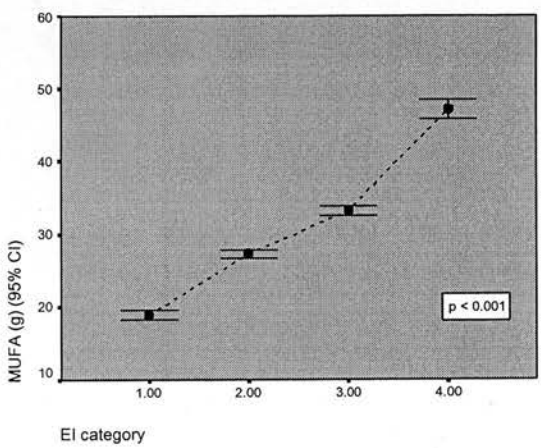


Fig 5.4, Cont. Nutrient intake across EI categories

Fig 5.4e: PUFA

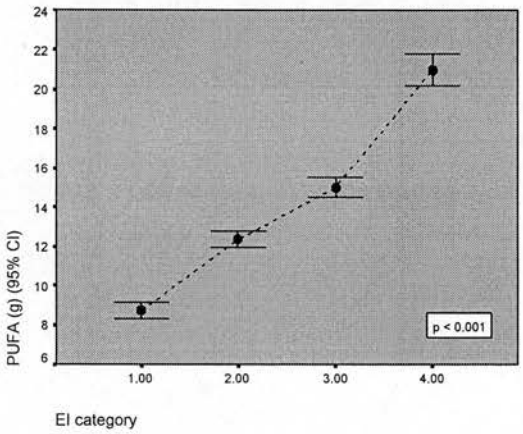


Fig 5.4f: Cholesterol

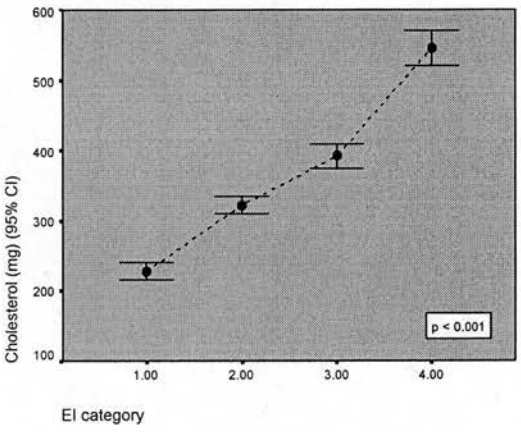


Fig 5.4g: Alcohol

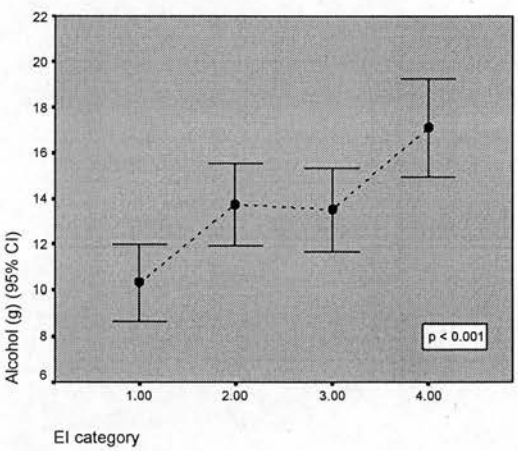


Fig 5.4h: Calcium

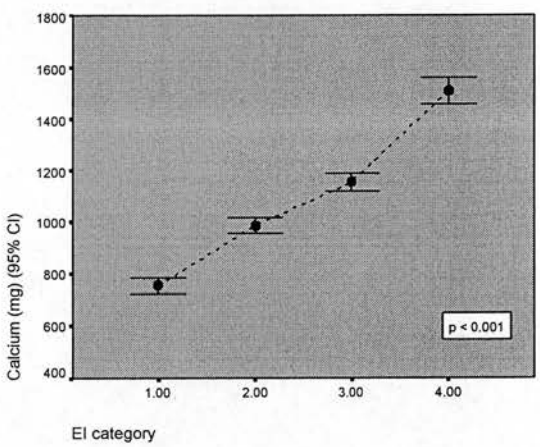


Fig 5.4l: Selenium

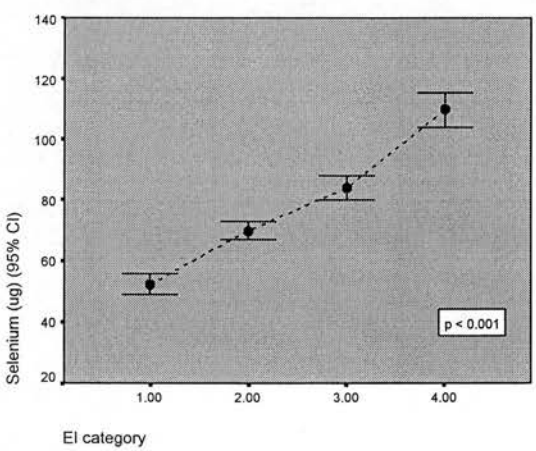


Fig 5.4j: Retinol

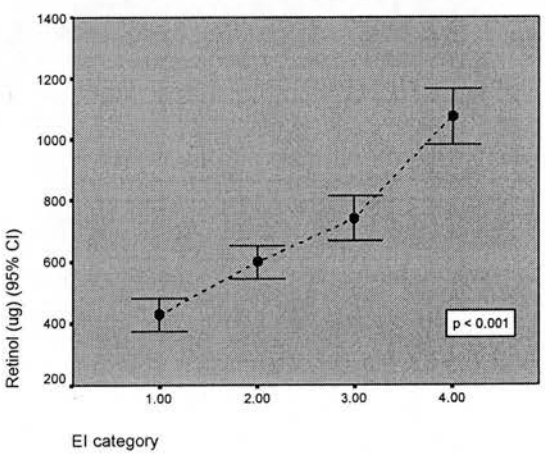


Fig 5.4, cont.: Nutrient intake across EI categories

Fig 5.4k: Carotenes

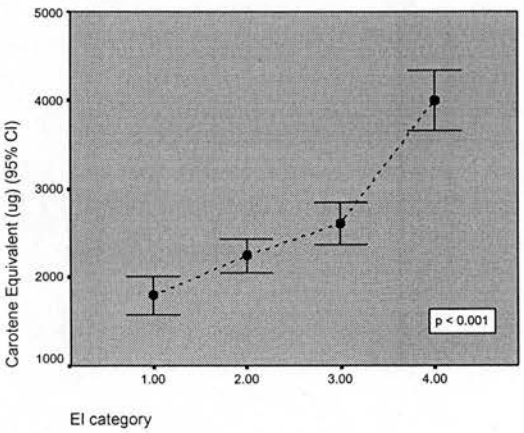


Fig 5.4l: Vitamin E

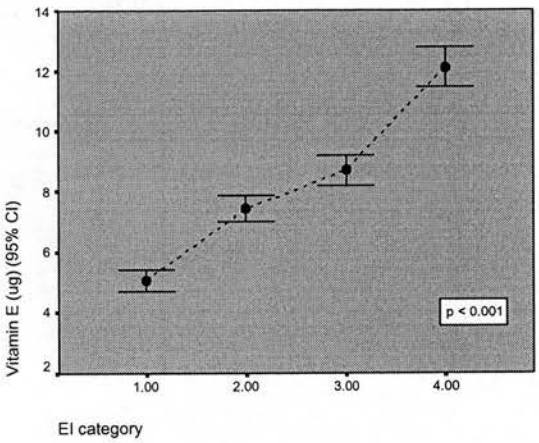


Fig 5.4m: Vitamin C

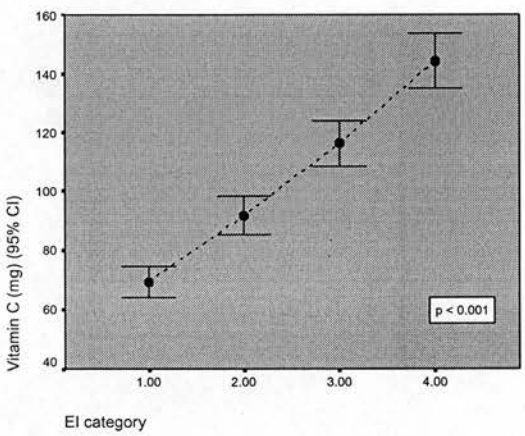


Fig 5.4n: Isoflavones

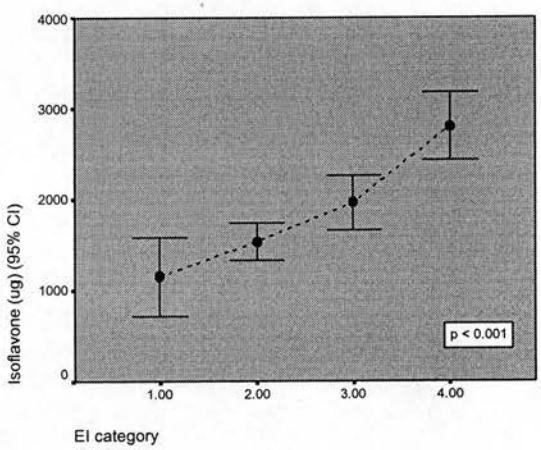


Figure 5.5: Nutrient intake across family history categories

Fig 5.5a: PUFA

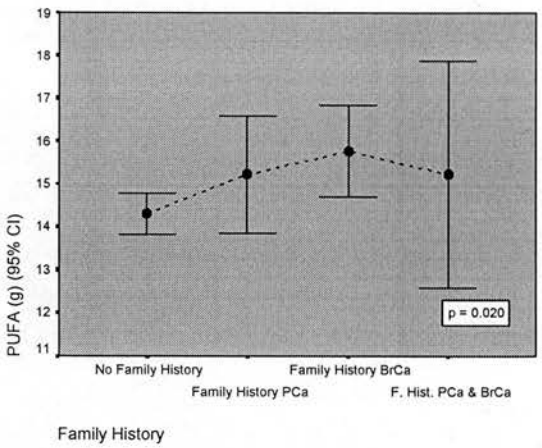


Fig 5.5b: Selenium

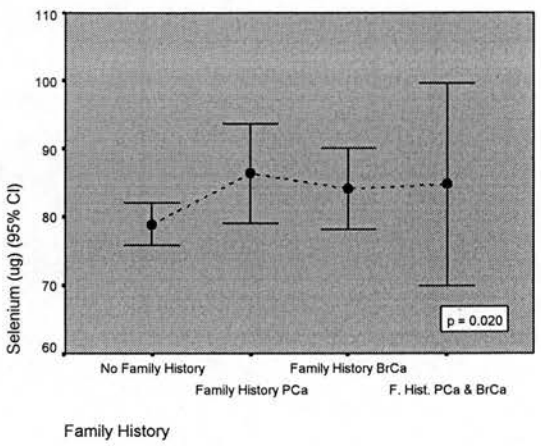


Fig 5.5c: Vitamin E

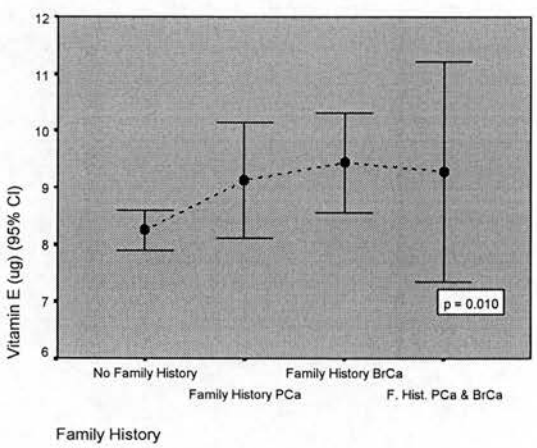


Figure 5.6: Nutrient intake across Carstairs deprivation index

Fig 5.6a: EI

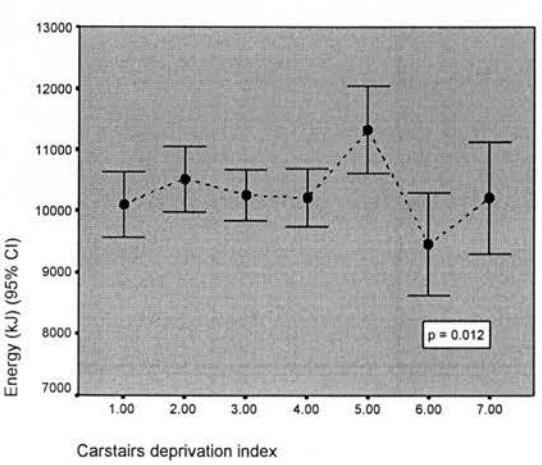


Fig 5.6b: Protein

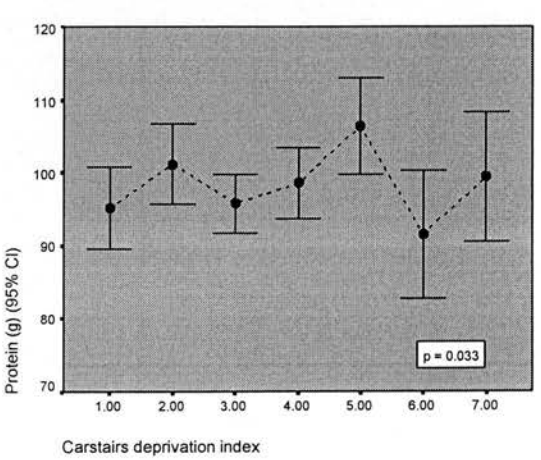


Fig 5.6, Cont.: Nutrient intake across Carstairs deprivation index

Fig 5.6c: Total fat

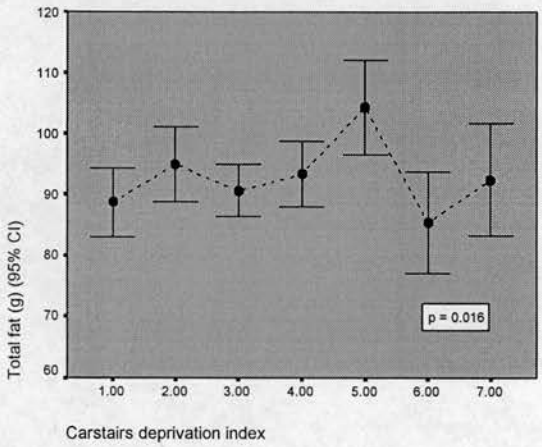


Fig 5.6d: Saturated fat

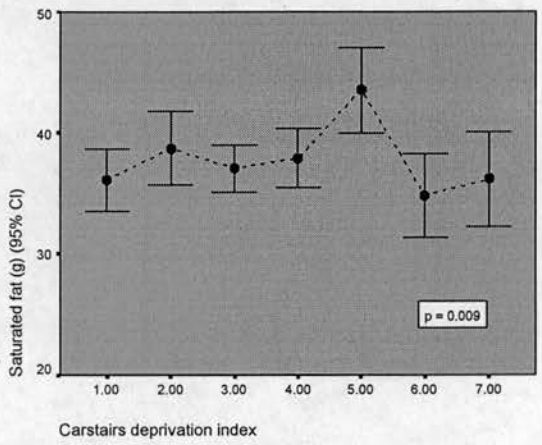


Fig 5.6e: MUFA

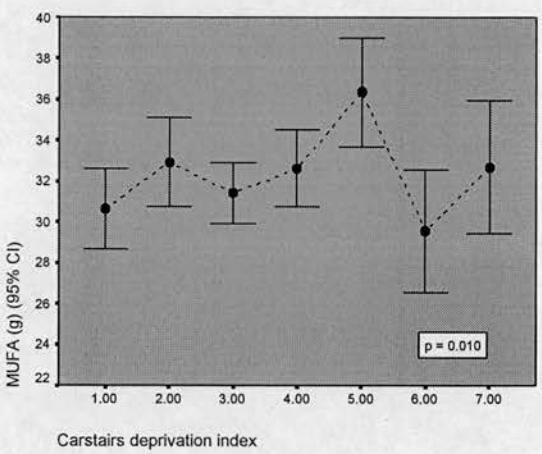


Fig 5.6f: PUFA

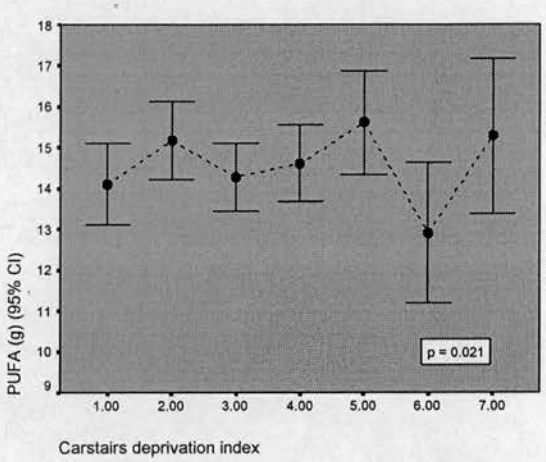


Fig 5.6g: Cholesterol

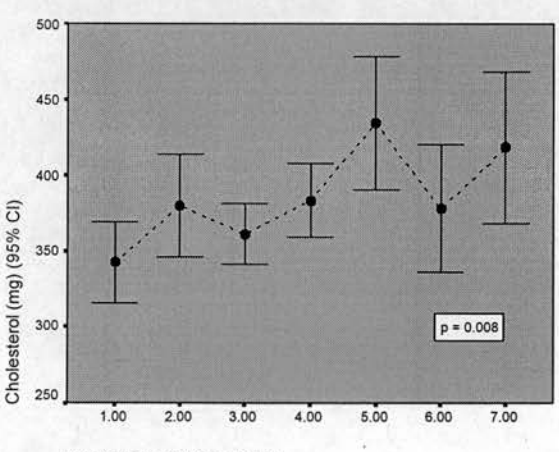


Fig 5.6h: Calcium

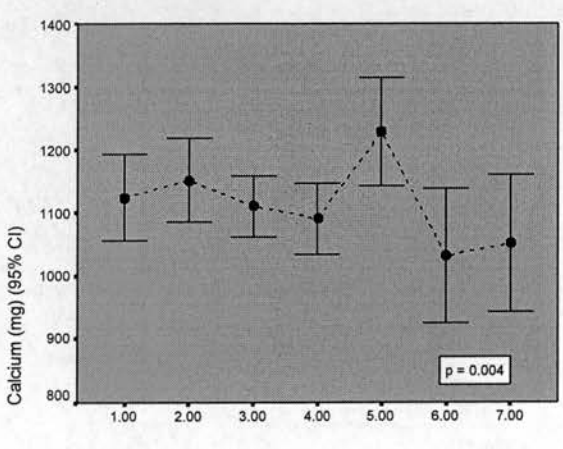


Fig 5.6, Cont.: Nutrient intake across Carstairs deprivation index

Fig 5.6i: Retinol

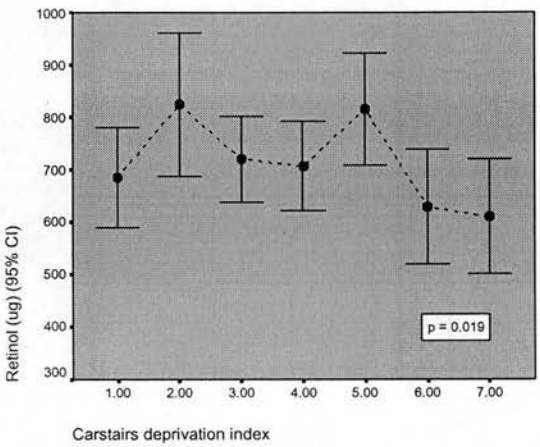


Fig 5.6j: Carotenes

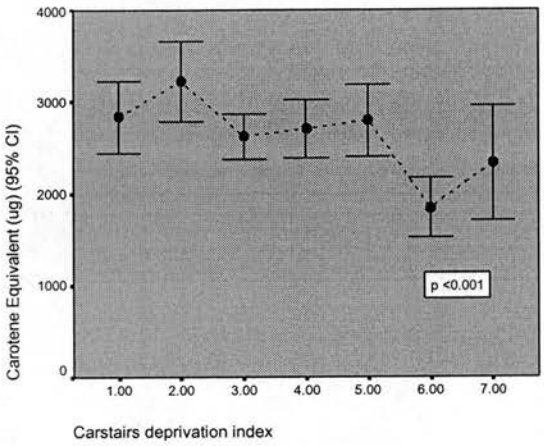


Fig 5.6k: Vitamin C

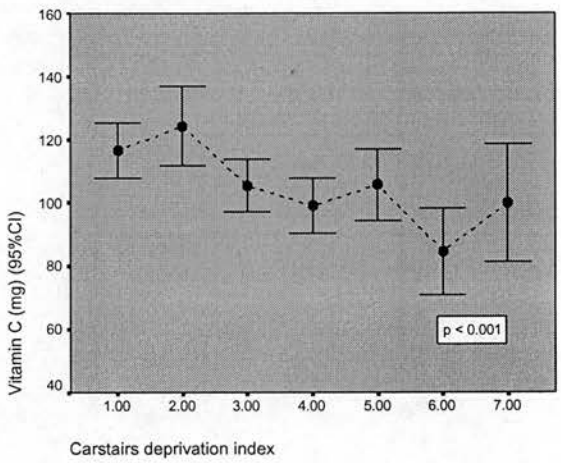


Figure 5.7: Nutrient intake across smoking status

Fig 5.7a: PUFA

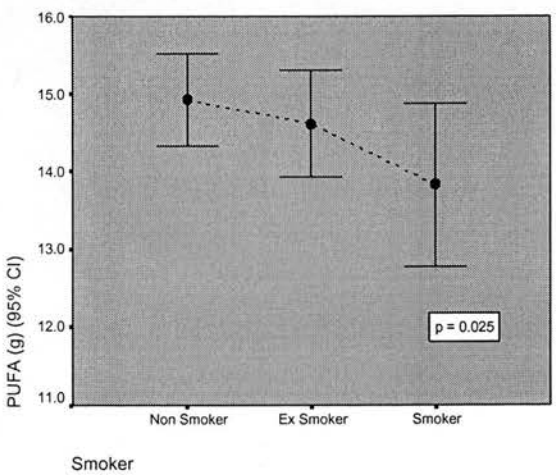


Fig 5.7b: Cholesterol

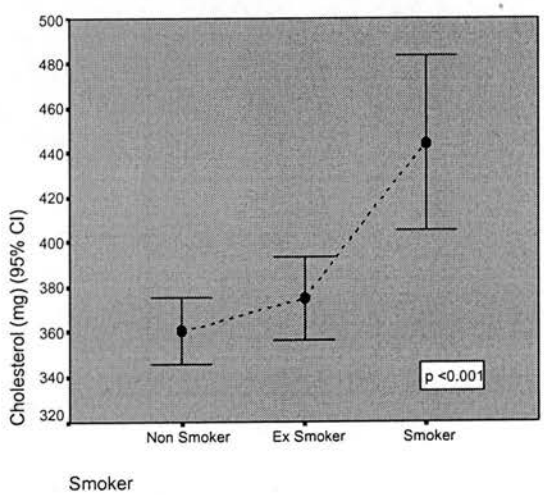


Figure 5.7, cont.: Nutrient intake across smoking status

Fig 5.7c: Alcohol

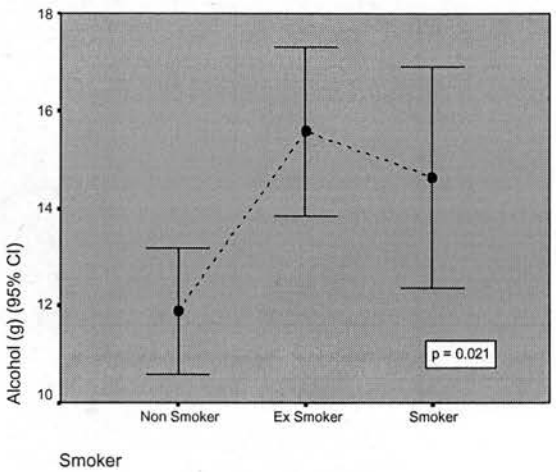


Fig 5.7d: Retinol

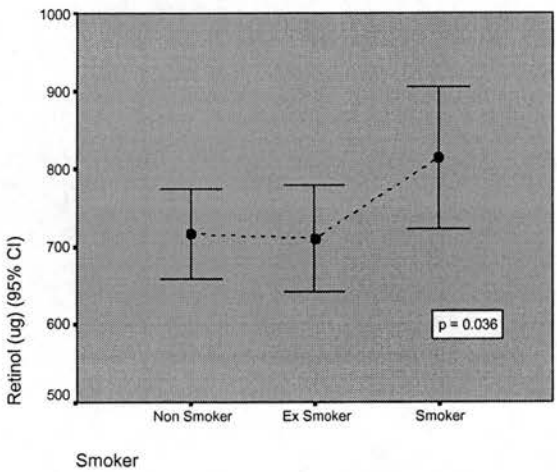


Fig 5.7e: Carotenes

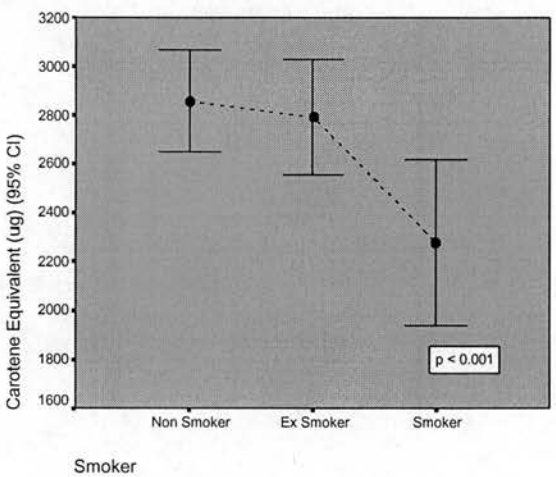


Fig 5.7f: Vitamin E

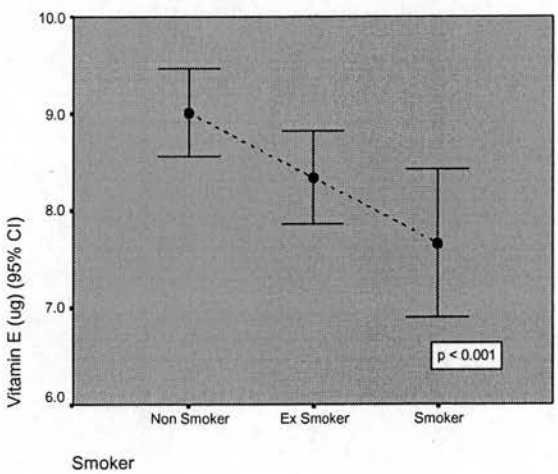


Fig 5.7g: Vitamin C

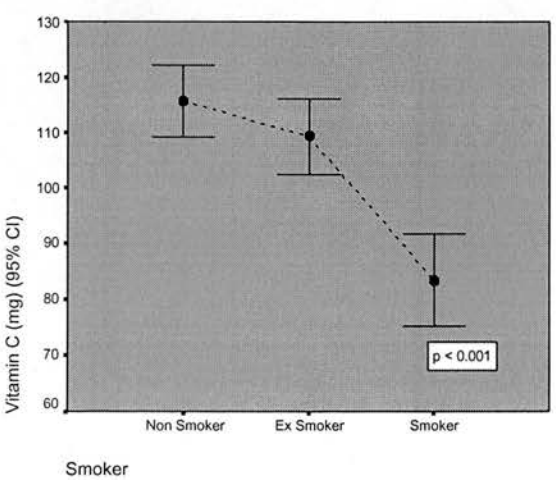


Fig 5.7h: Isoflavones

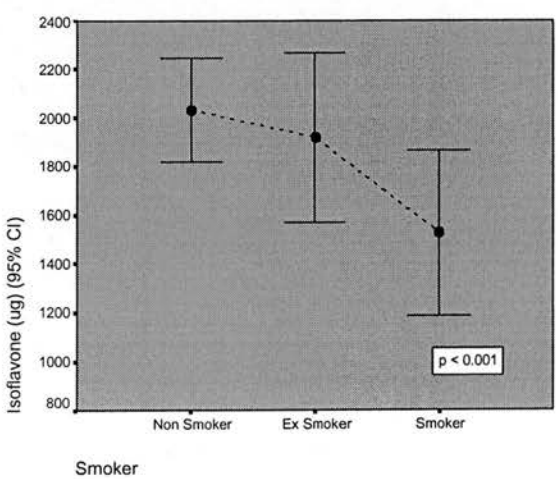


Figure 5.8: Nutrient intake across EI:BMR ratio categories

Fig 5.8a: EI

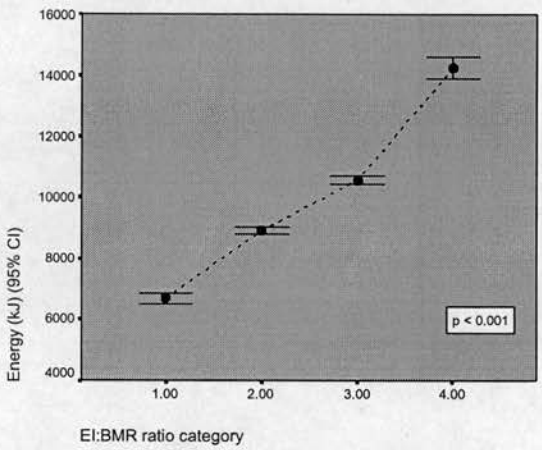


Fig 5.8b: Protein

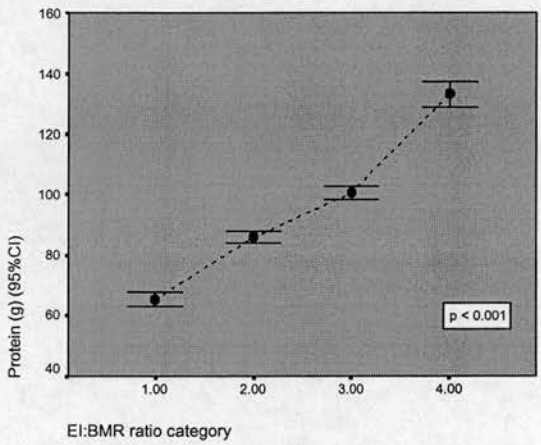


Fig 5.8c: Total fat

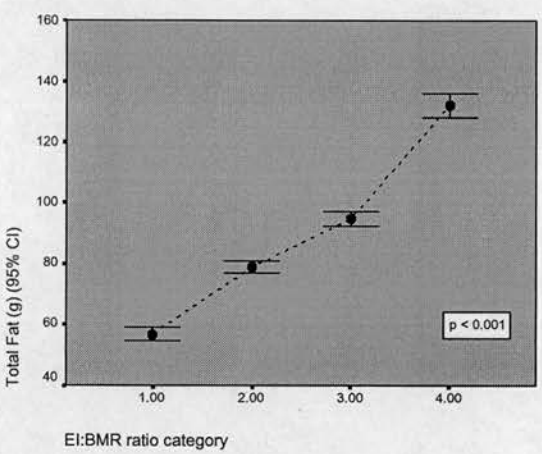


Fig 5.8d: Saturated fat

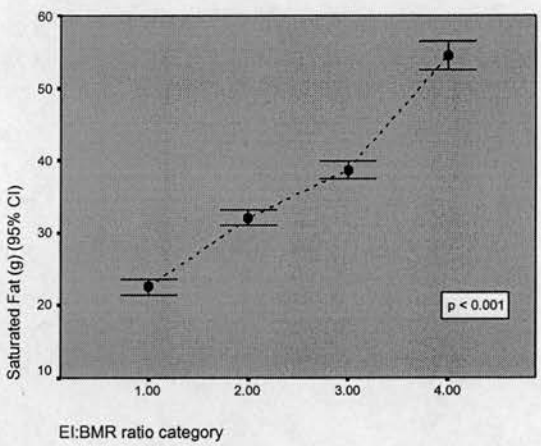


Fig 5.8e: MUFA

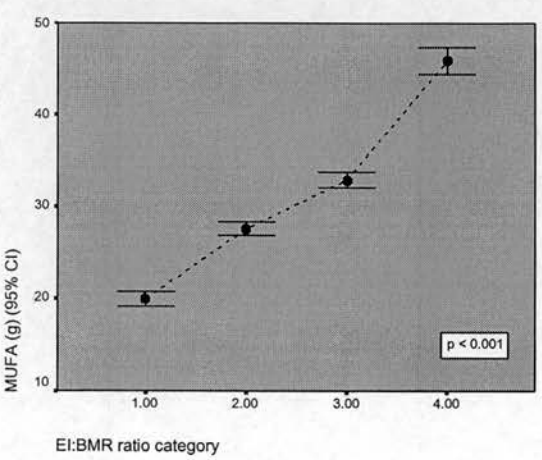


Fig 5.8f: PUFA

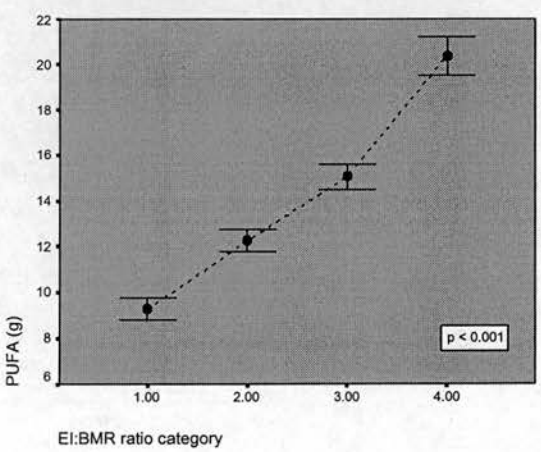


Fig 5.8, Cont.: Nutrient intake across EI:BMR ratio categories

Fig 5.8g: Cholesterol

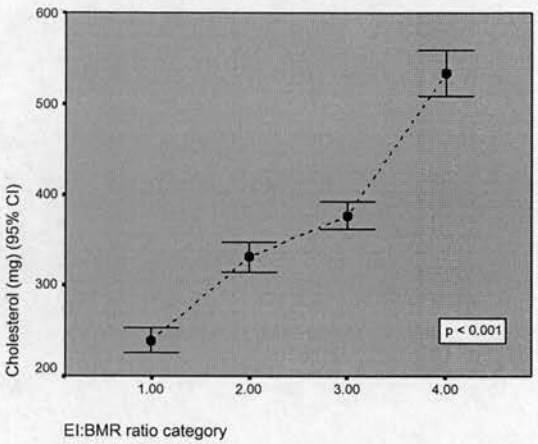


Fig 5.8h: Alcohol

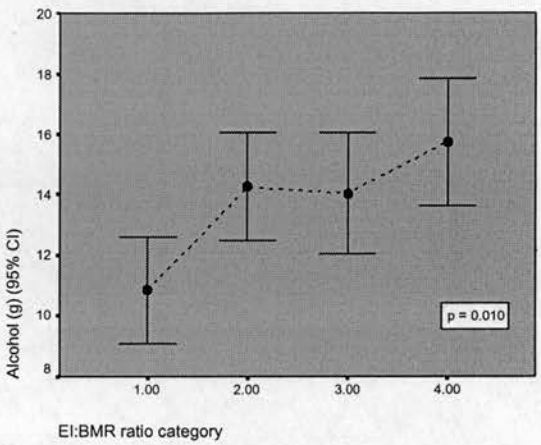


Fig 5.8i: Calcium

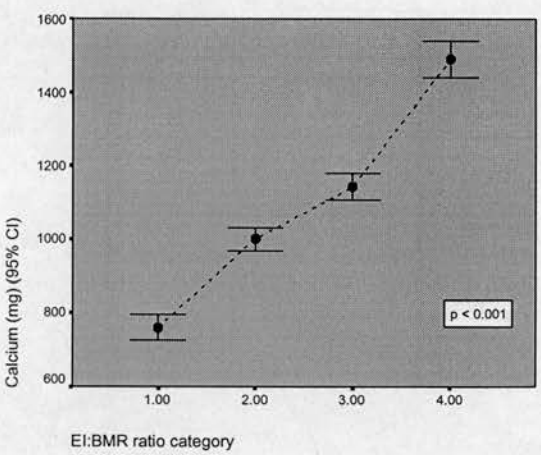


Fig 5.8j: Selenium

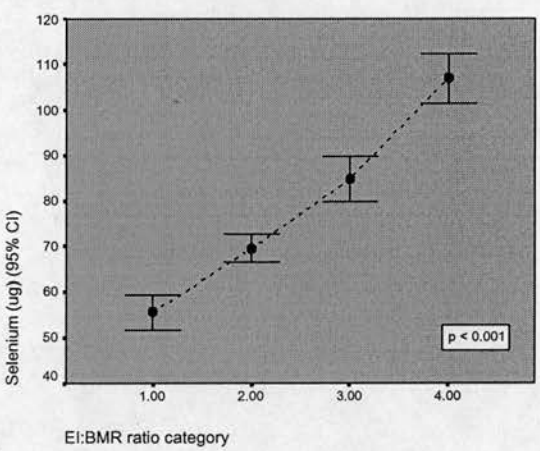


Fig 5.8k: Retinol

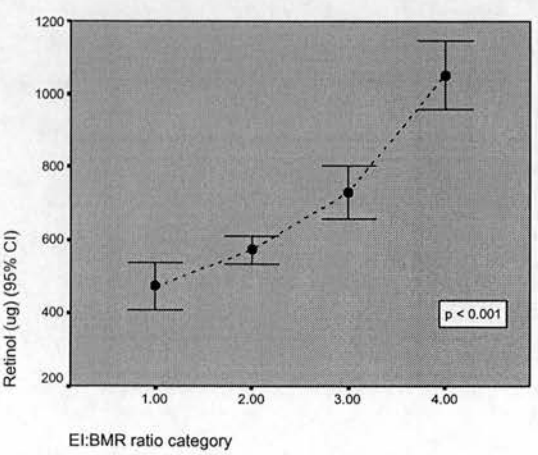


Fig 5.8l: Carotenes

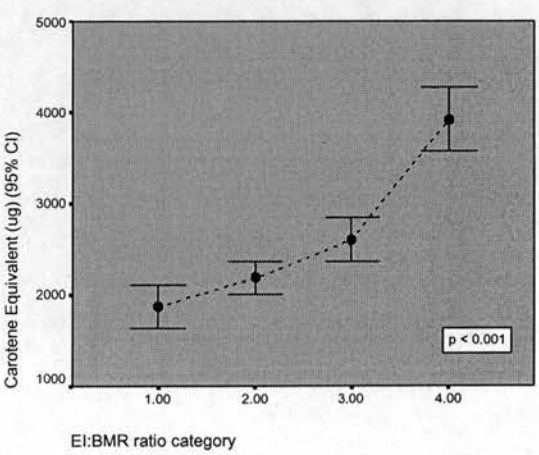


Fig 5.8, Cont.: Nutrient intake across EI:BMR ratio categories

Fig 5.8m: Vitamin E

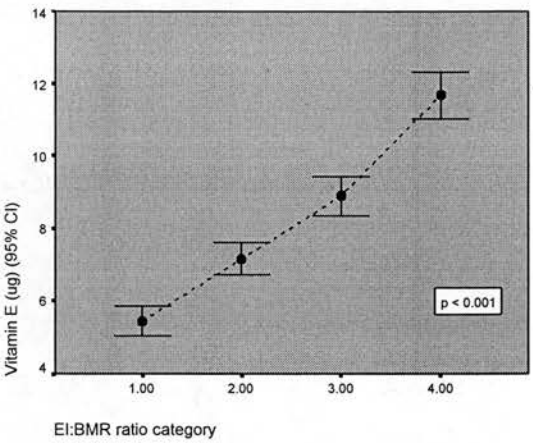


Fig 5.8n: Vitamin C

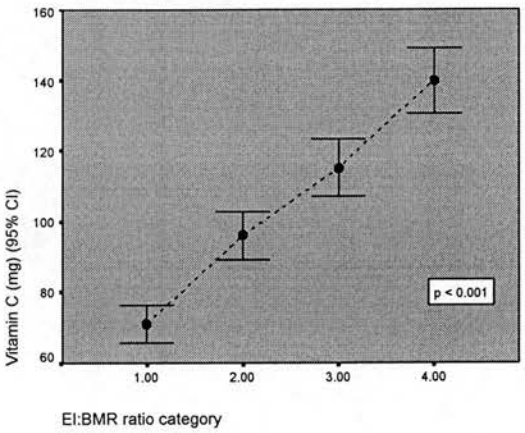


Fig 5.8o: Isoflavones

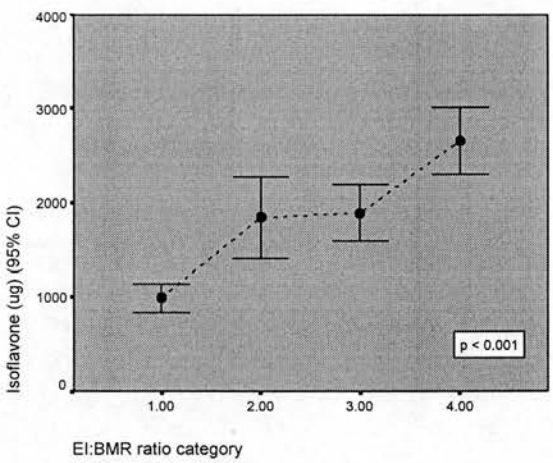
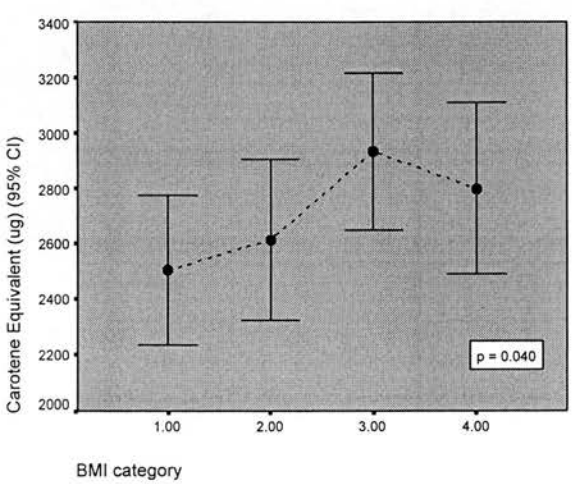


Figure 5.9: Nutrient intake across BMI categories

Fig 5.9a: Carotenes



5.3.7 Odds Ratio analysis

Crude ORs

The majority of nutrients were observed to have positive crude ORs (OR ≥ 1.3) between the reference (lowest) and highest intake categories, with the exception of carotenes and vitamin C for which no association was observed, and alcohol which was observed to have an inverse, though non-significant, association with PCa risk, see Table 5.10. Several of these positive associations were shown to be significant, including: EI (OR 1.56, 95%CI 1.08-2.27), protein (OR 1.46, 95%CI 1.01-2.11), total fat (OR 1.86, 95%CI 1.27-2.74), saturated fat (OR 1.56, 95%CI 1.07-2.27), MUFA (OR 1.85, 95%CI 1.26-2.73), cholesterol (OR 2.00, 95% 1.36-2.95), calcium (OR 1.52, 95%CI 1.05-2.22) and retinol (OR 1.47, 95%CI 1.01-2.13).

Crude ORs for other non á priori nutrients are found in Appendix: Table 8.3.

Significant crude ORs between the reference (lowest) and highest categories were also observed for the majority of potential confounding variables, including: age (OR 1.97, 95%CI 1.36-2.83) and EI: BMR ratio (OR 1.75, 95%CI 1.19-2.56), and also for family history of PCa (OR 2.05, 95%CI 1.32-3.17), family history of BrCa (OR 1.56, 95%CI 1.03-2.37), ex-smoker (OR 1.36, 95%CI 1.01-1.81). See Appendix: Table 8.4

Score test for trends

In addition, a dose response effect was found for total energy, protein, total fat and its constituents (excluding PUFA) and calcium, with the crude ORs of these nutrients being observed to increase significantly with higher intake categories, see Table 5.10.

Score tests for other nutrients are found in Appendix: Table 8.3.

Test for interaction

ORs (and 95% CIs) for nutrient intakes stratified by each confounding variable category were computed using the Mantel Haenszel method, in order to examine the ORs within each individual confounding variable category and to test for interaction.

The results showed that there was no evidence for interaction between the nutrient variables and confounding variables, with the exception of vitamin C with total energy and EI/BMR ratio, and PUFA with the Carstairs deprivation index.

Log likelihood ratio test

The Log Likelihood test was used to examine the effect of each nutrient variable on PCa risk, whilst adjusting for the confounding variables. Only cholesterol was observed to have a significant effect on PCa risk.

Adjusted ORs

The controlling for confounding variables, including the use of energy adjusted nutrient intakes (using the residual method), had a great effect on the observed associations with PCa risk, see Table 5.10. Whereas before the controlling for confounding variables, significant positive crude associations were observed for protein, fat and its constituents, calcium and retinol, only cholesterol continued to have a significant adjusted OR (OR 1.57, 95%CI 1.04-2.37). Whereas the borderline significant inverse association between alcohol intake and PCa risk became stronger when adjusted for (OR 0.66, 95%CI 0.44-0.99). In addition, several nutrients were observed to become inversely, though non-significantly associated with PCa, including PUFA, calcium, selenium, carotene and vitamin E. A borderline significant dose response effect was observed for cholesterol only ($p = 0.054$).

Adjusted ORs for other nutrients are found in Appendix: Table 8.3.

Table 5.10: Crude and adjusted ORs for nutrient intake

Nutrient Variable		Frequency		Crude OR		Adjusted OR[a]	
		Case (n)	Control (n)	OR	(95% CI)	OR	(95% CI)
Total Energy (kJ)	0 - 7874	87	121	1.00	-	1.00	-
	7874 - 9684	105	121	1.21	(0.82-1.77)	1.02	(0.59-1.76)
	9684 - 11757	106	121	1.22	(0.83-1.78)	1.03	(0.53-2.01)
	> 11757	135	120	1.56	(1.08-2.27)	0.96	(0.41-2.25)
				Score test for linear trend: p = 0.022 [b], 0.996 [c]			
Protein (g)	0 - 74.7	92	121	1.00	-	1.00	-
	74.7 - 92.1	104	124	1.10	(0.76-1.61)	0.99	(0.67-1.46)
	92.1 - 112.7	104	118	1.16	(0.79-1.69)	0.91	(0.61-1.36)
	> 112.7	133	120	1.46	(1.01-2.11)	1.00	(0.67-1.48)
				Score test for linear trend: p = 0.042 [b], 0.964 [c]			
Total Fat (g)	0 - 65.3	73	121	1.00	-	1.00	-
	65.3 - 84.9	113	121	1.55	(1.05-2.29)	1.11	(0.75-1.64)
	84.9 - 109.6	112	121	1.53	(1.04-2.27)	1.11	(0.75-1.65)
	> 109.6	135	120	1.86	(1.27-2.74)	1.10	(0.74-1.65)
				Score test for linear trend: p = 0.003 [b], 0.949 [c]			
Saturated Fat (g)	0 - 25.3	83	123	1.00	-	1.00	-
	25.3 - 34.0	97	119	1.21	(0.82-1.78)	1.03	(0.69-1.54)
	34.0 - 46.3	127	121	1.56	(1.07-2.27)	1.03	(0.69-1.54)
	> 46.3	126	120	1.56	(1.07-2.27)	1.15	(0.77-1.72)
				Score test for linear trend: p = 0.009 [b], 0.903 [c]			
MUFA (g)	0 - 22.8	73	121	1.0	-	1.00	-
	22.8 - 29.9	117	124	1.56	(1.06-2.30)	1.17	(0.79-1.75)
	29.9 - 38.3	110	119	1.53	(1.04-2.27)	1.21	(0.81-1.81)
	> 38.3	133	119	1.85	(1.26-2.73)	1.25	(0.83-1.87)
				Score test for linear trend: p = 0.004 [b], 0.714 [c]			
PUFA (g)	0 - 9.7	90	123	1.00	-	1.00	-
	9.7 - 13.3	110	119	1.26	(0.87-1.84)	0.88	(0.60-1.30)
	13.3 - 17.8	124	121	1.40	(0.97-2.03)	1.01	(0.69-1.49)
	> 17.8	109	120	1.24	(0.85-1.81)	0.86	(0.57-1.28)
				Score test for linear trend: p = 0.221 [b], 0.782 [c]			
Cholesterol (mg)	0 - 242	71	121	1.00	-	1.00	-
	242 - 326	92	122	1.29	(0.86-1.92)	0.95	(0.63-1.43)
	326 - 450	129	120	1.83	(1.24-2.70)	1.26	(0.85-1.88)
	> 450	141	120	2.00	(1.36-2.95)	1.57	(1.04-2.37)
				Score test for linear trend: p = 0.0001 [b], 0.054 [c]			

Cont.

Table 5.10, Cont.: Crude and adjusted ORs for nutrient intake

Nutrient Variable		Frequency		Crude OR		Adjusted OR [a]	
		Case (n)	Control (n)	OR	(95% CI)	OR	(95% CI)
Alcohol (g)	0 - 3.4	129	122	1.00	-	1.00	-
	3.4 - 9.9	112	120	0.88	(0.62-1.26)	0.80	(0.55-1.17)
	9.9 - 21.6	102	122	0.79	(0.55-1.14)	0.72	(0.49-1.07)
	> 21.6	90	119	0.72	(0.49-1.04)	0.66	(0.44-0.99)
				Score test for linear trend: p = 0.060 [b], 0.196 [c]			
Calcium (mg)	0 - 812	84	121	1.00	-	1.00	-
	812 - 1039	104	121	1.24	(0.84-1.82)	1.15	(0.77-1.71)
	1039 - 1321	118	121	1.40	(0.96-2.05)	1.33	(0.90-1.97)
	> 1321	127	120	1.52	(1.05-2.22)	0.81	(0.54-1.23)
				Score test for linear trend: p = 0.022 [b], 0.091 [c]			
Selenium (µg)	0 - 56	102	121	1.00	-	1.00	-
	56 - 73	103	122	1.00	(0.69-1.45)	0.92	(0.62-1.35)
	73 - 94	105	122	1.02	(0.70-1.48)	0.67	(0.45-0.99)
	> 94	123	118	1.24	(0.86-1.78)	0.88	(0.59-1.29)
				Score test for linear trend: p = 0.257 [b], 0.222 [c]			
Retinol (µg)	0 - 348	86	121	1.00	-	1.00	-
	348 - 571	124	121	1.44	(0.99-2.10)	1.11	(0.75-1.65)
	571 - 838	98	121	1.14	(0.78-1.67)	0.94	(0.63-1.40)
	> 838	125	120	1.47	(1.01-2.13)	1.21	(0.82-1.80)
				Score test for linear trend: p = 0.141 [b], 0.587 [c]			
Carotene (µg)	0 - 1308	117	121	1.00	-	1.00	-
	1308 - 2187	103	121	0.88	(0.61-1.27)	0.73	(0.49-1.07)
	2187 - 3447	95	121	0.81	(0.56-1.18)	0.77	(0.52-1.13)
	> 3447	118	120	1.02	(0.71-1.46)	0.76	(0.51-1.14)
				Score test for linear trend: p = 0.972 [b], 0.367 [c]			
Vitamin E (µg)	0 - 4.89	82	121	1.00	-	1.00	-
	4.89 - 7.27	131	121	1.60	(1.10-2.33)	0.92	(0.62-1.37)
	7.27 - 10.56	103	121	1.26	(0.85-1.85)	1.07	(0.72-1.57)
	> 10.56	117	120	1.44	(0.98-2.11)	0.86	(0.57-1.28)
				Score test for linear trend: p =0.206 [b], 0.714 [c]			

Cont.

Table 5.10, Cont.: Crude and adjusted ORs for nutrient intake

Nutrient Variable		Frequency		Crude OR		Adjusted OR [a]	
		Case (n)	Control (n)	OR	(95% CI)	OR	(95% CI)
Vitamin C (mg)	0 - 62.5	103	121	1.00	-	1.00	-
	62.5 - 90.5	92	121	0.89	(0.61-1.30)	1.13	(0.76-1.69)
	90.5 - 134.7	126	121	1.22	(0.85-1.76)	1.12	(0.75-1.67)
	> 134.7	112	120	1.10	(0.76-1.58)	1.18	(0.79-1.78)
				Score test for linear trend: p = 0.320 [b], 0.870 [c]			
Isoflavones (μg)	0 - 581.1	95	121	1.00	-	1.00	-
	581.1 - 1050.9	100	121	1.05	(0.72-1.54)	1.12	(0.76-1.67)
	1050.9 - 1982.8	112	121	1.18	(0.81-1.71)	1.11	(0.75-1.65)
	> 1982.8	126	120	1.34	(0.93-1.93)	1.18	(0.79-1.75)
				Score test for linear trend: p = 0.094 [b], 0.874 [c]			

N.B.
MUFA = Mono unsaturated Fat
PUFA = Poly unsaturated Fat
EI = Energy Intake
[a] = Adjusted for Age, EI (residual method), Family History of PCa and BrCa, Deprivation Index, Smoking and EI/BMR Ratio.
[b] = Crude ORs, [c] = adjusted ORs.

5.3.8 Low energy responders (LERs) analysis

As reported in the subjects characteristics section, 157 subjects (17%) were classified as LERs (see Table 5.3) with significantly more controls reported as LERs than cases. In order to examine further the effect this may have on the results and also to eliminate any possible effect this potential bias may have, the above analysis was repeated.

Nutrient intake by LER status

As expected, intake for all nutrients was observed to be significantly lower in the LERs than non-LERs, see Table 5.11.

Nutrient intake: by status, omitting LERs

The omission of LERs had a great effect on the significance of the variation of nutrient intakes by status. Although intakes for most nutrient were still higher within the cases, apart from alcohol and carotene for which intakes were lower in the cases, these differences were significant for cholesterol, alcohol and retinol intake only (the latter two with the T-Test only) see Table 5.12.

Table 5.11: Distribution of nutrient variables by LER status

Nutrient Daily Intake Variables	Non Low Energy Responders (n=759)		Low Energy Responders (n=157)		Test for difference between Low Energy Responder Status	
	Mean (s.d.)	Median (I-QR)	Mean (s.d.)	Median (I-QR)	T-test * (p-value)	Mann-Whitney U Test (p-value)
Total Energy (kJ)	11159 (3071)	10464 (9045-12884)	6402 (1114)	6488 (5798-7042)	<0.001	<0.001
Protein (g)	105.72 (31.52)	100.30 (84.10-120.50)	63.01 (15.16)	62.30 (52.25-72.20)	<0.001	<0.001
Total Fat (g)	101.15 (33.47)	95.80 (78.10-118.90)	54.04 (14.87)	53.50 (43.30-65.30)	<0.001	<0.001
Saturated Fat (g)	41.36 (15.55)	39.10 (30.20-49.70)	21.42 (7.21)	20.60 (16.35-26.35)	<0.001	<0.001
MUFA (g)	35.16 (11.78)	33.30 (26.80-41.30)	18.85 (5.42)	19.00 (14.75-22.85)	<0.001	<0.001
PUFA (g)	15.79 (6.25)	14.70 (11.30-18.70)	8.85 (3.30)	8.30 (6.55-10.55)	<0.001	<0.001
Cholesterol (mg)	412 (183)	383 (292-497)	229 (92)	220 (163-292)	<0.001	<0.001
Alcohol (g)	14.5 (15.2)	9.7 (3.2-21.6)	10.8 (12.6)	6.1 (1.7-15.6)	0.004	0.002
Calcium (mg)	1200 (388)	1151 (926-1402)	736 (244)	722 (568-862)	<0.001	<0.001
Selenium (μg)	86 (39)	79 (63-101)	53 (27)	50 (38-60)	<0.001	<0.001
Iodine (μg)	196 (85)	180 (140-232)	119 (57)	107 (85-144)	<0.001	<0.001
Retinol (μg)	779 (619)	618 (427-920)	482 (477)	311 (207-529)	<0.001	<0.001
Carotene (μg)	2893 (2242)	2290 (1364-3763)	1871 (1692)	1556 (768-2502)	<0.001	<0.001
Vitamin E (μg)	9.20 (4.77)	7.83 (5.72-11.66)	5.18 (2.78)	4.26 (3.27-6.23)	<0.001	<0.001
Vitamin C (mg)	115.9 (65.6)	101.5 (71.6-143.4)	66.3 (33.5)	60.4 (42.7-84.6)	<0.001	<0.001
Isoflavone (μg)	2107.04 (2841.55)	1236.80 (695.70-2518.30)	910.58 (1003.60)	602.10 (382.10-1044.40)	<0.001	<0.001

N.B.
* using transformed data
s.d. = Standard Deviation
I-QR = Inter-Quartile Range
MUFA = Mono Unsaturated Fat
PUFA = Poly Unsaturated Fat
Carotene = Carotene Equivalent
Vitamin E = α-Tocopherol Equivalent

Table 5.12: Nutrient intake by status, omitting LERs

Nutrient Daily Intake Variables	Cases (n=359)		Controls (Population and BPH controls) (n=371)		Test for difference between Cases and Controls	
	Mean (s.d.)	Median (I-QR)	Mean (s.d.)	Median (I-QR)	T-test * (p-value)	Mann-Whitney U Test (p-value)
Total Energy (kJ)	11283 (3074)	10729 (9183-12896)	11039 (3067)	10249 (8914-12867)	0.20	0.16
Protein (g)	106.88 (31.22)	101.80 (85.00-122.10)	104.61 (31.81)	98.95 (83.80-118.98)	0.28	0.23
Total Fat (g)	102.88 (33.50)	97.30 (79.60-119.60)	99.50 (33.40)	95.00 (76.25-116.35)	0.09	0.09
Saturated Fat (g)	42.34 (15.97)	40.20 (31.20-50.10)	40.43 (15.09)	38.10 (29.63-49.58)	0.05	0.10
MUFA (g)	35.71 (11.53)	33.50 (27.70-41.90)	34.64 (12.00)	33.10 (25.90-40.53)	0.09	0.08
PUFA (g)	15.84 (6.12)	14.90 (11.70-18.50)	15.73 (6.38)	14.35 (10.90-18.77)	0.70	0.52
Cholesterol (mg)	428 (192)	404 (313-506)	396 (172)	362 (278-482)	0.005	0.004
Alcohol (g)	13.9 (15.5)	8.2 (2.4-20.8)	15.0 (14.9)	10.3 (3.6-23.8)	0.02	0.09
Calcium (mg)	1207 (381)	1162 (936-1420)	1194 (394)	1139 (917-1396)	0.40	0.43
Selenium (μg)	88 (45)	81 (63-102)	84 (32)	79 (62-100)	0.68	0.76
Retinol (μg)	821 (665)	622 (460-1000)	739 (569)	615 (403-867)	0.03	0.07
Carotene (μg)	2856 (2195)	2284 (1339-3847)	2928 (2288)	2295 (1383-3732)	0.56	0.85
Vitamin E (μg)	9.31 (4.90)	7.79 (5.75-11.91)	9.10 (4.65)	7.84 (5.69-11.05)	0.69	0.71
Vitamin C (mg)	116.7 (69.0)	105.6 (70.1-142.4)	115.1 (62.3)	98.9 (73.0-144.1)	0.93	0.88
Isoflavone (μg)	2159.65 (2578.53)	1340.80 (727.20-2604.00)	2056.74 (3074.58)	1181.20 (680.28-2388.10)	0.34	0.18

N.B.
* using transformed data
s.d. = Standard Deviation
I-QR = Inter-Quartile Range
MUFA = Mono Unsaturated Fat
PUFA = Poly Unsaturated Fat
Carotene = Carotene Equivalent
Vitamin E = α-Tocopherol Equivalent

5.3.9 Odds Ratio analysis, omitting LERs

Crude ORs

As with the observed ORs for all subjects, the majority of nutrients were observed to have positive crude ORs (OR ≥ 1.3) between the reference (lowest) and highest intake categories, with the exception of PUFA, selenium and carotene for which no association was observed, and also alcohol and vitamin C which were observed to have an inverse, though non significant, association with PCa risk, see Table 5.13. However, although far fewer of these positive associations were shown to be significant than for all subjects, those which were significant had far stronger crude ORs, for example total fat (crude OR 2.16, 95%CI 1.26-3.72), MUFA (crude OR 2.15, 95%CI 1.25-3.70), cholesterol (crude OR 1.90, 95%CI 1.18-3.04) and retinol (crude OR 1.78, 95%CI 1.13-2.81).

Score test for trends

A dose response effect was found for total fat, MUFA, cholesterol and retinol, with the crude ORs of these nutrients being observed to increase significantly with higher intake categories, see Table 5.13.

Adjusted ORs

As with the observed ORs for all subjects, the controlling for confounding variables, including the use of energy adjusted nutrient intakes (using the Residual Method), had a great effect on the observed associations with PCa risk, see Table 5.13. No ORs remained significant when adjusted for, with many nutrients that had previously reported positive associations with PCa risk, being observed to either have little or no association (e.g. total fat and MUFA) or having an inverse, though non-significant, association with PCa risk, (e.g. calcium and vitamin E). This same pattern towards an inverse association was seen for nutrients that had previously shown no association with PCa risk, (e.g. PUFA, selenium and carotene). Whereas the inverse, though non-significant, association between alcohol intake and PCa risk continued to be observed. A borderline significant dose response effect was observed for calcium only ($p = 0.048$).

Table 5.13: Crude and adjusted ORs for nutrient intake, omitting LERs

Nutrient Variable		Frequency		Crude OR		Adjusted OR [a]	
		Case (n)	Control (n)	OR	(95% CI)	OR	(95% CI)
Total Energy (kJ)	0 - 7874	30	36	1.00	-	1.00	-
	7874 - 9684	100	111	1.08	(0.62-1.88)	1.00	(0.52-1.95)
	9684 - 11757	106	121	1.05	(0.61-1.82)	1.00	(0.47-2.13)
	> 11757	135	120	1.35	(0.78-2.33)	0.92	(0.37-2.32)
				Score test for linear trend: p = 0.180 [b], 0.994 [c]			
Protein (g)	0 - 74.7	43	48	1.00	-	1.00	-
	74.7 - 92.1	93	105	0.99	(0.60-1.63)	1.02	(0.66-1.57)
	92.1 - 112.7	102	115	0.99	(0.61-1.62)	0.74	(0.48-1.15)
	> 112.7	133	120	1.24	(0.76-2.00)	0.97	(0.63-1.50)
				Score test for linear trend: p = 0.254 [b], 0.436 [c]			
Total Fat (g)	0 - 65.3	30	46	1.00	-	1.00	-
	65.3 - 84.9	118	101	1.92	(1.10-3.35)	1.05	(0.68-1.63)
	84.9 - 109.6	84	121	1.79	(1.04-3.09)	1.00	(0.65-1.55)
	> 109.6	139	120	2.16	(1.26-3.72)	0.99	(0.63-1.55)
				Score test for linear trend: p = 0.026 [b], 0.993 [c]			
Saturated Fat (g)	0 - 25.3	37	54	1.00	-	1.00	-
	25.3 - 34.0	85	97	1.28	(0.77-2.13)	1.10	(0.70-1.71)
	34.0 - 46.3	123	117	1.53	(0.94-2.51)	0.98	(0.63-1.53)
	> 46.3	126	120	1.53	(0.94-2.50)	1.13	(0.72-1.78)
				Score test for linear trend: p = 0.076 [b], 0.899 [c]			
MUFA (g)	0 - 22.8	26	50	1.00	-	1.00	-
	22.8 - 29.9	103	102	1.94	(1.12-3.38)	1.29	(0.83-2.00)
	29.9 - 38.3	109	117	1.79	(1.04-3.09)	1.30	(0.83-2.03)
	> 38.3	133	119	2.15	(1.25-3.70)	1.16	(0.73-1.84)
				Score test for linear trend: p = 0.032 [b], 0.640 [c]			
PUFA (g)	0 - 9.7	48	60	1.00	-	1.00	-
	9.7 - 13.3	96	98	1.22	(0.76-1.97)	0.86	(0.56-1.31)
	13.3 - 17.8	119	112	1.33	(0.84-2.11)	0.90	(0.59-1.38)
	> 17.8	108	118	1.14	(0.72-1.82)	0.78	(0.50-1.22)
				Score test for linear trend: p = 0.676 [b], 0.740 [c]			
Cholesterol (mg)	0 - 242	40	63	1.00	-	1.00	-
	242 - 326	72	97	1.17	(0.71-1.93)	0.90	(0.57-1.42)
	326 - 450	118	111	1.67	(1.04-2.70)	1.23	(0.79-1.92)
	> 450	141	117	1.90	(1.18-3.04)	1.56	(0.98-2.48)
				Score test for linear trend: p = 0.001 [b], 0.075 [c]			

Cont.

Table 5.13, cont.: Crude and adjusted ORs for nutrient intake, omiting LERs

Nutrient Variable		Frequency		Crude OR		Adjusted OR [a]	
		Case (n)	Control (n)	OR	(95% CI)	OR	(95% CI)
Alcohol (g)	0 - 3.4	105	91	1.00	-	1.00	-
	3.4 - 9.9	95	96	0.86	(0.57-1.28)	0.89	(0.59-1.36)
	9.9 - 21.6	88	97	0.79	(0.53-1.18)	0.66	(0.43-1.01)
	> 21.6	83	104	0.69	(0.46-1.04)	0.74	(0.47-1.17)
				Score test for linear trend: p = 0.066 [b], 0.233 [c]			
Calcium (mg)	0 - 812	44	56	1.00	-	1.00	-
	812 - 1039	91	95	1.22	(0.75-1.99)	1.14	(0.74-1.78)
	1039 - 1321	112	118	1.21	(0.75-1.94)	1.40	(0.90-2.17)
	> 1321	124	119	1.33	(0.83-2.12)	0.76	(0.48-1.21)
				Score test for linear trend: p = 0.293 [b], 0.048 [c]			
Selenium (µg)	0 - 56	60	60	1.00	-	1.00	-
	56 - 73	93	99	0.94	(0.59-1.48)	0.95	(0.62-1.45)
	73 - 94	97	114	0.85	(0.54-1.33)	0.63	(0.41-0.99)
	> 94	121	115	1.05	(0.68-1.63)	0.85	(0.55-1.32)
				Score test for linear trend: p = 0.795 [b], 0.187 [c]			
Retinol (µg)	0 - 348	48	72	1.00	-	1.00	-
	348 - 571	108	101	1.60	(1.01-2.54)	1.13	(0.73-1.75)
	571 - 838	94	113	1.25	(0.79-1.97)	0.90	(0.58-1.42)
	> 838	121	102	1.78	(1.13-2.81)	1.43	(0.91-2.25)
				Score test for linear trend: p = 0.059 [b], 0.187 [c]			
Carotene (µg)	0 - 1308	88	88	1.00	-	1.00	-
	1308 - 2187	85	91	0.93	(0.61-1.42)	0.75	(0.49-1.14)
	2187 - 3447	85	98	0.87	(0.57-1.31)	0.85	(0.55-1.31)
	> 3447	113	111	1.02	(0.69-1.51)	0.85	(0.54-1.33)
				Score test for linear trend: p = 0.970 [b], 0.606 [c]			
Vitamin E (µg)	0 - 4.89	46	61	1.00	-	1.00	-
	4.89 - 7.27	114	108	1.40	(0.88-2.23)	0.81	(0.52-1.24)
	7.27 - 10.56	96	108	1.18	(0.73-1.89)	0.87	(0.57-1.34)
	> 10.56	115	111	1.37	(0.86-2.19)	0.75	(0.48-1.16)
				Score test for linear trend: p = 0.416 [b], 0.606 [c]			

Cont.

Table 5.13, cont.: Crude and adjusted ORs for nutrient intake, omiting LERs

Nutrient Variable		Frequency		Crude OR		Adjusted OR [a]	
		Case (n)	Control (n)	OR	(95% CI)	OR	(95% CI)
Vitamin C (mg)	0 - 62.5	77	64	1.00	-	1.00	-
	62.5 - 90.5	70	99	0.59	(0.37-0.93)	1.22	(0.79-1.88)
	90.5 - 134.7	115	108	0.89	(0.58-1.35)	1.13	(0.72-1.75)
	> 134.7	109	117	0.77	(0.51-1.18)	1.07	(0.68-1.68)
				Score test for linear trend: p = 0.737 [b], 0.838 [c]			
Isoflavones (μg)	0 - 581.1	64	74	1.00	-	1.00	-
	581.1 - 1050.9	82	98	0.97	(0.62-1.51)	1.06	(0.68-1.65)
	1050.9 - 1982.8	105	106	1.15	(0.74-1.76)	1.15	(0.74-1.77)
	> 1982.8	120	110	1.26	(0.83-1.93)	1.22	(0.79-1.88)
				Score test for linear trend: p = 0.171 [b], 0.827 [c]			

N.B.
MUFA = Mono unsaturated Fat
PUFA = Poly unsaturated Fat
EI = Energy Intake
[a] = Adjusted for Age, EI (residual method), Family History of PCa and BrCa, Deprivation Index, Smoking and EI/BMR Ratio.
[b] = Crude ORs, [c] = adjusted ORs.

5.3.10 Nutrient analysis: stratified by age group

Although no interaction was observed between age and nutrient intake, and that only a handful of nutrients were observed to vary significantly across age categories, the nutrient analysis by age group was still conducted. As, in addition to the significant positive association between age and PCa risk (OR 1.97, 95%CI 1.36-2.83), closer examination of the distribution of nutrient intake across the four age categories showed that in general, nutrient intake within the younger two categories was higher than the older two categories. Furthermore, tests for interaction between age group and nutrient intakes observed an interaction with several nutrients, including alcohol and selenium intake.

As shown in Table 5.14, 310 of subjects were in the younger age group (≤ 65yrs), with the remaining 606 subjects in the older age group (> 65 yrs), the distribution of cases and controls varied significantly between age groups (chi square test, $p < 0.001$), with more controls within the younger age group and more cases within the older age group. This significant variation was due to a larger number of younger BPH controls than older BPH controls being included in the study which, unlike the population controls, were not age-frequency matched to cases.

Table 5.14: Distribution of subjects by age group

	Frequencies (n)		
	Cases (%)	**Controls (population & BPH controls) (%)**	**Total subjects (%)**
Younger age group (≤ 65 yrs)	119 (27.5)	191 (39.5)	310 (33.8)
Older age group (> 65 yrs)	314 (72.5)	292 (60.5)	606 (66.2)
Total	***433 (100)***	***483 (100)***	***916 (100)***

Nutrient intake by age group

Intake of most nutrients was higher in the younger age group, with intake in the younger age group being significantly higher for EI, protein, total fat, MUFA, PUFA, cholesterol, alcohol, selenium and vitamin E (T-Test only, except for alcohol), see Table 5.15.

Table 5.15: Distribution of nutrient intake by age group

Nutrient Daily Intake Variables	Younger age group (≤65 yrs) n=310		Older age group (>65 yrs) n=606		Test for difference between age groups	
	Mean (s.d.)	Median (I-QR)	Mean (s.d.)	Median (I-QR)	T-test * (p-value)	Mann-Whitney U Test (p-value)
Total Energy (kJ)	10518 (3675)	10125 (7901-12742)	10254 (3174)	9810 (8150-11938)	0.001	0.39
Protein (g)	99.58 (36.15)	93.70 (77.07-118.83)	97.79 (32.06)	93.25 (76.35-113.53)	0.01	0.53
Total Fat (g)	93.66 (38.12)	88.25 (67.30-116.50)	92.78 (34.57)	88.15 (68.85-111.85)	0.03	0.93
Saturated Fat (g)	37.93 (17.45)	34.85 (25.08-48.23)	37.95 (15.69)	35.75 (26.98-47.23)	0.10	0.66
MUFA (g)	32.73 (13.30)	30.95 (23.40-40.80)	32.18 (12.17)	30.45 (23.98-38.65)	0.01	0.68
PUFA (g)	14.82 (6.40)	14.10 (10.07-18.30)	14.48 (6.41)	13.40 (10.00-17.50)	0.01	0.26
Cholesterol (mg)	385 (206)	353 (252-470)	378 (172)	349 (260-463)	0.03	0.95
Alcohol (g)	17.5 (16.6)	12.6 (4.2-27.1)	12.0 (13.5)	7.7 (1.8-18.1)	<0.001	<0.001
Calcium (mg)	1133 (455)	1092 (805-1396)	1114 (379)	1060 (865-1325)	0.07	0.91
Selenium (μg)	81 (37)	77 (56-99)	80 (40)	73 (58-94)	0.04	0.48
Retinol (μg)	730 (558)	585 (373-928)	727 (632)	566 (368-856)	0.05	0.50
Carotene (μg)	2844 (2167)	2258 (1377-3843)	2653 (2202)	2110 (1193-3405)	0.05	0.12
Vitamin E (μg)	8.58 (4.72)	7.42 (5.06-10.89)	8.48 (4.76)	7.16 (5.13-10.59)	0.04	0.54
Vitamin C (mg)	104.6 (66.7)	87.9 (59.2-138.6)	108.9 (62.7)	96.2 (65.6-135.4)	0.50	0.12
Isoflavone (μg)	1887.87 (2244.15)	1112.70 (570.15-2368.75)	1909.18 (2848.07)	1087.85 (626.33-2130.15)	0.17	0.96

N.B.
* using transformed data
s.d. = Standard Deviation
I-QR = Inter-Quartile Range
MUFA = Mono Unsaturated Fat
PUFA = Poly Unsaturated Fat
Carotene = Carotene Equivalent
Vitamin E = α-Tocopherol Equivalent

5.3.11 Odds Ratio analysis, stratified by age group

Crude ORs

The effect of nutrient intake on PCa risk was observed to vary greatly between the age groups, see Table 5.16. For the younger age group, positive associations with PCa risk were observed for the majority of nutrients, with the exception of alcohol, carotene, vitamin C and isoflavones for which no association was observed. Within those nutrients observing a positive association, significant crude ORs for the highest intake category compared to the reference category were observed for EI (crude OR 2.03, 95%CI 1.07-3.86), protein (crude OR 2.10, 95%CI 1.09-4.05), MUFA (crude OR 1.91, 95%CI 1.00-3.68), Cholesterol (crude OR 2.01, 95%CI 1.05-3.82), selenium (crude OR 2.07, 95%CI 1.08-3.97) and retinol (crude OR 2.18, 95%CI 1.12-4.24).

However, for the older age group, although a positive association with PCa risk was also observed for the majority of nutrients, an inverse, though non-significant, association was observed for alcohol, whilst no association was observed between PCa risk and selenium, carotene and vitamin C. Within those nutrients for which a positive association was observed, significant crude ORs for the highest intake category compared to the reference category were observed for total fat (crude OR 1.88, 95%CI 1.16-3.04), saturated fat (crude OR 1.63, 95%CI 1.02-2.62), MUFA (crude OR 1.83, 95%CI 1.13-2.96) and cholesterol (crude OR 1.99, 95%CI 1.22-3.23).

Score test for trends

Within the younger age group, a dose response effect was found for protein, cholesterol, selenium and retinol, with the crude ORs of these nutrients being observed to increase significantly with higher intake categories, see Table 5.16. Whereas for the older age group, a dose response effect was found for total fat, saturated fat, MUFA, cholesterol and alcohol, with the crude ORs of these nutrients being observed to increase significantly with higher intake categories, except for alcohol which showed an inverse dose response effect, with the crude ORs being observed to decrease significantly with higher intake categories.

Adjusted ORs

The controlling for confounding variables, including the use of energy adjusted nutrient intakes (using the residual method), had a great effect on the observed ORs for nutrients in both age groups, see Table 5.16.

Within the younger age group, although most of nutrients remained positively associated with PCa risk, in particular protein whose OR was found to be significant (adjusted OR 2.34, 95% CI 1.13-4.87), several nutrients were observed to become inversely associated with PCa risk, including calcium, carotene, vitamin E and isoflavones, although none of these inverse associations were found to be significant. Whereas alcohol continued to show no association with PCa risk.

Within the older age group, a large number of nutrients previously shown to be either positively or non-associated with PCa risk, were observed to become inversely associated with PCa risk, including protein, PUFA, calcium, selenium and carotene, of which the OR for selenium was found to be significant (adjusted OR 0.61, 95%CI 0.37-0.99). In addition, the inverse association between alcohol and PCa risk became significant (adjusted OR 0.54, 95%CI 0.32-0.89). No significant dose response effects were observed for either age group.

Table 5.16: Crude and adjusted ORs for nutrient intake, stratified by age group

Nutrient Variable		Age Group							
		Younger (≤ 65 years)				Older (> 65 years)			
		Crude OR		Adjusted OR [a]		Crude OR		Adjusted OR [a]	
		OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Total Energy (kJ)	0 - 7874	1.00	-	1.00	-	1.00	-	1.00	-
	7874 - 9684	1.70	(0.83-3.45)	2.37	(0.95-5.93)	0.97	(0.61-1.54)	0.56	(0.26-1.17)
	9684 - 11757	1.20	(0.60-2.38)	2.25	(0.68-7.49)	1.18	(0.74-1.88)	0.62	(0.26-1.50)
	> 11757	2.03	(1.07-3.86)	4.88	(0.93-25.50)	1.39	(0.87-2.21)	0.44	(0.15-1.29)
		Score test for linear trend: p = 0.062[b], 0.163[c]				Score test for linear trend: p = 0.105[b],0.338[c]			
Protein (g)	0 - 74.7	1.00	-	1.00	-	1.00	-	1.00	-
	74.7 - 92.1	1.53	(0.76-3.05)	1.72	(0.82-3.61)	0.95	(0.60-1.50)	0.79	(0.49-1.28)
	92.1 - 112.7	1.52	(0.74-3.14)	1.89	(0.91-3.90)	0.98	(0.62-1.55)	0.67	(0.41-1.09)
	> 112.7	2.10	(1.09-4.05)	2.34	(1.13-4.87)	1.28	(0.81-2.02)	0.66	(0.41-1.08)
		Score test for linear trend: p = 0.030[b], 0.159[c]				Score test for linear trend: p = 0.286[b], 0.283[c]			
Total Fat (g)	0 - 65.3	1.00	-	1.00	-	1.00	-	1.00	-
	65.3 - 84.9	1.52	(0.77-3.01)	1.24	(0.63-2.44)	1.55	(0.96-2.49)	1.05	(0.64-1.73)
	84.9 - 109.6	0.94	(0.46-1.92)	1.17	(0.58-2.36)	1.84	(1.14-2.97)	1.05	(0.64-1.72)
	> 109.6	1.87	(0.97-3.63)	1.32	(0.64-2.74)	1.88	(1.16-3.04)	0.98	(0.60-1.60)
		Score test for linear trend: p = 0.143[b], 0.890[c]				Score test for linear trend: p = 0.008[b], 0.989[c]			
Saturated Fat (g)	0 - 25.3	1.00	-	1.00	-	1.00	-	1.00	-
	25.3 - 34.0	0.70	(0.34-1.41)	0.92	(0.46-1.82)	1.46	(0.91-2.36)	1.12	(0.68-1.85)
	34.0 - 46.3	1.21	(0.64-2.30)	0.81	(0.41-1.63)	1.72	(1.07-2.75)	1.13	(0.68-1.87)
	> 46.3	1.39	(0.74-2.62)	1.34	(0.63-2.85)	1.63	(1.02-2.62)	1.03	(0.63-1.68)
		Score test for linear trend: p = 0.143[b], 0.529[c]				Score test for linear trend: p = 0.038[b],0.933[c]			
MUFA (g)	0 - 22.8	1.00	-	1.00	-	1.00	-	1.00	-
	22.8 - 29.9	1.54	(0.76-3.06)	1.04	(0.51-2.09)	1.53	(0.95-2.46)	1.20	(0.73-1.97)
	29.9 - 38.3	0.83	(0.41-1.69)	1.41	(0.70-2.84)	1.97	(1.21-3.21)	1.07	(0.65-1.77)
	> 38.3	1.91	(1.00-3.68)	1.21	(0.57-2.57)	1.83	(1.13-2.96)	1.25	(0.77-2.04)
		Score test for linear trend: p = 0.145[b], 0.706[c]				Score test for linear trend: p = 0.010[b],0.893[c]			
PUFA (g)	0 - 9.7	1.00	-	1.00	-	1.00	-	1.00	-
	9.7 - 13.3	1.79	(0.89-3.60)	1.50	(0.75-3.02)	1.08	(0.68-1.69)	0.65	(0.40-1.05)
	13.3 - 17.8	1.42	(0.72-2.81)	0.88	(0.44-1.75)	1.41	(0.90-2.22)	1.02	(0.63-1.65)
	> 17.8	1.31	(0.67-2.55)	0.90	(0.44-1.83)	1.29	(0.81-2.06)	0.78	(0.48-1.28)
		Score test for linear trend: p = 0.661[b], 0.459[c]				Score test for linear trend: p = 0.157[b], 0.170[c]			
Cholesterol (mg)	0 - 242	1.00	-	1.00	-	1.00	-	1.00	-
	242 - 326	0.63	(0.30-1.33)	1.02	(0.51-2.03)	1.65	(1.01-2.71)	0.96	(0.57-1.61)
	326 - 450	1.21	(0.63-2.36)	0.75	(0.35-1.59)	2.19	(1.34-3.57)	1.44	(0.89-2.35)
	> 450	2.01	(1.05-3.82)	1.99	(0.97-4.08)	1.99	(1.22-3.23)	1.34	(0.81-2.21)
		Score test for linear trend: p = 0.006[b], 0.089[c]				Score test for linear trend: p = 0.004[b], 0.189[c]			

Table 5.16, Cont.: Crude and adjusted ORs for nutrient intake, stratified by age group

Nutrient Variable		Age Group							
		Younger (≤ 65 years)				Older (> 65 years)			
		Crude OR		Adjusted OR [a]		Crude OR		Adjusted OR [a]	
		OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Alcohol (g)	0 - 3.4	1.00	-	1.00	-	1.00	-	1.00	-
	3.4 - 9.9	0.57	(0.27-1.19)	0.78	(0.37-1.65)	1.09	(0.71-1.66)	0.79	(0.50-1.25)
	9.9 - 21.6	1.14	(0.58-2.25)	1.19	(0.57-2.48)	0.71	(0.46-1.10)	0.58	(0.36-0.94)
	> 21.6	1.10	(0.58-2.10)	1.02	(0.50-2.09)	0.63	(0.39-1.03)	0.54	(0.32-0.89)
		Score test for linear trend: p = 0.307[b], 0.697[c]				Score test for linear trend: p = 0.022[b], 0.079[c]			
Calcium (mg)	0 - 812	1.00	-	1.00	-	1.00	-	1.00	-
	812 - 1039	1.09	(0.55-2.19)	1.04	(0.52-2.10)	1.19	(0.74-1.90)	1.12	(0.68-1.84)
	1039 - 1321	1.46	(0.75-2.82)	1.05	(0.53-2.06)	1.29	(0.81-2.06)	1.40	(0.85-2.31)
	> 1321	1.54	(0.83-2.86)	0.86	(0.44-1.70)	1.50	(0.93-2.43)	0.76	(0.45-1.29)
		Score test for linear trend: p = 0.125[b], 0.959[c]				Score test for linear trend: p = 0.088[b], 0.128[c]			
Selenium (µg)	0 - 56	1.00	-	1.00	-	1.00	-	1.00	-
	56 - 73	1.33	(0.65-2.75)	1.25	(0.63-2.48)	0.80	(0.51-1.26)	0.76	(0.49-1.23)
	73 - 94	1.83	(0.94-3.56)	0.85	(0.41-1.79)	0.76	(0.48-1.20)	0.56	(0.34-0.92)
	> 94	2.07	(1.08-3.97)	1.83	(0.93-9.63)	0.96	(0.61-1.53)	0.61	(0.37-0.99)
		Score test for linear trend: p = 0.016[b], 0.183[c]				Score test for linear trend: p = 0.851[b],0.078[c]			
Retinol (µg)	0 - 348	1.00	-	1.00	-	1.00	-	1.00	-
	348 - 571	1.48	(0.75-2.96)	0.63	(0.30-1.35)	1.39	(0.88-2.19)	1.42	(0.89-2.30)
	571 - 838	0.99	(0.49-1.99)	1.26	(0.61-2.59)	1.22	(0.76-1.96)	0.84	(0.51-1.37)
	> 838	2.18	(1.12-4.24)	1.61	(0.80-3.23)	1.22	(0.77-1.93)	1.00	(0.62-1.63)
		Score test for linear trend: p = 0.048[b], 0.106[c]				Score test for linear trend: p = 0.596[b],0.138[c]			
Carotene (µg)	0 - 1308	1.00	-	1.00	-	1.00	-	1.00	-
	1308 - 2187	0.69	(0.35-1.36)	0.60	(0.30-1.21)	1.03	(0.66-1.61)	0.84	(0.53-1.36)
	2187 - 3447	0.82	(0.41-1.61)	0.78	(0.40-1.56)	0.82	(0.53-1.29)	0.81	(0.50-1.31)
	> 3447	1.03	(0.55-1.95)	0.77	(0.38-1.55)	1.07	(0.69-1.67)	0.85	(0.52-1.40)
		Score test for linear trend: p = 0.716[b], 0.533[c]				Score test for linear trend: p = 0.974[b], 0.790[c]			
Vitamin E (µg)	0 - 4.89	1.00	-	1.00	-	1.00	-	1.00	-
	4.89 - 7.27	2.06	(1.04-4.09)	1.08	(0.53-2.19)	1.39	(0.88-2.20)	0.86	(0.53-1.39)
	7.27 - 10.56	1.07	(0.53-2.15)	0.97	(0.49-1.91)	1.36	(0.84-2.18)	1.07	(0.66-1.73)
	> 10.56	1.56	(0.80-3.04)	0.65	(0.31-1.35)	1.41	(0.88-2.25)	0.94	(0.58-1.53)
		Score test for linear trend: p = 0.571[b],0.597[c]				Score test for linear trend: p = 0.213 [b],0.876[c]			

Cont.

Table 5.16, Cont.: Crude and adjusted ORs for nutrient intake, stratified by age group

Nutrient Variable		Age Group							
		Younger (≤ 65 years)				Older (> 65 years)			
		Crude OR		Adjusted OR [a]		Crude OR		Adjusted OR [a]	
		OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Vitamin C (mg)	0 - 62.5	1.00	-	1.00	-	1.00	-	1.00	-
	62.5 - 90.5	0.89	(0.47-1.70)	1.20	(0.61-2.37)	0.88	(0.55-1.41)	1.13	(0.69-1.86)
	90.5 - 134.7	1.06	(0.55-2.05)	1.23	(0.58-2.58)	1.20	(0.77-1.88)	1.03	(0.63-1.68)
	> 134.7	1.19	(0.63-2.23)	0.92	(0.43-1.96)	1.02	(0.65-1.62)	1.29	(0.78-2.14)
		Score test for linear trend: p = 0.508[b], 0.839[c]				Score test for linear trend: p = 0.593[b], 0.688[c]			
Isoflavones (μg)	0 - 581.1	1.00	-	1.00	-	1.00	-	1.00	-
	581.1 - 1050.9	1.12	(0.57-2.23)	1.00	(0.50-1.98)	0.95	(0.60-1.51)	1.24	(0.76-2.04)
	1050.9 - 1982.8	1.30	(0.68-2.47)	1.44	(0.71-2.93)	1.08	(0.68-1.72)	0.99	(0.61-1.61)
	> 1982.8	1.15	(0.62-2.15)	0.84	(0.40-1.76)	1.44	(0.90-2.29)	1.41	(0.87-2.30)
		Score test for linear trend: p = 0.590[b], 0.682[c]				Score test for linear trend: p = 0.091[b], 0.213[c]			

N.B.
MUFA = Mono unsaturated Fat
PUFA = Poly unsaturated Fat
EI = Energy Intake
[a] = Adjusted for EI (residual method), Family History of PCa and BrCa, Deprivation Index, Smoking and EI/BMR ratio
[b] = crude ORs, [c] = adjusted ORs.

5.4 Food groups analysis

The following section reports the results for the food group analysis part of the study and includes the analysis of alcohol type.

5.4.1 Food group distribution

Distributions of food group consumption were all observed to have varying degrees of skewedness, with only total meat showing a distribution close to normality, see Figure 5.10. Due to this, food group variables were normalised by log transformation for the use in parametric tests, in addition to the use of non-parametric tests. For alcohol consumption, the majority of subjects reported to consume alcohol (82.9%), although the distribution of each alcohol type was skewed towards lower / no consumption.

5.4.2 Outliers

Analysis of the distributions also revealed outliers for many of the food groups. Several subjects were reported as having very high intakes of dairy products, in particular one subject whom reported consuming 60 eggs per week. Other subjects were reported as having very high intakes of soy foods in relation to the low mean intake, these tended to be subjects who did not eat meat and therefore used soy products as a meat alternative. The repeated checking of the FFQs showed that the subjects had indeed reported consuming high levels of these foods. It was therefore decided not to omit any of these outliers in the present analysis, especially as categorical variables for food group intake were used in the odds ratio analysis instead of the original continuous variables, thereby minimising the potential effect that these outliers would have on the observed ORs.

Figure 5.10: Distribution of food groups

Fig 5.10a: Total dairy products

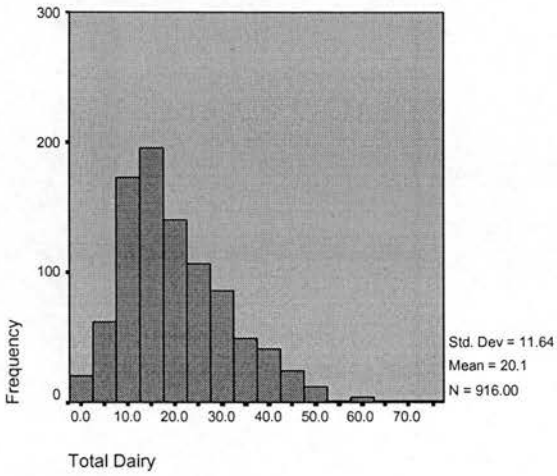


Fig 5.10b: Milk

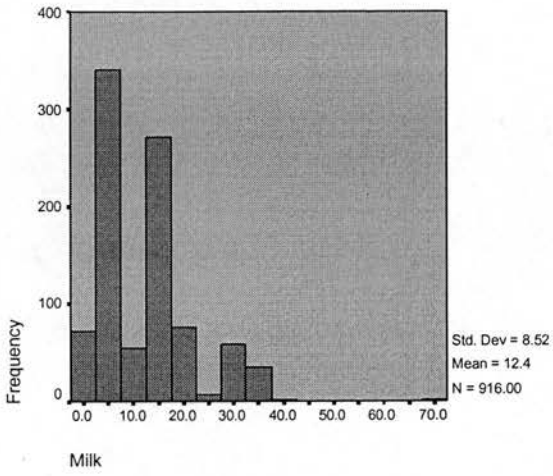


Fig 5.10c: Cheese

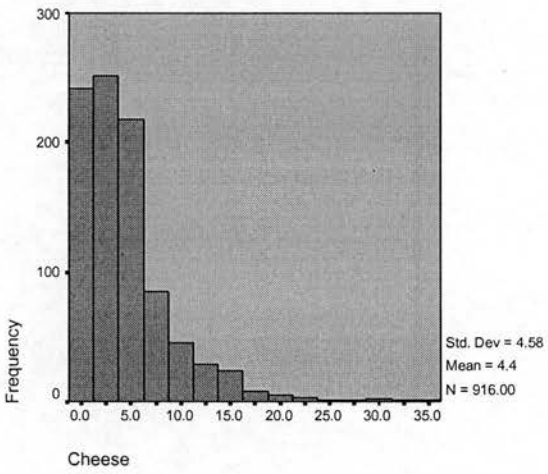


Fig 5.10d: Eggs

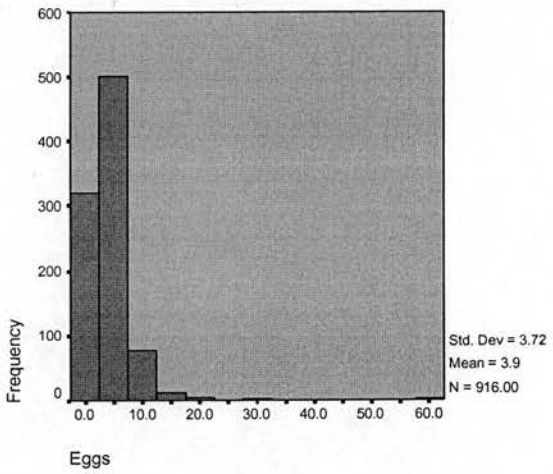


Fig 5.10e: Total meat

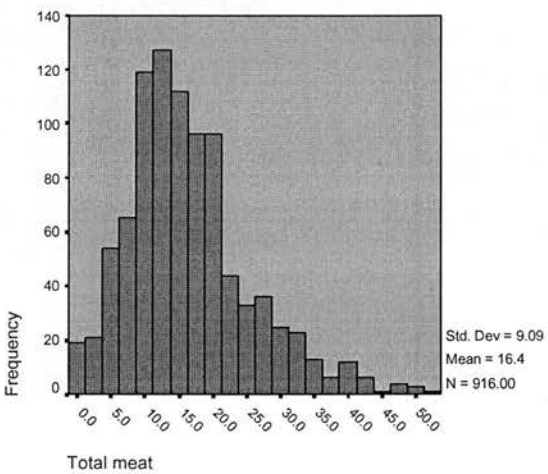


Fig 5.10f: Red meat

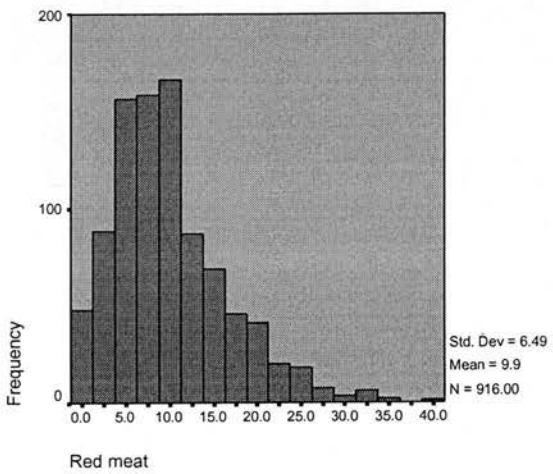


Fig 5.10g: Processed meat

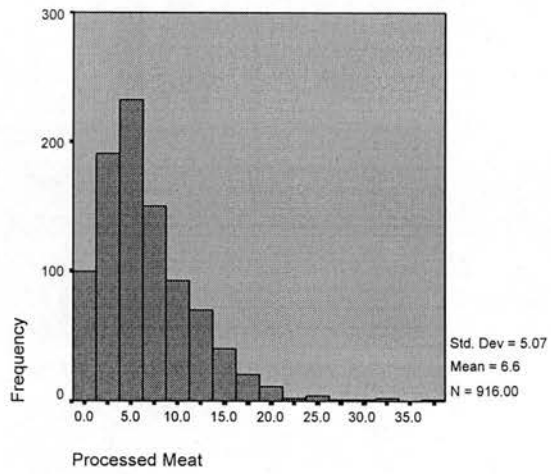


Fig 5.10h: Fish

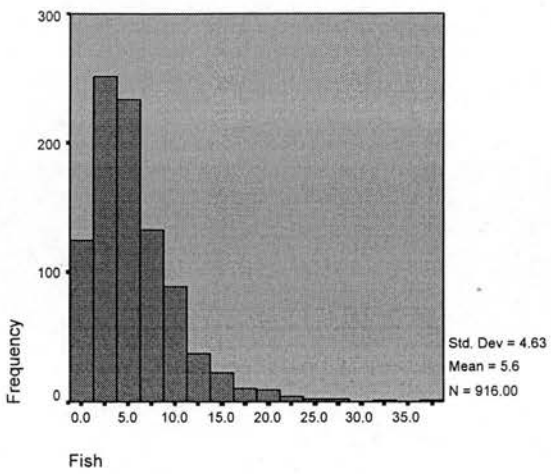


Fig 5.10i: Grilled meat

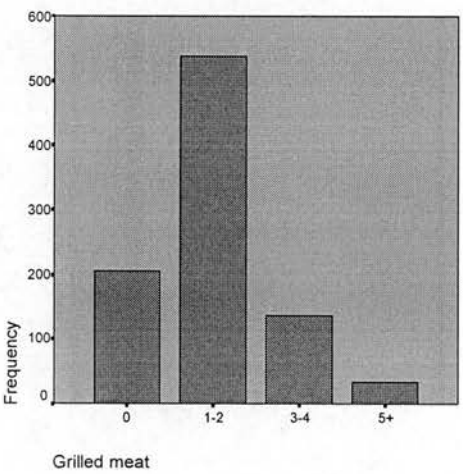


Fig 5.10j: Soy foods

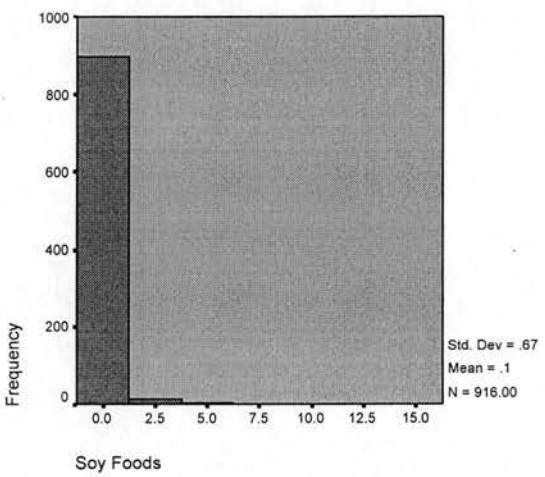


Fig 5.10k: Whole Fruit

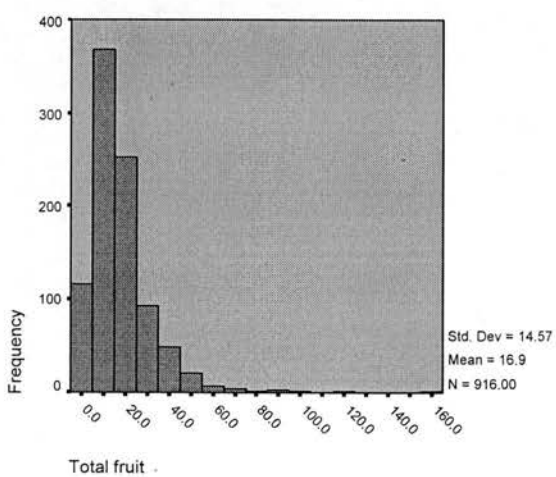


Fig 5.10l: Vegetables

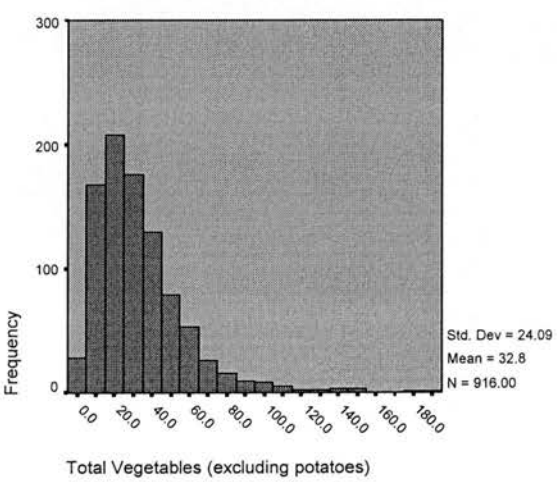


Fig 5.10m: Alcohol consumption

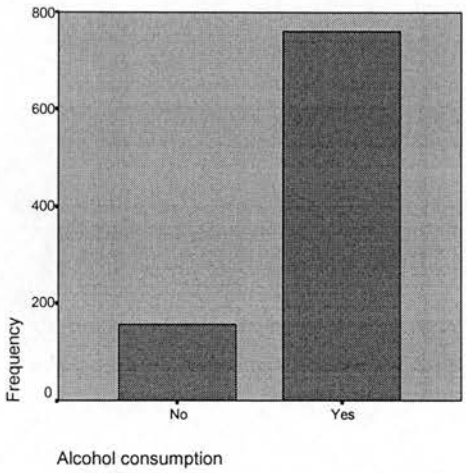


Fig 5.10n: Beer

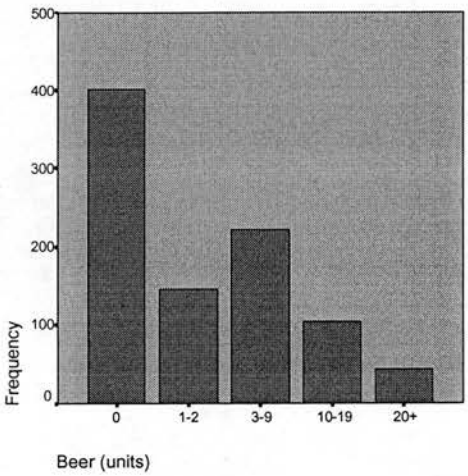


Fig 5.10o: Wine

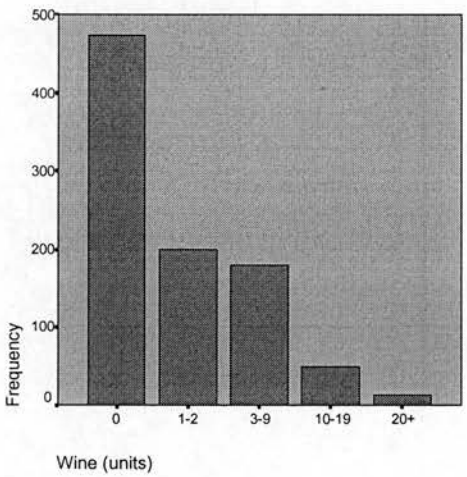
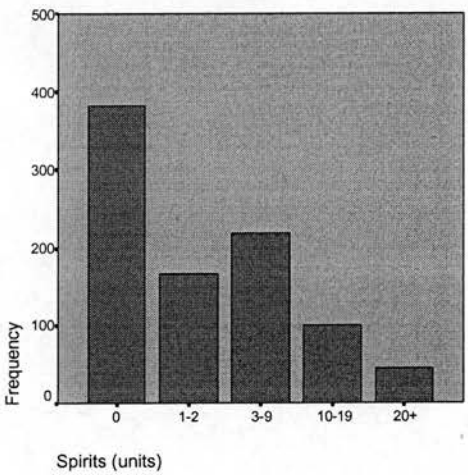


Fig 5.10p: Spirits



5.4.3 Food group intake: by case-control status

Controls were observed to have lower intakes of all food groups compared to cases, with the exception of total vegetables for which intake did not vary between status, and soy foods for which controls were observed to have a significantly higher intake than cases, see Table 5.17. These differences were shown to be significant for eggs, total meat, red meat and processed meat.

In addition, no significant variation across both grilled meat and the grilled meat score categories was observed, see Table 5.18. However, significantly more controls than cases reported to consume alcohol, with significantly more controls than cases consuming high quantities (10+ units per week) of wine. Controls also consumed higher quantities of both beer and spirits, although these were shown to be non-significant, see Table 5.18.

Table 5.17: Distribution of continuous food group variables, by status

Food Groups (helpings per week)	Cases (n=437)		Controls (Population and BPH controls) (n=483)		Test for difference between Cases and Controls
	Mean (s.d.)	Median (I-QR)	Mean (s.d.)	Median (I-QR)	Mann-Whitney U Test (p-value)
Total Dairy	20.49 (11.96)	18.00 (11.00-28.25)	19.70 (11.34)	17.00 (11.50-26.00)	0.34
Milk	12.75 (8.64)	14.00 (7.00-14.00)	12.06 (8.41)	10.00 (7.00-14.00)	0.30
Cheese	4.59 (4.91)	3.00 (1.00-6.00)	4.28 (4.26)	3.00 (1.00-6.00)	0.68
Eggs	4.25 (4.26)	3.00 (2.00-6.00)	3.60 (3.13)	3.00 (2.00-5.00)	0.01
Total Meat	17.16 (8.99)	16.00 (11.00-21.00)	15.75 (9.14)	14.00 (9.50-20.50)	0.01
Red Meat	10.49 (6.28)	9.00 (6.00-14.00)	9.40 (6.64)	8.00 (5.00-12.00)	0.001
Processed Meat	6.88 (5.09)	6.00 (3.00-9.00)	6.28 (5.04)	5.00 (2.50-9.00)	0.02
Total Vegetables (excluding potatoes)	32.63 (23.63)	28.00 (15.50-42.50)	32.98 (24.51)	27.00 (16.50-42.50)	0.89
Total WholeFruit	17.35 (16.02)	14.50 (7.00-22.00)	16.50 (13.13)	13.50 (7.50-21.50)	0.72
Fish	5.49 (4.11)	5.00 (2.50-8.00)	5.69 (5.05)	4.50 (2.00-8.00)	0.63
Soy Foods	0.07 (0.39)	0.00 (0.00-0.00)	0.13 (0.84)	0.00 (0.00-0.00)	0.04

N.B.
s.d. = Standard Deviation
I-QR = Inter-Quartile Range

Table 5.18: Distribution of categorical food group variables, by status

Food Groups (helpings per week)	Cases (% within status)	Controls (Population and BPH controls) (% within status)
Grilled Meat:		
No grilled meat	91 (21.0%)	115 (23.8%)
1-2	256 (59.1%)	283 (58.6%)
3-4	71 (16.4%)	67 (13.9%)
5+	15 (3.5%)	18 (3.7%)
Total	***433 (100%)***	***483 (100%)***
	Chi-Square Test (p-value) = 0.61	
Grilled Meat Score:		
No grilled meat	91 (21.0%)	115 (23.8%)
1	23 (5.3%)	17 (3.5%)
2	116 (26.8%)	130 (26.9%)
3	124 (28.6%)	145 (30.0%)
4+	79 (18.2%)	76 (15.7%)
Total	***433 (100%)***	***483 (100%)***
	Chi-Square Test (p-value) = 0.48	

Cont.

Table 5.18, cont.: Distribution of categorical food group variables, by status

Alcohol Types (units per week)	Cases (% within status)	Controls (Population and BPH controls) (% within status)
Alcohol consumption:		
No	88 (20.3%)	69 (14.3%)
Yes	345 (79.7%)	414 (85.7%)
Total	***433 (100%)***	***483 (100%)***
	Chi-Square Test (p-value) = 0.015	
Beer		
No alcohol consumption	88 (20.3%)	69 (14.3%)
Alcohol consumption other than beer	113 (26.1%)	131 (27.1%)
1-2 units	69 (15.9%)	76 (15.7%)
3-9 units	95 (21.9%)	127 (26.3%)
10+ units	68 (15.7%)	80 (16.6%)
Total	***433 (100%)***	***483 (100%)***
	Chi-Square Test (p-value) = 0.227	
Wine		
No alcohol consumption	88 (20.3%)	69 (14.3%)
Alcohol consumption other than wine	136 (31.4%)	181 (37.5%)
1-2 units	93 (21.5%)	107 (22.2%)
3-9 units	95 (21.9%)	85 (17.6%)
10+ units	21 (4.9%)	41 (8.5%)
Total	***433 (100%)***	***483 (100%)***
	Chi-Square Test (p-value) = 0.015	
Spirits		
No alcohol consumption	88 (20.3%)	69 (14.3%)
Alcohol consumption other than spirits	99 (22.9%)	127 (26.3%)
1-2 units	84 (19.4%)	84 (17.4%)
3-9 units	103 (23.8%)	116 (24.0%)
10+ units	59 (13.6%)	87 (18%)
Total	***433 (100%)***	***483 (100%)***
	Chi-Square Test (p-value) = 0.086	

5.4.4 Correlation between individual food groups

As expected, crude correlations showed that most food groups were associated with each other, see Appendix: Table 8.5. Therefore the correlation analysis was redone using EI-adjusted food groups.

Certain patterns within and between general food groups continued to be observed, though they tended to be weaker. Both milk and cheese were strongly positively correlated with total dairy products but not with each other. Meat products were strongly positively associated with each other, with the exception of fish, which was positively associated with vegetables. Eggs were also observed to be positively associated with most meat products, whilst vegetables were positively associated with fruit. Within alcohol types, spirits were observed to be positively associated with beer and to a lesser extent with wine, see Table 5.19.

Table 5.19: correlation coefficients for energy adjusted food groups

		Total Dairy	Milk	Cheese	Eggs	Total Meat	Red Meat	Processed Meat	Fish	Soy foods	Vegetables	Whole Fruit	Beer	Wine	Spirits	Grilled Meat	Grilled Meat Score
Total Dairy	Rho	1.000	**.769**	**.418**	-.014	**-.131**	**-.139**	-.073	-.060	.028	-.057	-.052	-.038	.030	**-.103**	.051	.037
	P value	.	.000	.000	.666	.000	.000	.027	.070	.400	.083	.114	.253	.362	.002	.126	.259
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Milk	Rho	**.769**	1.000	.048	-.006	-.062	-.064	-.023	**-.102**	.053	**-.131**	**-.093**	-.090	**-.101**	**-.092**	.078	.056
	P value	.000	.	.144	.862	.059	.052	.493	.002	.111	.000	.005	.007	.002	.005	.019	.092
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Cheese	Rho	**.418**	.048	1.000	**.086**	-.011	-.022	.028	.055	.028	.034	-.038	.083	**.121**	-.005	-.012	.006
	P value	.000	.144	.	.009	.736	.508	.406	.098	.395	.308	.256	.012	.000	.891	.724	.869
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Eggs	Rho	-.014	-.006	**.086**	1.000	**.202**	**.287**	**.170**	-.028	.016	**-.128**	**-.180**	**.119**	**-.136**	-.081	**.168**	**.141**
	P value	.666	.862	.009	.	.000	.000	.000	.396	.623	.000	.000	.000	.000	.015	.000	.000
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Total Meat	Rho	**-.131**	-.062	-.011	**.202**	1.000	**.796**	**.739**	.004	.053	.022	**-.152**	**.140**	-.043	**.109**	**.296**	**.260**
	P value	.000	.059	.736	.000	.	.000	.000	.893	.106	.505	.000	.000	.199	.001	.000	.000
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Red Meat	Rho	**-.139**	-.064	-.022	**.287**	**.796**	1.000	**.463**	-.063	.026	-.065	**-.216**	**.137**	**-.010**	**.108**	**.378**	**.320**
	P value	.000	.052	.508	.000	.000	.	.000	.056	.431	.050	.000	.000	.003	.001	.000	.000
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Processed Meat	Rho	-.073	-.023	.028	**.170**	**.739**	**.463**	1.000	-.018	.073	-.075	**-.145**	**.157**	**-.096**	.060	**.178**	**.184**
	P value	.027	.493	.406	.000	.000	.000	.	.590	.027	.024	.000	.000	.004	.067	.000	.000
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Fish	Rho	-.060	**-.102**	.055	-.028	.004	-.063	-.018	1.000	**.092**	**.286**	**.135**	.006	**.153**	.058	.011	**-.081**
	P value	.070	.002	.098	.396	.893	.056	.590	.	.005	.000	.000	.858	.000	.080	916	.014
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Soy foods	Rho	.028	.053	.028	.016	.053	.026	.073	**.092**	1.000	**.094**	**.131**	-.064	.027	-.056	**-.118**	**-.119**
	P value	.400	.111	.395	.623	.106	.431	.027	.005	.	.004	.000	.052	.418	.092	.000	.000
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Vegetables	Rho	-.057	**-.131**	.034	**-.128**	.022	-.065	-.075	**.286**	**.094**	1.000	**.346**	.024	**.117**	-.009	**-.118**	**-.133**
	P value	.083	.000	.308	.000	.505	.050	.024	.000	.004	.	.000	.471	.000	.790	.000	.000
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916

Cont.

Table 5.19: Food group correlations (energy adjusted), cont.

		Total Dairy	Milk	Cheese	Eggs	Total Meat	Red Meat	Processed Meat	Fish	Soy foods	Vegetables	Whole Fruit	Beer	Wine	Spirits	Grilled Meat	Grilled Meat Score
Whole Fruit	Rho	-.052	**-.093**	-.038	**-.180**	**-.152**	**-.216**	**-.145**	**.135**	**.131**	**.346**	1.000	**-.120**	.031	**-.122**	**-.210**	**-.196**
	P value	.114	.005	.256	.000	.000	.000	.000	.000	.000	.000	.	.000	.349	.000	.000	.000
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Beer	Rho	-.037	**-0.090**	.083	**.119**	**.140**	**.137**	**.157**	.006	-.064	.024	**-.120**	1.000	.067	**.222**	**.094**	**.084**
	P value	.253	.007	.012	.000	.000	.000	.000	.858	.052	.471	.000	.	.041	.000	.004	.011
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Wine	Rho	.030	**-.101**	**.121**	**-.136**	-.043	**-.010**	**-.096**	**.153**	.027	**.117**	.031	.067	1.000	**.163**	-.036	-.060
	P value	.362	.002	.000	.000	.199	.003	.004	.000	.418	.000	.349	.041	.	.000	.275	.069
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Spirits	Rho	**-.103**	**-.092**	-.005	-.081	**.109**	**.108**	.060	.058	-.056	-.009	**-.122**	**.222**	**.163**	1.000	**.140**	**.106**
	P value	.002	.005	.891	.015	.001	.001	.067	.080	.092	.790	.000	.000	.000	.	.000	.001
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Grilled meat	Rho	.051	.078	-.012	**.168**	**.297**	**.378**	**.178**	**-.084**	**-.118**	**-.118**	**-.210**	**.094**	-.036	**.140**	1.000	**.882**
	P value	.126	.019	.724	.000	.000	.000	.000	.011	.000	.000	.000	.004	.275	.000	.	.000
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Grilled meat score	Rho	.037	.056	.006	**.141**	**.260**	**.320**	**.184**	**-.081**	**-.119**	**-.133**	**-.196**	**.084**	-.060	**.106**	**.882**	1.000
	P value	.259	.092	.869	.000	.000	.000	.000	.014	.000	.000	.000	.011	.069	.001	.000	.
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916

Bold = Correlation is significant at the 99% level (2-tailed).

5.4.5 Food groups by confounding variables

The correlation between food group consumption and confounding variables were examined using Spearman's rank correlations, see Table 5.20. As expected, both energy intake and the EI: BMR ratio were significantly positively correlated with all food groups, except for soy foods and wine, as was BMI to a lesser extent and with fewer food groups. Age was significantly inversely correlated with total meat, processed meat and beer and spirits, whereas family history of PCa / BrCa was positively correlated with processed meat, total vegetables and wine. For both the Carstairs Deprivation Index and smoking status a similar pattern was observed. Significant positive correlations were observed with eggs, most meat products and beer, whereas significant inverse correlations were observed with fish, soy foods, total vegetables, total fruit and wine, and also for most dairy products (Carstairs Deprivation Index only).

In order to examine the association between food groups and confounding variables further, mean food group consumption was compared across confounding variable categories. The associations that were observed to be significant are shown in Figures 5.11 to 5.17. As expected, consumption for all food groups increased significantly across total energy and the EI / BMR ratio categories, with the exception of soy foods (Figures 5.11 and 5.16). Most food groups also varied significantly across the Carstairs deprivation index (Figure. 5.14), the consumption of total dairy, cheese, fish, soy food, fruit and vegetables were shown to decrease with increasing deprivation index categories, whilst the consumption of eggs and other meat products was observed in increase with increasing deprivation index categories. In addition, consumption of beer and wine also varied significantly across Carstairs deprivation index categories, no pattern was observed for beer, however wine consumption was observed to be significantly lower with the higher deprivation categories.

Consumption for the majority of food groups also varied significantly with smoking status (Figure 5.16), particularly for eggs and red meat consumption which were observed to be higher within smokers and ex-smokers, and cheese, fish and soy food for which consumption was observed to be higher in non-smokers. Grilled meat consumption and gilled meat score were lower in non-smokers and ex-smokers compared to smokers,

whereas smoker tended to consume more spirits but less wine than ex-smokers and non-smokers.

The consumption of certain food groups also varied with BMI category, eggs and meat products increased significantly across BMI categories, as did grilled meat and beer consumption, whereas soy food consumption was observed to decrease significantly. However, only soy food and beer consumption was observed to vary significantly with age categories (Figure 5.12), whereas only the consumption of total meat, processed meat and vegetables varied significantly with family history categories (Figure 5.13).

Table 5.20: Correlation matrix for food groups and confounding variables

		Total Dairy	Milk	Cheese	Eggs	Total meat	Red meat	Fish	Processed Meat	Soy Foods	Total Vegetables	Whole Fruit	Beer	Wine	Spirits	Grilled meat	Grilled Meat Score
Age (years)	Rho	.014	-.036	.030	-.031	**-.105**	-.035	-.050	**-.125**	-.021	-.030	.044	**-.227**	-.064	**-.075**	-.031	-.055
	p value	.667	.272	.367	.355	.001	.288	.134	.000	.521	.358	.180	.000	.054	.024	.345	.098
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Energy intake (kJ)	Rho	**.346**	**.250**	**.309**	**.296**	**.544**	**.499**	**.373**	**.412**	.019	**.450**	**.337**	**.196**	.010	**.110**	**.177**	**.159**
	p value	.000	.000	.000	.000	.000	.000	.000	.000	.566	.000	.000	.000	.760	.001	.000	.000
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Family History	Rho	.010	.043	.016	-.007	**.100**	.061	.059	**.098**	.032	**.098**	.022	.008	**.066**	.019	.042	.039
	p value	.765	.193	.626	.832	.002	.066	.076	.003	.336	.003	.516	.815	.045	.558	.203	.242
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Carstairs Deprivation index	Rho	**-.174**	**-.079**	**-.105**	**.175**	**.114**	**.177**	**-.092**	**.125**	**-.091**	**-.139**	**-.155**	**.092**	**-.316**	.032	**.072**	**.111**
	p value	.000	.018	.002	.000	.001	.000	.006	.000	.006	.000	.000	.006	.000	.334	.030	.001
	N	899	899	899	899	899	899	899	899	899	899	899	899	899	899	899	899
Smoker	Rho	-.033	.015	-.057	**.193**	**.077**	**.157**	-.061	**.072**	**-.120**	**-.110**	**-.220**	**.067**	**-.171**	**.147**	**.102**	**.093**
	p value	.318	.650	.087	.000	.021	.000	.068	.031	.000	.001	.000	.046	.000	.000	.002	.005
	N	901	901	901	901	901	901	901	901	901	901	901	901	901	901	901	901
EI / BMR Ratio	Rho	**.325**	**.243**	**.267**	**.259**	**.478**	**.451**	**.336**	**.359**	.008	**.398**	**.297**	**.147**	-.034	**.069**	**.145**	**.127**
	p value	.000	.000	.000	.000	.000	.000	.000	.000	.812	.000	.000	.000	.308	.039	.000	.000
	N	887	887	887	887	887	887	887	887	887	887	887	887	887	887	887	887
BMI	Rho	-.027	-.010	.008	**.110**	**.161**	**.150**	.032	**.152**	-.063	**.077**	.047	**.104**	-.009	**.076**	**.102**	**.098**
	p value	.426	.773	.816	.001	.000	.000	.342	.000	.062	.022	.166	.002	.794	.024	.002	.003
	N	887	887	887	887	887	887	887	887	887	887	887	887	887	887	887	887

N.B
Significant correlation coefficients ($p < 0.05$) are highlighted in **bold**

Figure 5.11: Food group consumption across energy intake categories

Fig 5.11a: Total dairy

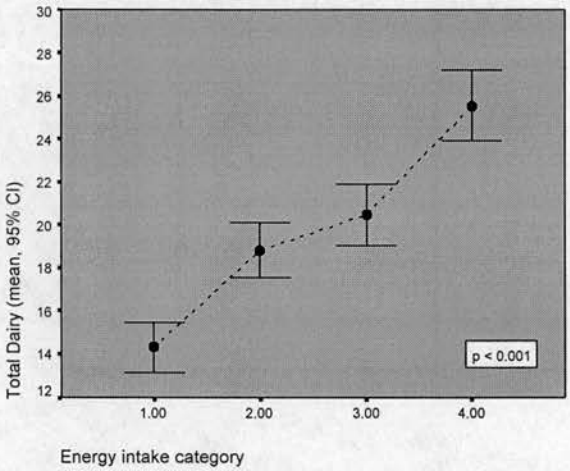


Fig 5.11b: Milk

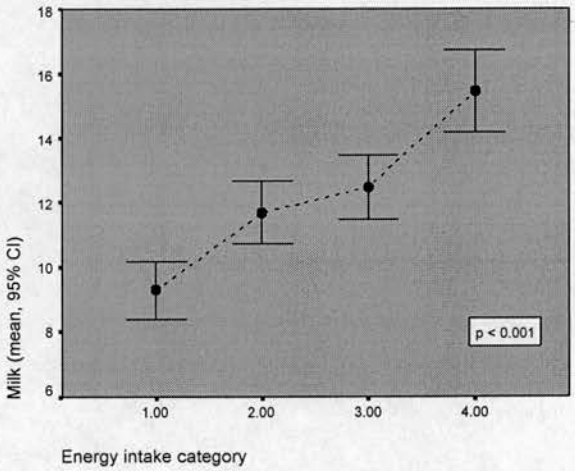


Fig 5.11c: Cheese

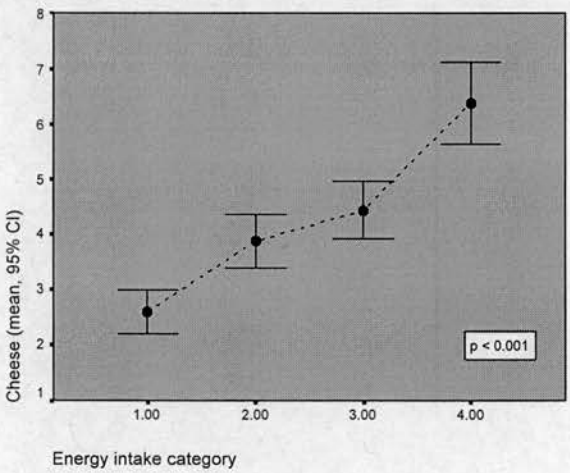


Fig 5.11d: Eggs

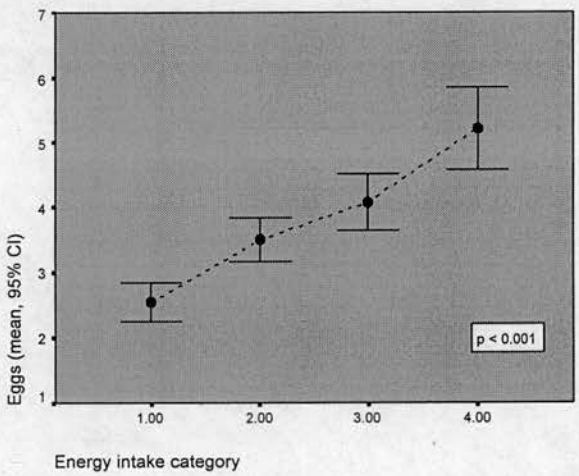


Fig 5.11e: Total meat

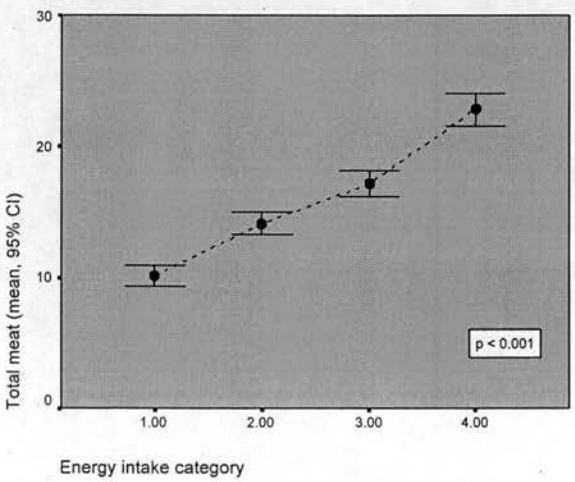


Fig 5.11f: Red meat

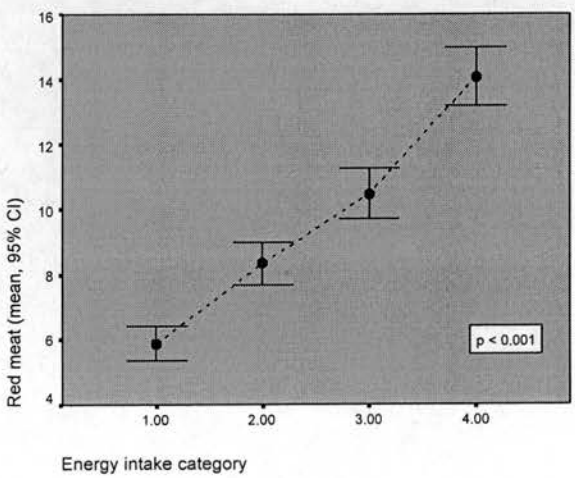


Fig 5.11g: Processed meat

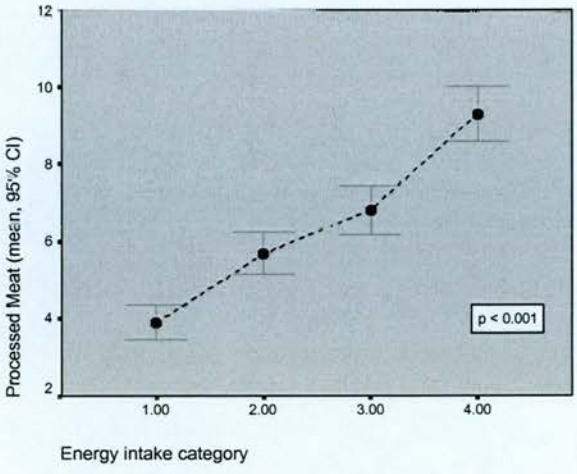


Fig 5.11h: Fish

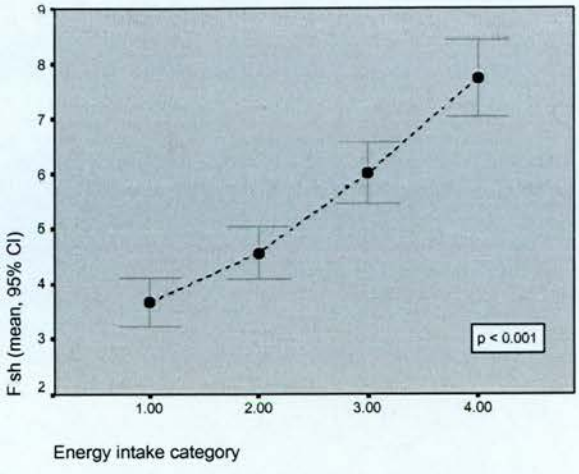


Fig 5.11i: Total vegetables

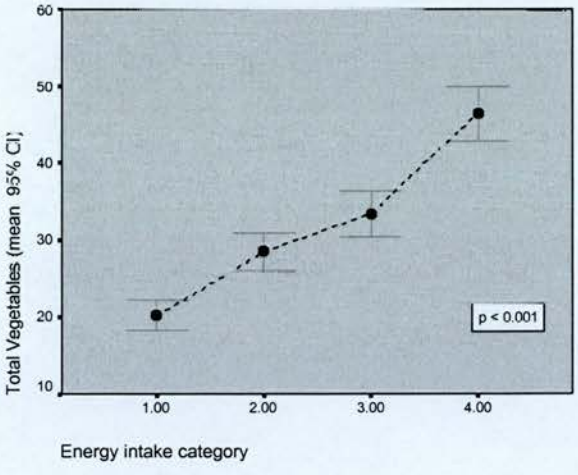


Fig 5.11j: Total fruit

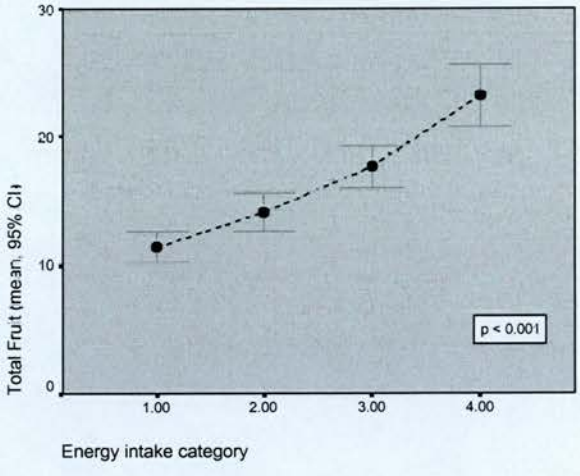


Fig 5.11k: Grilled meat frequency

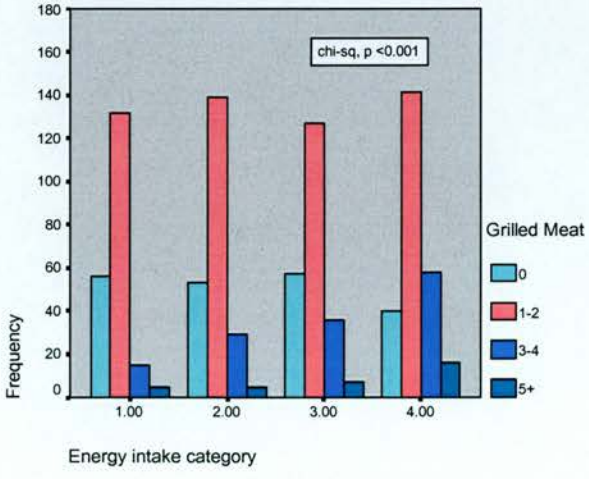


Fig 5.11l: Grilled meat score

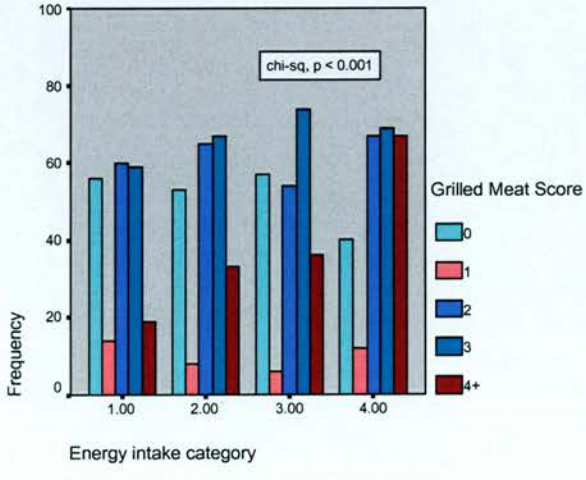


Fig 5.11m: Beer

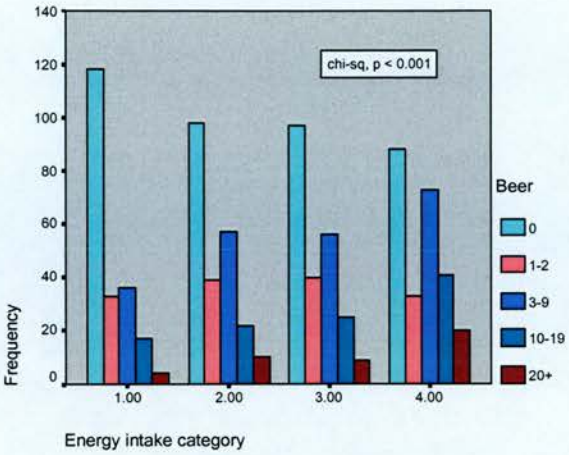


Fig 5.11n: Wine

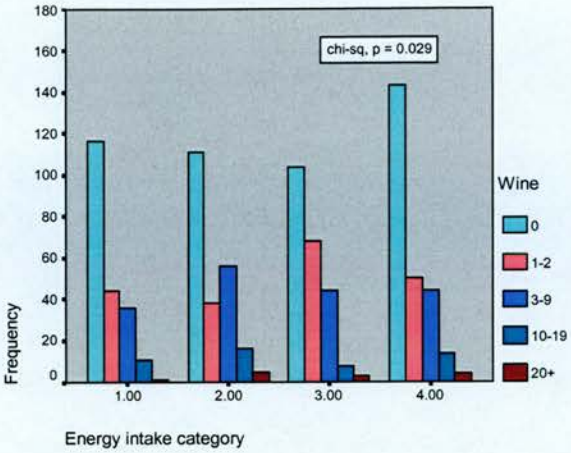


Fig 5.11o: Spirits

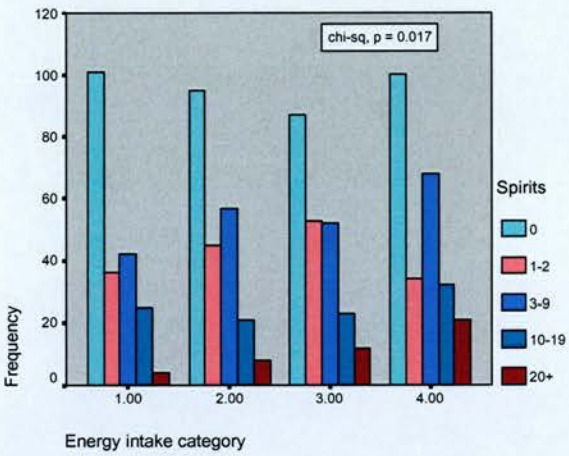


Figure 5.12: Food group consumption across age categories

Fig 5.12a: Soy food

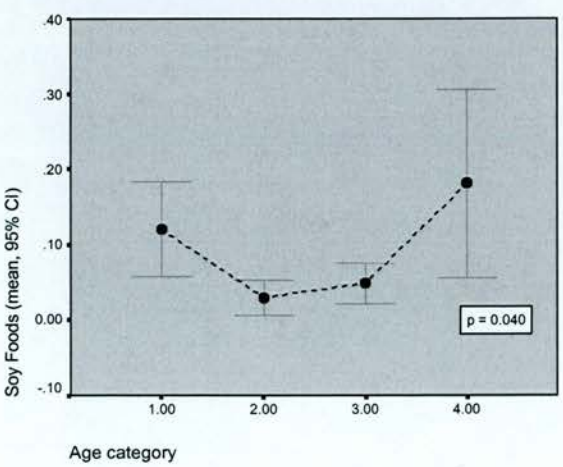


Fig 5.12b: Beer

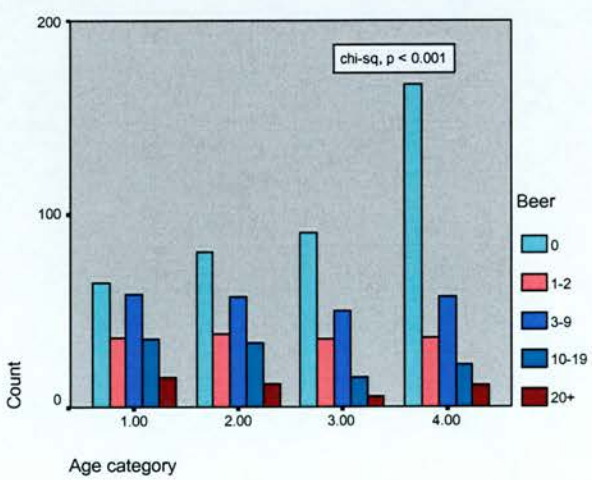


Figure 5.13: Food group consumption across family history categories

Fig 5.13a: Total meat

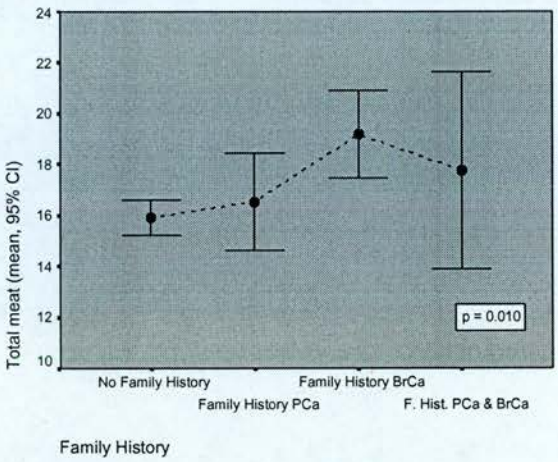


Fig 5.13b: Processed meat

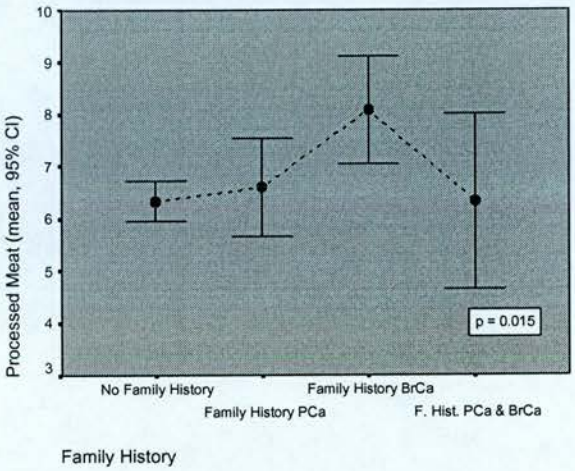


Fig 5.13c: Total vegetables

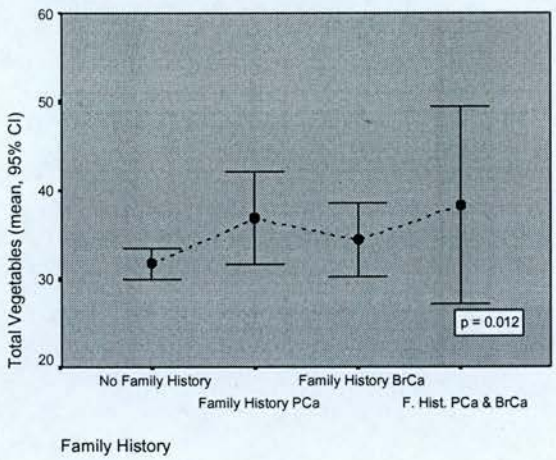


Figure 5.14: Food group consumption across Carstairs deprivation index

Fig 5.14a: Total dairy

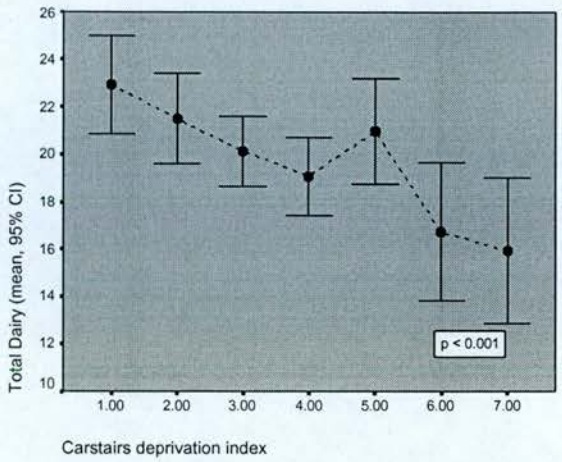


Fig 5.14b: Cheese

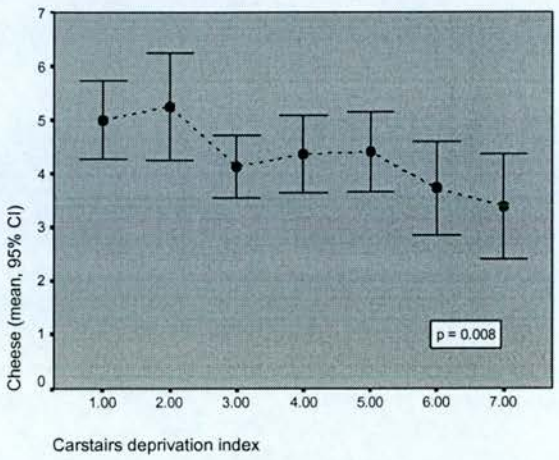


Fig 5.14c: Eggs

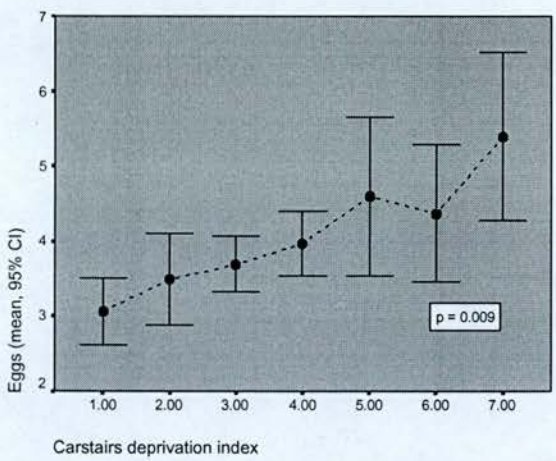


Fig 5.14d: Total meat

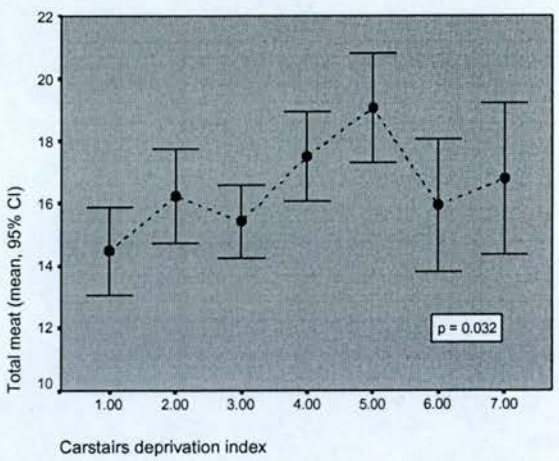


Fig 5.14e: Red meat

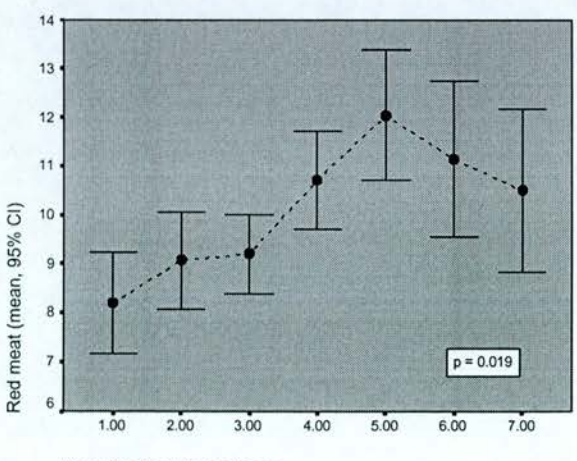


Fig 5.14g: Processed meat

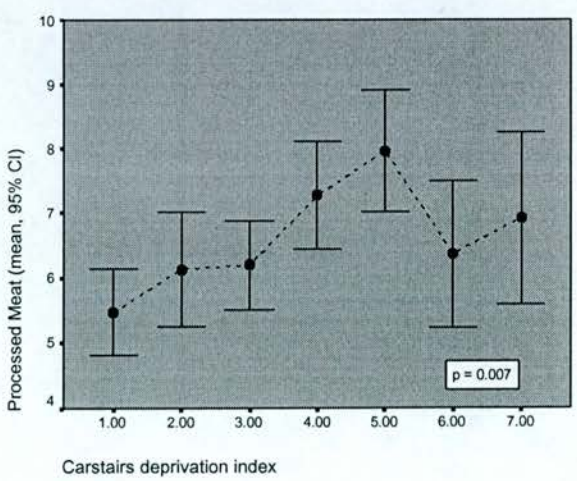


Fig 5.14h: Fish

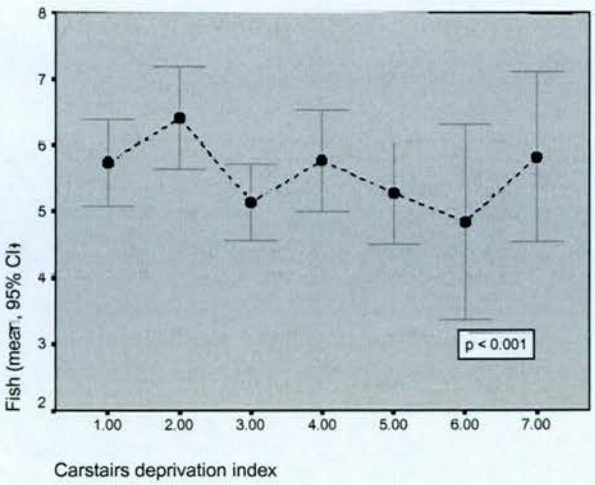


Fig 5.14i: Soy food

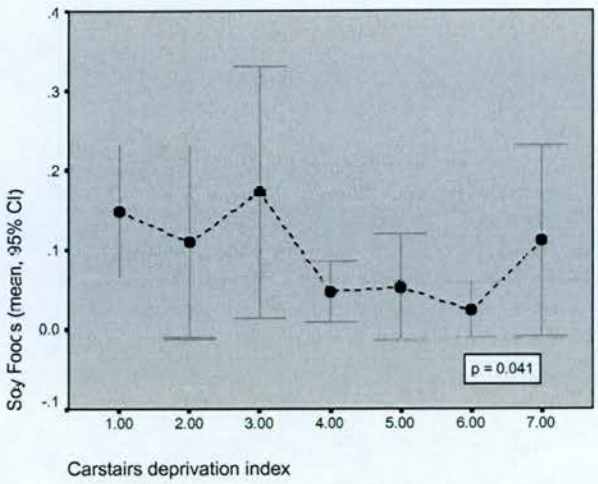


Fig 5.14j: Total vegetables

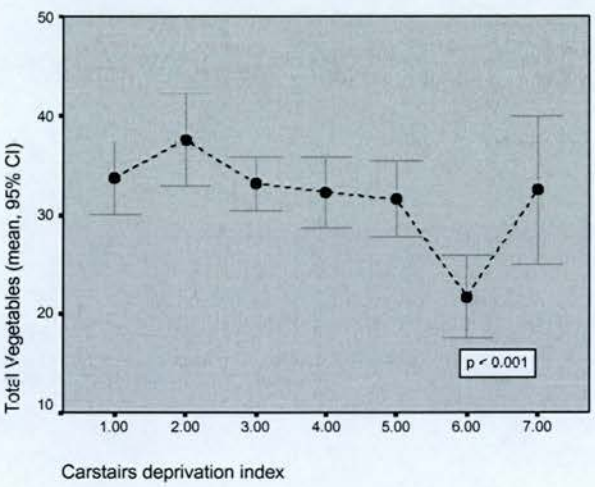


Fig 5.14k: Total fruit

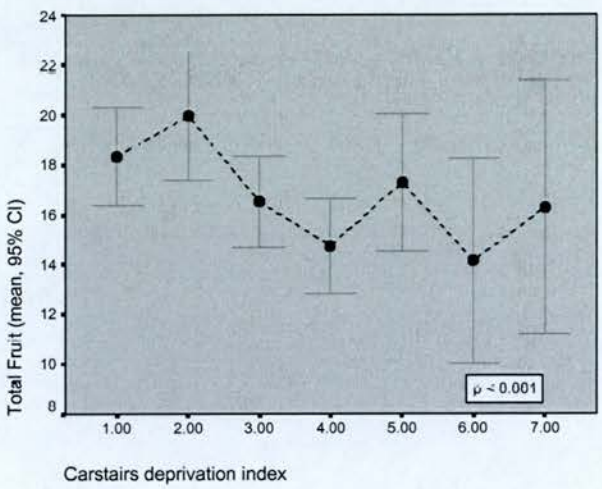


Fig 5.14l: Beer

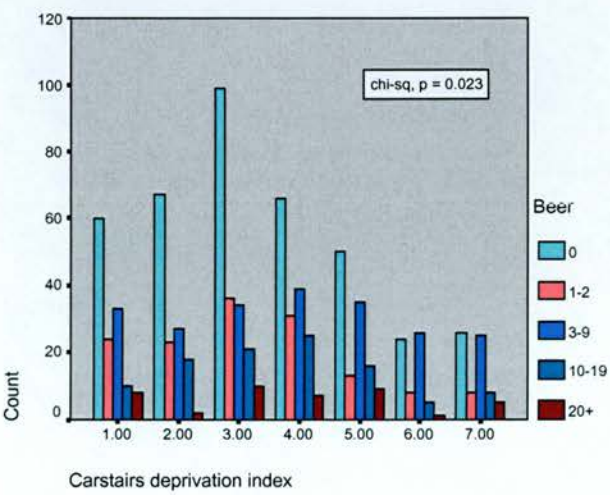


Fig 5.14m: Wine

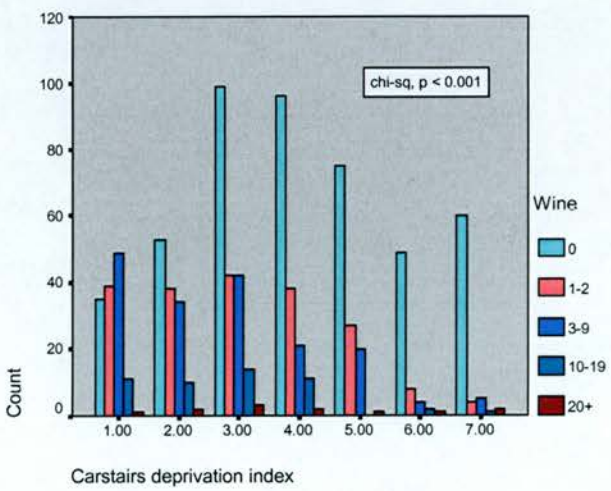


Fig 5.15g: Total fruit

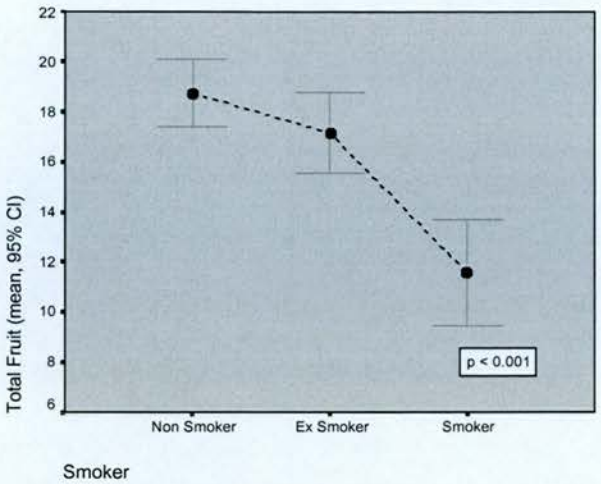


Fig 5.15h: Grilled meat

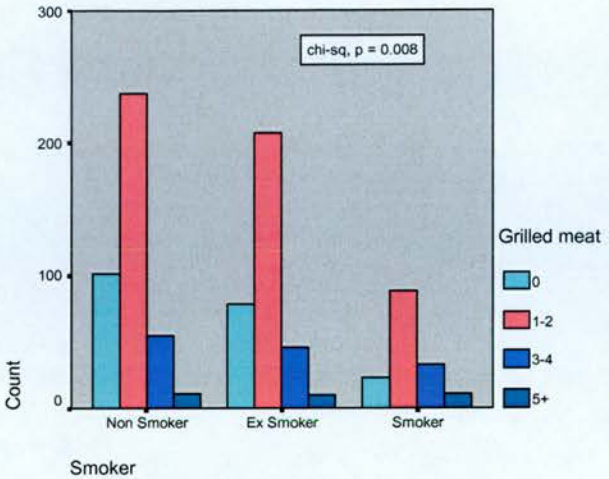


Fig 5.15i: Grilled meat score

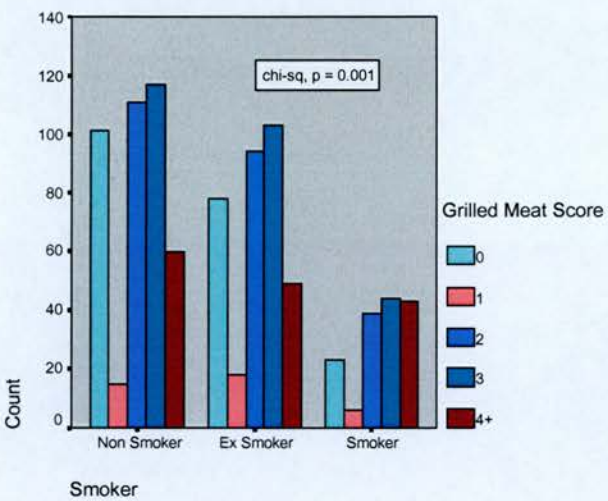


Fig 5.15j: Wine

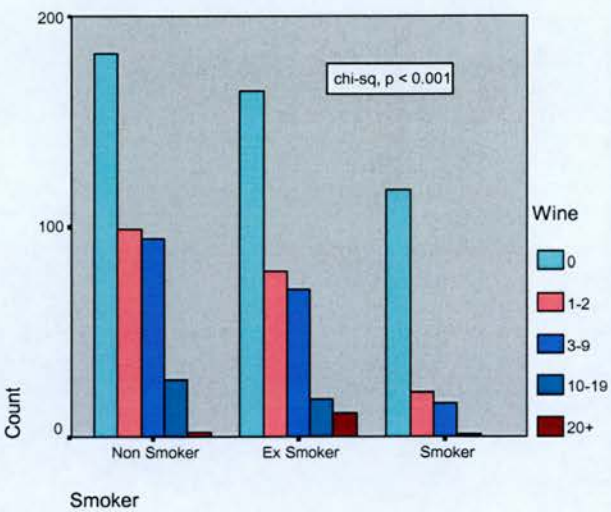


Fig 5.15k: Spirits

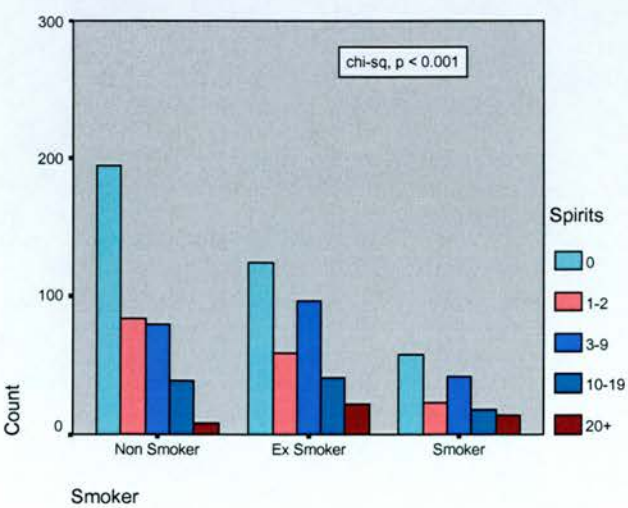


Figure 5.16: Food group consumption across EI / BMR ratio category

Fig 5.16a: Total dairy

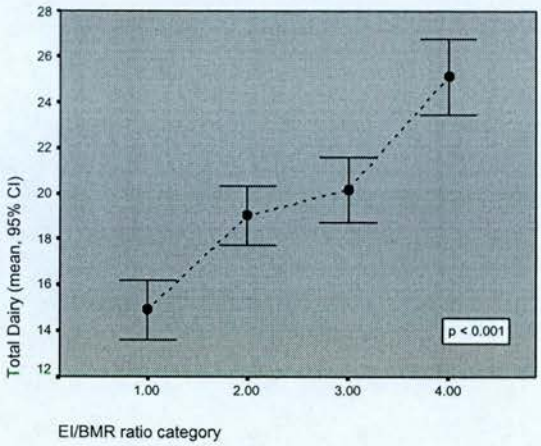


Fig 5.16b: Milk

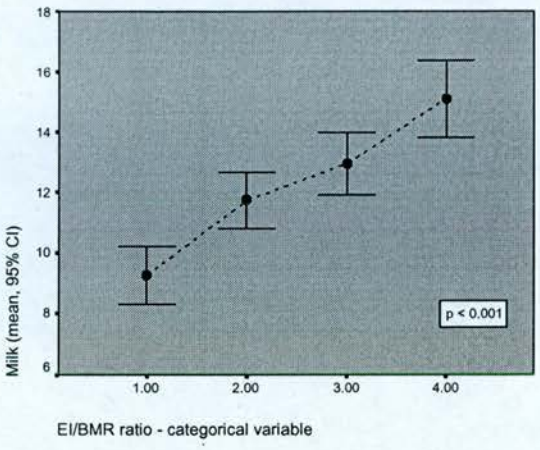


Fig 5.16c: Cheese

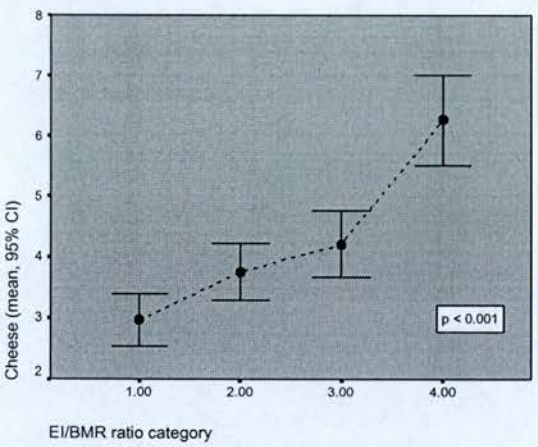


Fig 5.16d: Eggs

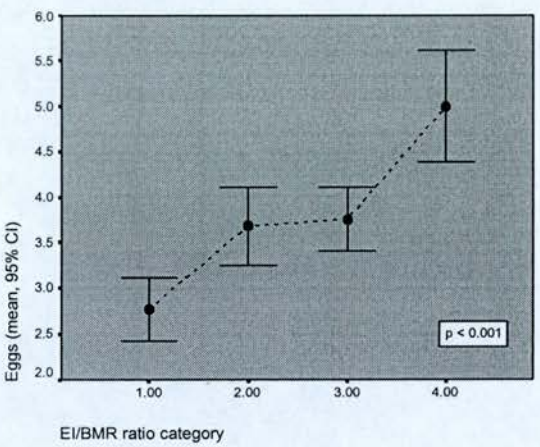


Fig 5.16e: Total meat

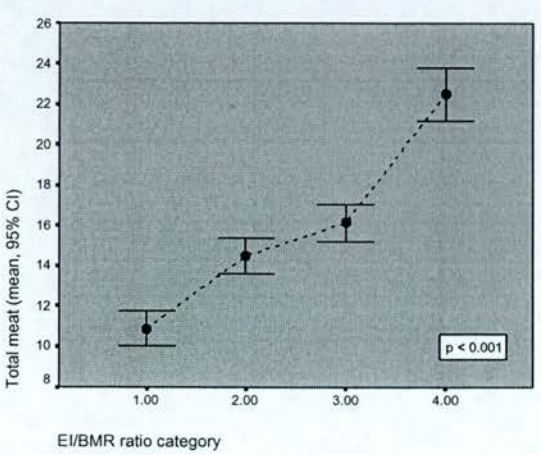


Fig 5.16f: Red meat

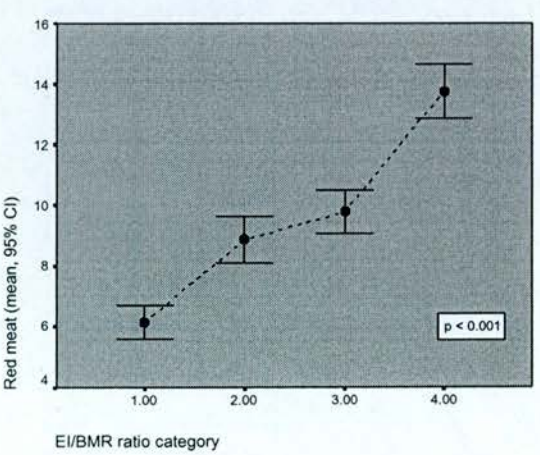


Fig 5.16g: Processed meat

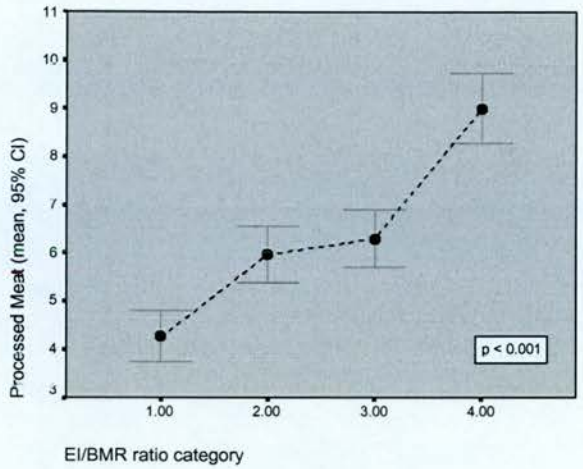


Fig 5.16h: Fish

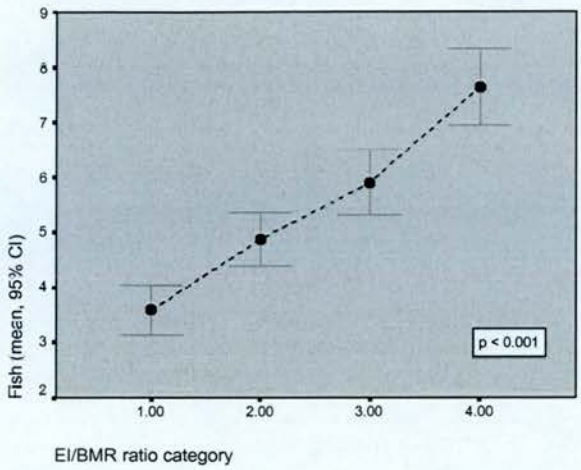


Fig 5.16i: Total vegetables

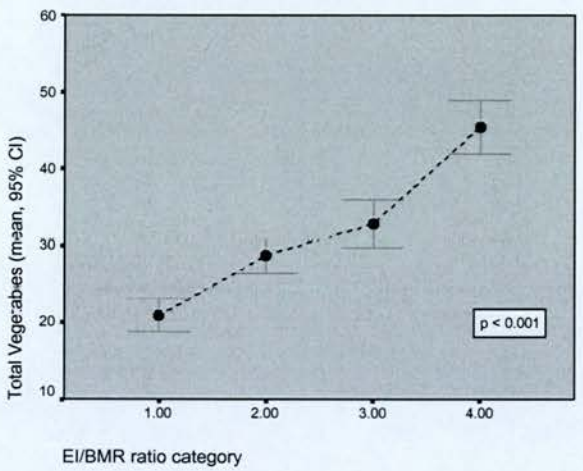


Fig 5.16j: Total fruit

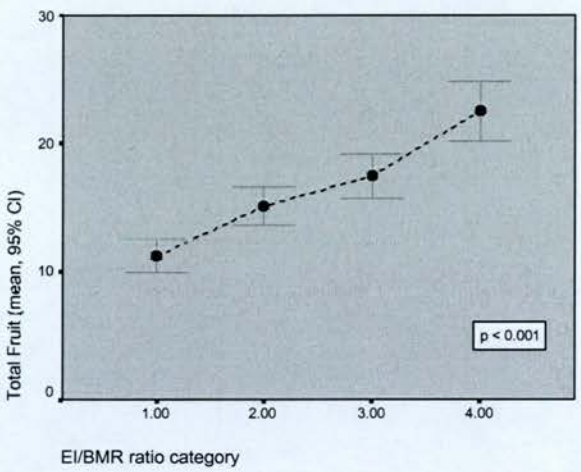


Fig 5.16l: Grilled meat

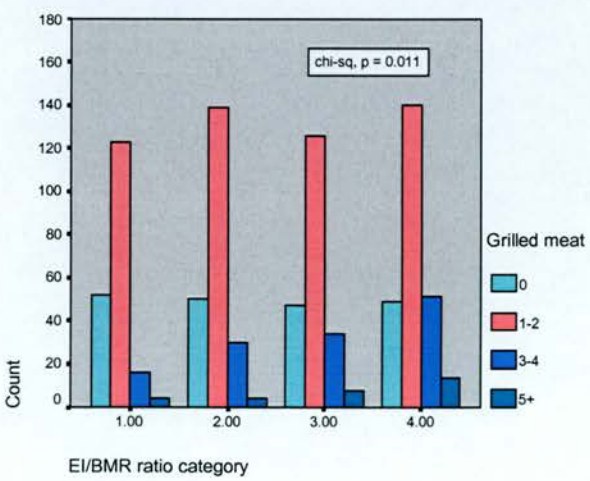


Fig 5.16m: Beer

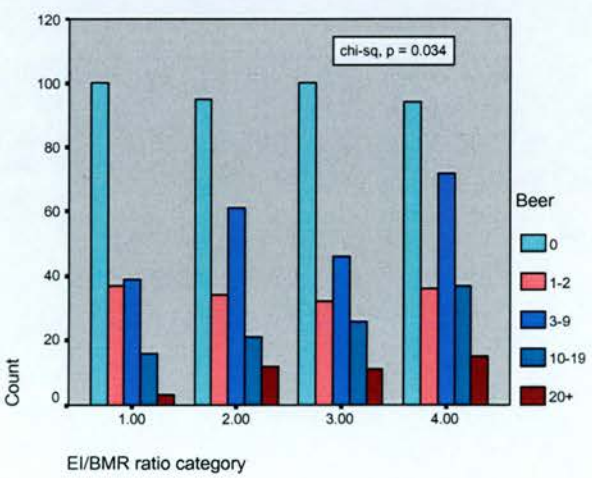


Fig 5.16n: Spirits

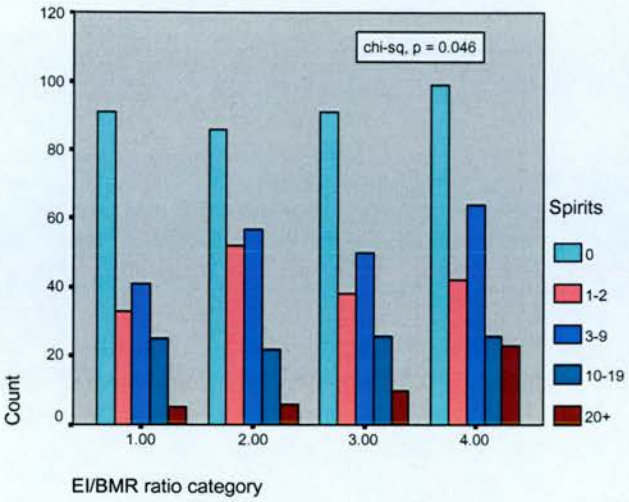


Figure 5.17: Food group consumption across BMI category

Fig 5.17a: Eggs

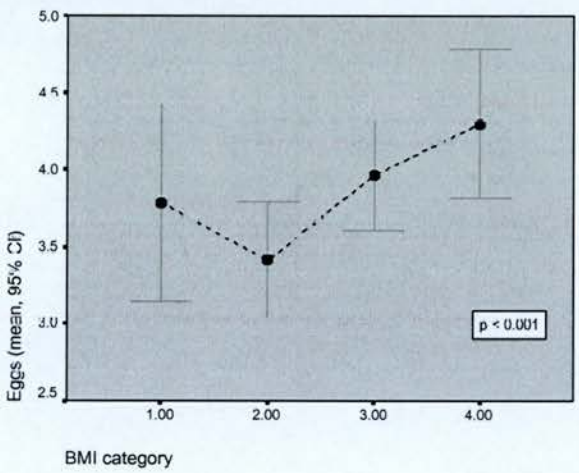


Fig 5.17b: Total meat

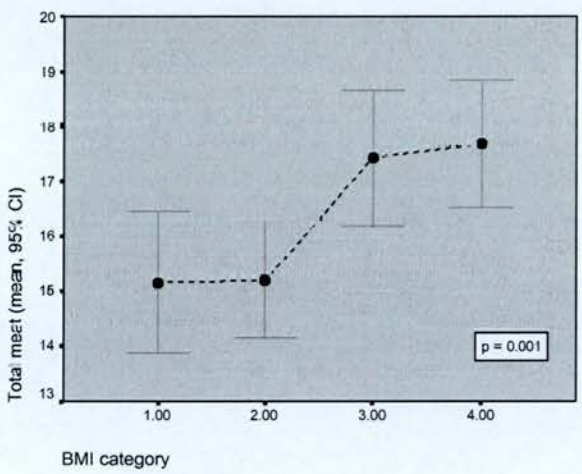


Fig 5.17c: Red meat

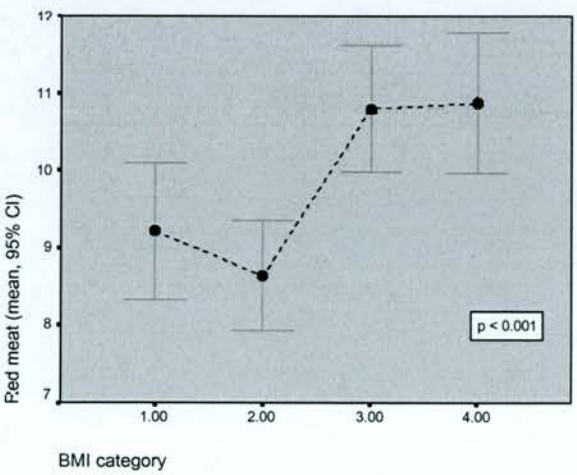


Fig 5.17d: Processed meat

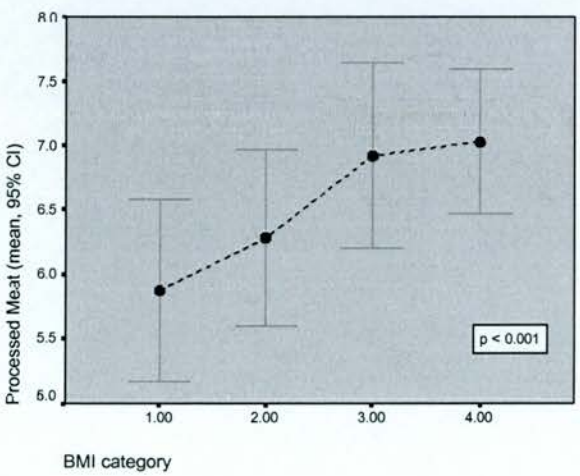


Fig 5.17e: Soy food

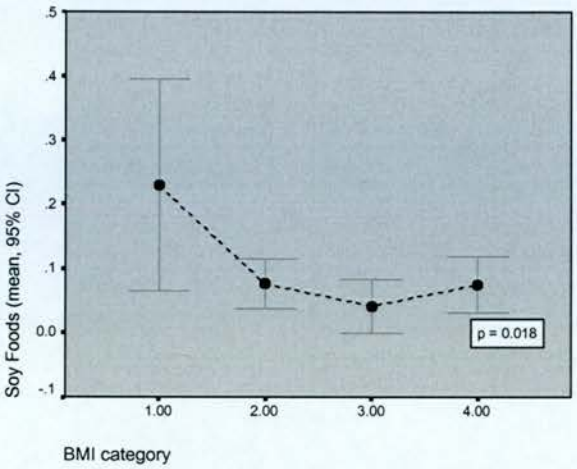


Fig 5.17f: Grilled meat

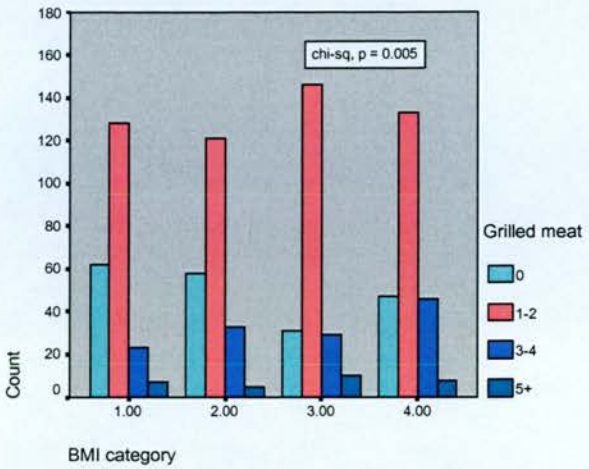


Fig 5.17g: Grilled meat score

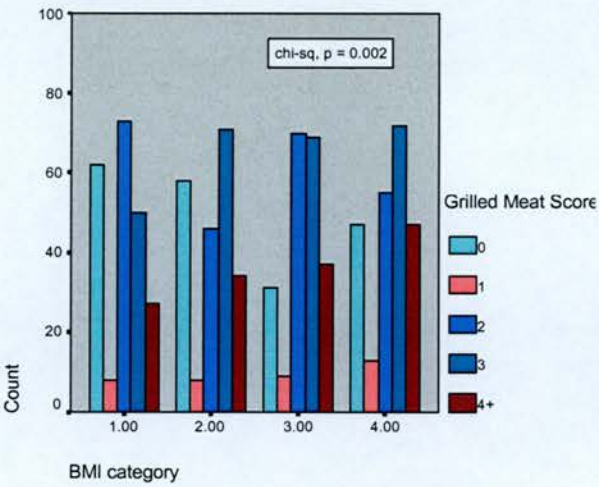
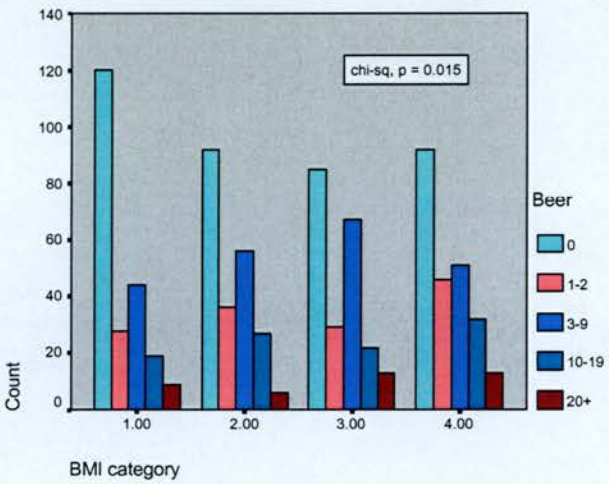


Fig 5.17h: Beer



5.4.6 The association between food groups and nutrient intake

The association between food group consumption and nutrient intakes adjusting for EI was also examined using Spearman's rank correlations, see Table 5.21. See Appendix: Table 8.6 for crude correlation coefficients.

As expected meat products, were highly positively associated with protein and, with the exception of fish, most fats expecially MUFA and cholesterol, whereas fish was highly positively associated with PUFA and selenium. Dairy products, with the exception of eggs, were highly positively associated with calcium, whilst eggs with highly correlated with fats, especially cholesterol and MUFA. Both fruit and vegetables were inversely associated with fats, with the exception of PUFA, and highly positively associated with most antioxidants. Alcohol, as expected, was highly positively associated with all alcohol types. Soy foods were also weakly positively associated with isoflavones.

Table 5.21: Correlations between EI-adjusted food groups and nutrient intake

		Total Dairy	Milk	Cheese	Eggs	Total Meat	Red Meat	Processed Meat	Fish	Soy foods	Vegetables	Whole Fruit	Beer	Wine	Spirits	Grilled Meat	Grilled Meat Score
Protein	Rho	**.198**	**.209**	**.089**	**.184**	**.541**	**.473**	**.211**	**.319**	-.017	**.188**	-.062	.010	-.078	-.023	**.106**	**.085**
	P value	.000	.000	.007	.000	.000	.000	.000	.000	.614	.000	.060	.766	.019	.481	.001	.010
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Total Fat	Rho	**.092**	.040	**.257**	**.323**	**.222**	**.294**	**.174**	-.048	.029	**-.266**	**-.370**	**-.145**	**-.115**	**-.093**	**.179**	**.168**
	P value	.005	.225	.000	.000	.000	.000	.000	.150	.381	.000	.000	.000	.001	.005	.000	.000
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Saturated Fat	Rho	**.193**	**.132**	**.282**	**.242**	**.105**	**.198**	**.085**	**-.214**	-.006	**-.364**	**-.327**	**-.140**	**-.122**	**-.083**	**.160**	**.156**
	P value	.000	.000	.000	.000	.001	.000	.010	.000	.856	.000	.000	.000	.000	.013	.000	.000
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
MUFA	Rho	.002	-.014	**.178**	**.366**	**.306**	**.369**	**.240**	-.001	.041	**-.217**	**-.361**	**-.094**	**-.099**	-.044	**.206**	**.193**
	P value	.944	.663	.000	.000	.000	.000	.000	.984	.213	.000	.000	.005	.003	.185	.000	.000
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
PUFA	Rho	**-.139**	**-.151**	.031	.003	**.097**	.016	**.088**	**.314**	.050	**.227**	-.025	-.054	.036	-.055	-.026	-.025
	P value	.000	.000	.356	.916	.003	.636	.008	.000	.130	.000	.452	.105	.281	.094	.433	.447
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Cholesterol	Rho	.036	.032	**.128**	**.791**	**.367**	**.449**	**.209**	-.022	-.056	**-.231**	**-.302**	.039	**-.169**	.020	**.204**	**.169**
	P value	.273	.327	.000	.000	.000	.000	.000	.498	.090	.000	.000	.243	.000	.539	.000	.000
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Alcohol	Rho	-.030	**-.114**	**.134**	**.085**	**.088**	.071	.080	**.163**	.025	**.098**	-.065	**.574**	**.513**	**.566**	**.124**	.080
	P value	.358	.001	.000	.010	.007	.031	.015	.000	.458	.003	.049	.000	.000	.000	.000	.016
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Calcium	Rho	**.791**	**.735**	**.295**	.002	**-.183**	**-.181**	-.070	-.049	.027	-.040	-.010	**-.118**	**-.135**	**-.183**	.018	.026
	P value	.000	.000	.000	.944	.000	.000	.034	.138	.421	.225	.756	.000	.000	.000	.579	.437
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Selenium	Rho	-.026	-.054	.052	.063	.076	.056	-.026	**.480**	.073	**.232**	.041	-.015	**.096**	-.008	-.033	-.043
	P value	.427	.104	.116	.058	.022	.088	.435	.000	.026	.000	.211	.647	.004	.800	.314	.191
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916

Cont.

Table 5.21, cont.: Correlations between EI-adjusted food groups and nutrient intake.

		Total Dairy	Milk	Cheese	Eggs	Total Meat	Red Meat	Processed Meat	Fish	Soy foods	Vegetables	Whole Fruit	Beer	Wine	Spirits	Grilled Meat	Grilled Meat Score
Retinol	Rho	**.195**	**.126**	**.181**	**.270**	**.084**	**.185**	.078	-.021	-.026	**-.208**	**-.229**	.001	.011	-.066	**.084**	.077
	P value	.000	.000	.000	.000	.011	.000	.018	.516	.440	.000	.000	.981	.746	.047	.011	.019
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Carotene	Rho	-.002	**-.083**	.026	-.060	.056	.021	-.041	**.248**	.073	**.727**	**.249**	-.007	.071	-.076	-.031	-.040
	P value	.956	.012	.423	.068	.088	.529	.216	.000	.026	.000	.000	.843	.031	.021	.344	.230
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Vitamin E	Rho	-.051	**-.092**	.033	**-.082**	**-.085**	**-.172**	-.054	**.142**	.048	**.281**	**.238**	**-.104**	.007	**-.122**	**-.081**	-.071
	P value	.121	.005	.323	.013	.010	.000	.105	.000	.143	.000	.000	.002	.841	.000	.014	.032
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Vitamin C	Rho	.007	-.080	.009	**-.214**	**-.127**	**-.195**	**-.156**	**.188**	.071	**.568**	**.672**	-.075	**.129**	**-.105**	**-.161**	**-.148**
	P value	.828	.016	.778	.000	.000	.000	.000	.000	.032	.000	.000	.024	.000	.001	.000	.000
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Isoflavone	Rho	.000	.011	-.039	**-.116**	**-.120**	**-.113**	-.052	-.077	**.130**	-.079	-.062	-.077	.040	**-.113**	-.071	-.044
	P value	.992	.740	.243	.000	.000	.001	.113	.020	.000	.016	.061	.020	.222	.001	.031	.189
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916

Bold = Correlation is significant at the 99% level (2-tailed).

5.4.7 Odds ratio analysis

Crude ORs

All meat products and most dairy products were observed to have positive crude ORs (OR ≥ 1.3) between the reference (lowest) and highest intake categories, of which significant ORs were observed for eggs (OR 1.59, 95%CI 1.08-2.35), total meat (OR 1.53, 95%CI 1.05-2.25) and red meat (OR 1.92, 95%CI 1.32-2.79), see Table 5.22. Inverse crude ORs were observed for soy food and all alcohol types, these were observed to be significant except for beer, soy food OR 0.57 (95%CI 0.34-0.97); alcohol consumed OR 0.65 (95%CI 0.46-0.92); wine OR 0.40 (95%CI 0.21-0.75) and spirits OR 0.53 (95%CI 0.33-0.84). However, no association was observed for total dairy, milk, fish, total vegetables, total fruit and grilled meat.

Score test for trends

In addition, a dose response effect was found for eggs, total meat, red meat, alcohol consumed and spirits, with the crude ORs being observed to increase significantly with higher consumption of eggs, total meat and red meat, and to decrease significantly with higher intakes of spirits and also for soy food and alcohol consumers compared non consumers, see Table 5.22.

Test for interaction

ORs (and 95% CIs) for food group intakes stratified by each confounding variable category were computed using the Mantel Haenszel method, in order to examine the ORs within each individual confounding variable category and to test for interaction.

The results showed that there was no evidence for interaction between the food group variables and confounding variables.

Log likelihood ratio test

The Log Likelihood test was used to examine the effect of each food group variable on PCa risk, whilst adjusting for the confounding variables.

A significant effect on PCa risk, whilst adjusting for confounding variables, was observed for total meat, red meat, soy foods, alcohol consumed, wine and spirits.

Adjusted ORs

The controlling of confounding variables, including the use of energy adjusted nutrient intake (using the residual method), had a great effect on the observed association with PCa risk, with the exception of alcohol types whose ORs remained similar to those of the crude ORs, see Table 5.22. Whereas before the controlling for confounding variables, significant positive crude associations were observed for eggs, the majority of meat products and a significant inverse crude association for soy products. Only red meat remained significant (OR 1.64, 95%CI 1.09-2.48). In addition, an inverse association between vegetables and PCa risk was observed to become significant (OR 0.62, 95%CI 0.41-0.93). Significant dose-response effects were observed for total vegetables ($p = 0.021$), alcohol consumption ($p = 0.012$), wine ($p = 0.003$) and spirits ($p = 0.045$).

Table 5.22: Crude and adjusted odds ratios

Food Groups (helpings per week)		Frequency		Crude OR		Adjusted OR [a]	
		Case (n)	Control (n)	OR	(95% CI)	OR	(95% CI)
Total Dairy	0 - 11.0	111	119	1.00	-	1.00	-
	11.5 - 17.5	104	127	0.88	(0.61-1.27)	1.06	(0.71-1.57)
	18.0 - 26.5	100	126	0.85	(0.59-1.23)	0.98	(0.66-1.45)
	> 26.5	118	111	1.14	(0.79-1.64)	1.02	(0.69-1.52)
				Score test for linear trend: p = 0.54 [b], 0.983 [c]			
Milk	0 - 6.5	65	74	1.00	-	1.00	-
	7.0 - 12.0	148	179	0.94	(0.63-1.40)	1.09	(0.72-1.65)
	12.5 - 14.0	122	133	1.04	(0.69-1.58)	1.05	(0.70-1.56)
	> 14.0	98	97	1.15	(0.74-1.78)	1.15	(0.77-1.71)
				Score test for linear trend: p = 0.36 [b], 0.920 [c]			
Cheese	0 - 1.0	113	128	1.00	-	1.00	-
	1.5 - 3.0	112	118	1.08	(0.75-1.54)	1.08	(0.72-1.60)
	3.5 - 6.0	102	137	0.84	(0.59-1.21)	0.83	(0.56-1.23)
	> 6.0	106	100	1.20	(0.83-1.74)	0.90	(0.61-1.34)
				Score test for linear trend: p = 0.67 [b], 0.577 [c]			
Eggs	0 - 1.5	93	116	1.00	-	1.00	-
	2.0 - 3.0	124	158	0.98	(0.68-1.40)	0.97	(0.66-1.44)
	3.5 - 5.0	100	118	1.06	(0.72-1.55)	1.13	(0.76-1.68)
	> 5.0	116	91	1.59	(1.08-2.35)	1.41	(0.94-2.11)
				Score test for linear trend: p = 0.016 [b], 0.279 [c]			
Total Meat	0 - 10.0	91	141	1.00	-	1.00	-
	10.5 - 15.0	116	134	1.34	(0.93-1.93)	1.13	(0.77-1.68)
	15.5 - 21.0	123	104	1.83	(1.26-2.67)	1.43	(0.96-2.13)
	> 21.0	103	104	1.53	(1.05-2.25)	1.42	(0.94-2.13)
				Score test for linear trend: p = 0.007 [b], 0.225 [c]			
Red Meat	0 - 5.5	94	151	1.00	-	1.00	-
	6.0 - 8.5	101	104	1.56	(1.07-2.28)	1.25	(0.84-1.85)
	9.0 - 13.0	116	126	1.48	(1.03-2.13)	1.13	(0.76-1.69)
	> 13.0	122	102	1.92	(1.32-2.79)	1.64	(1.09-2.48)
				Score test for linear trend: p = 0.001 [b], 0.109 [c]			

Cont.

Table 5.22, Cont.: Crude and adjusted odds ratios

Food Groups (helpings per week)		Frequency		Crude OR		Adjusted OR [a]	
		Case (n)	Control (n)	OR	(95% CI)	OR	(95% CI)
Processed Meat	0 - 3.0	113	150	1.00	-	1.00	-
	3.5 - 5.5	88	113	1.03	(0.71-1.50)	1.21	(0.81-1.79)
	6.0 - 9.0	127	108	1.56	(1.09-2.23)	1.26	(0.85-1.87)
	> 9.0	105	112	1.24	(0.87-1.79)	1.40	(0.94-2.10)
				Score test for linear trend: p = 0.06 [b], 0.416 [c]			
Fish	0 - 2.0	107	125	1.00	-	1.00	-
	2.5 - 4.5	105	132	0.93	(0.65-1.34)	0.98	(0.66-1.46)
	5.0 - 8.0	133	121	1.28	(0.90-1.84)	1.19	(0.80-1.77)
	> 8.0	88	105	0.98	(0.67-1.44)	0.81	(0.54-1.20)
				Score test for linear trend: p = 0.58 [b], 0.281 [c]			
Total Vegetables (excluding potatoes)	0 -16.5	124	125	1.00	-	1.00	-
	17.0 - 26.5	85	118	0.73	(0.50-1.06)	0.67	(0.45-0.99)
	27.0 - 42.5	117	120	0.98	(0.69-1.40)	1.01	(0.68-1.50)
	> 42.5	107	120	0.90	(0.63-1.29)	0.62	(0.41-0.93)
				Score test for linear trend: p = 0.91 [b], 0.021 [c]			
Total Whole Fruit	0 - 7.5	120	121	1.00	-	1.00	-
	8.0 - 13.5	88	125	0.71	(0.50-1.03)	0.94	(0.64-1.40)
	14.0 - 21.5	113	118	0.97	(0.67-1.39)	1.00	(0.70-1.51)
	> 21.5	112	119	0.95	(0.66-1.36)	0.99	(0.65-1.49)
				Score test for linear trend: p = 0.85 [b], 0.989 [c]			
Soy Food	0	410	440	1.00	-	1.00	-
	≥ 1	23	43	0.57	(0.34-0.97)	0.81	(0.53-1.24)
				Score test for linear trend: p = 0.036 [b],0.339 [c]			
Grilled Meat	0	91	115	1.00	-	1.00	-
	1-2	256	283	1.14	(0.83-1.58)	1.11	(0.78-1.57)
	3-4	71	67	1.34	(0.87-2.07)	1.29	(0.80-2.06)
	5+	15	18	1.05	(0.50-2.21)	1.07	(0.48-2.39)
				Score test for linear trend: p = 0.32 [b], 0.802 [c]			

Cont.

Table 5.22, cont.: Crude and adjusted odds ratios

Food Groups (units per week)		Frequency		Crude OR		Adjusted OR [a]	
		Case (n)	Control (n)	OR	(95% CI)	OR	(95% CI)
Grilled Meat Score	0	91	115	1.00	-	1.00	-
	1	23	17	1.71	(0.86-3.41)	1.90	(0.89-4.06)
	2	116	130	1.13	(0.78-1.64)	1.04	(0.70-1.55)
	3	124	145	1.08	(0.75-1.56)	1.07	(0.72-1.59)
	4+	79	76	1.31	(0.86-2.00)	1.29	(0.81-2.04)
				Score test for linear trend: p = 0.41 [b], 0.462 [c]			
Alcohol Consumed	No	88	69	1.00	-	1.00	-
	Yes	345	414	0.65	(0.46-0.92)	0.62	(0.42-0.90)
				Score test for linear trend: p = 0.016 [b], 0.012 [c]			
Beer	No alcohol consumption	88	69	1.00	-	1.00	-
	Alcohol consumption other than beer	113	131	0.68	(0.45-1.01)	0.64	(0.42-0.99)
	1-2	69	76	0.71	(0.45-1.12)	0.67	(0.41-1.09)
	3-9	95	127	0.59	(0.39-0.89)	0.54	(0.35-0.85)
	10+	68	80	0.67	(0.42-1.05)	0.66	(0.40-1.08)
				Score test for linear trend: p = 0.057 [b], 0.115 [c]			
Wine	No alcohol consumption	88	69	1.00	-	1.00	-
	Alcohol consumption other than wine	136	181	0.59	(0.40-0.87)	0.54	(0.35-0.82)
	1-2	93	107	0.68	(0.45-1.04)	0.65	(0.41-1.02)
	3-9	95	85	0.88	(0.60-1.35)	0.90	(0.56-1.45)
	10+	21	41	0.40	(0.21-0.75)	0.38	(0.19-0.74)
				Score test for linear trend: p = 0.25 [b], 0.003 [c]			
Spirits	No alcohol consumption	88	69	1.00	-	1.00	-
	Alcohol consumption other than wine	99	127	0.61	(0.40-0.92)	0.59	(0.38-0.92)
	1-2	84	84	0.78	(0.51-1.22)	0.73	(0.46-1.17)
	3-9	103	116	0.70	(0.46-1.05)	0.67	(0.43-1.04)
	10+	59	87	0.53	(0.33-0.84)	0.48	(0.29-0.79)
				Score test for linear trend: p = 0.047 [b], 0.045 [c]			

N.B.
[a] = ORs adjusted for: Age, total energy (using residual method), family history of PCa & BrCa, deprivation index, smoking, EI/BMR ratio.
[b] = crude ORs. [c] = adjusted ORs.

5.4.8 Low energy responders (LERs) analysis

As reported in the subjects characteristics section, 157 subjects (17%) were classified as LERs, with significantly more controls reported as LERs than cases, see Table 5.3. In order to examine further the effect this may have on the results and also to eliminate any possible effect this potential bias may have, the above analysis was repeated with LERs omitted.

Food group by LER status

As expected, intake for all food groups were observed to be significantly lower in the LERs than non-LERs, see Tables 5.23 and 5.24, with the exception of soy food, grilled meat score and all alcohol types for which the observed differences in distribution were shown to be non-significant.

Table 5.23: Distribution of continuous food group variables, by LER status

Food Groups (helpings per week)	Non LERs (n=730)		LERs (n=157)		Test for difference between LER status
	Mean (s.d.)	Median (I-QR)	Mean (s.d.)	Median (I-QR)	Mann-Whitney U Test (p-value)
Total Dairy	21.28 (11.66)	19.00 (13.00-28.13)	14.83 (9.78)	12.50 (8.25-19.00)	<0.0001
Milk	13.18 (8.61)	14.00 (7.00-14.00)	9.06 (6.92)	7.00 (6.00-14.00)	<0.0001
Cheese	4.72 (4.79)	3.50 (1.88-6.00)	2.96 (3.19)	2.00 (0.50-4.00)	<0.0001
Eggs	4.13 (3.82)	3.25 (2.00-5.00)	2.68 (2.25)	2.00 (1.00-4.00)	<0.0001
Total Meat	17.69 (9.08)	16.00 (11.50-21.50)	10.37 (5.60)	10.00 (6.00-14.00)	<0.0001
Red Meat	10.71 (6.56)	9.50 (6.38-14.00)	6.09 (3.95)	5.50 (3.00-8.25)	<0.0001
Processed Meat	7.11 (5.18)	6.00 (3.50-10.00)	3.88 (3.29)	3.00 (1.50-5.50)	<0.0001
Fish	6.10 (4.79)	5.00 (2.88-8.00)	3.47 (3.06)	3.00 (1.00-5.00)	<0.0001
Total Vegetables (excluding potatoes)	35.57 (24.64)	30.75 (18.88-46.00)	19.86 (14.45)	16.00 (9.75-26.00)	<0.0001
Total Whole Fruit	18.26 (15.10)	15.00 (8.50-23.00)	10.76 (8.73)	9.00 (4.50-14.25)	<0.0001
Soy Food	0.11 (0.73)	0.00 (0.00-0.00)	0.06 (0.32)	0.00 (0.00-0.00)	0.25

N.B.
s.d. = Standard Deviation
I-QR = Inter-Quartile Range
29 subjects with missing LER status were omitted from the distribution analysis

Table 5.24: Distribution of categorical food group and alcohol type variables, by LER status

Food Groups (helpings per week)	Non LERs (% within Non LERs)	LERs (% within LERs)
Grilled Meat:		
No grilled meat	157 (21.5%)	41 (26.1%)
1-2	427 (58.5%)	101 (64.3%)
3-4	119 (16.3%)	12 (7.6%)
5+	27 (3.7%)	3 (1.9%)
Total	***730 (100%)***	***157 (100%)***
	Chi-Square Test (p-value) = 0.021	
Grilled Meat Score:		
No grilled meat	157 (21.5%)	41 (26.1%)
1	29 (4.0%)	9 (5.7%)
2	199 (27.3%)	45 (28.7%)
3	214 (29.3%)	48 (30.6%)
4+	131 (17.9%)	14 (8.9%)
Total	***730 (100%)***	***157 (100%)***
	Chi-Square Test (p-value) = 0.07	

Cont.

Table 5.24, cont.: Distribution of categorical food group and alcohol type variables, by LER status

Alcohol Types (units per week)	Non LERs (% within non LERs)	LERs (% within LERs)
Alcohol consumption:		
No	119 (16.3%)	32 (20.4%)
Yes	611 (83.7%)	125 (79.6%)
Total	***730 (100%)***	***157 (100%)***
	Chi-Square Test (p-value) = 0.22	
Beer		
No alcohol consumption	119 (16.3%)	32 (20.4%)
Alcohol consumption other than beer	188 (25.8%)	50 (31.8%)
1-2 units	111 (15.2%)	28 (17.8%)
3-9 units	188 (25.8%)	30 (19.1%)
10+ units	124 (17.0%)	17 (10.8%)
Total	***730 (100%)***	***157 (100%)***
	Chi-Square Test (p-value) = 0.06	
Wine		
No alcohol consumption	119 (16.3%)	32 (20.4%)
Alcohol consumption other than wine	242 (33.2%)	61 (38.9%)
1-2 units	168 (23.0%)	27 (17.2%)
3-9 units	150 (20.5%)	27 (17.2%)
10+ units	51 (7.0%)	10 (6.4%)
Total	***730 (100%)***	***157 (100%)***
	Chi-Square Test (p-value) = 0.26	
Spirits		
No alcohol consumption	119 (16.3%)	32 (20.4%)
Alcohol consumption other than spirits	176 (24.1%)	40 (25.5%)
1-2 units	139 (19.0%)	26 (16.6%)
3-9 units	176 (24.1%)	36 (22.9%)
10+ units	120 (16.4%)	23 (14.6%)
Total	***730 (100%)***	***157 (100%)***
	Chi-Square Test (p-value) = 0.71	

5.4.9 Odds Ratio analysis, omitting LERs

Crude ORs

The omission of LERs had little effect on the crude ORs, with the exception of fish, vegetables and fruit that became inversely, albeit non-significantly, associated with PCa risk, and soy foods whose inverse association became non-significant, see Table 5.25. ORs remained significant for total meat OR 1.62 (95%CI 1.03-2.54); red meat OR 1.89 (95%CI 1.23-2.90); alcohol consumed OR 0.67 (95%CI 0.45-0.99); wine OR 0.35 (95%CI 0.17-0.71) and spirits OR 0.5 (95%CI 0.30-0.84).

Score test for trends

A dose response effect was found for eggs, total meat, red meat, alcohol consumed and spirits. The crude ORs were observed to increase significantly with higher intake categories for eggs, total meat and red meat, and to decrease significantly with higher intake categories for alcohol consumed and spirits, see Table 5.25.

Adjusted ORs

As with the observed adjusted ORs for all subjects, the controlling for confounding factors had a great effect on the observed association with PCa risk, with the exception of the alcohol types for which adjusting for confounding factors had little effect, see Table 5.25. Of the meat products, only red meat remained significant (OR 1.98, 95%CI 1.24-3.17), whereas the positive association between eggs and PCa risk and the negative association between vegetables and PCa risk both became significant (eggs OR 1.67, 95%CI 1.05-2.64, vegetables OR 0.63, 95%CI 0.40-0.99). Significant dose-response effects were observed for red meat ($p = 0.022$), alcohol consumption ($p = 0.036$) and wine ($p = 0.006$) only.

Table 5.25: Crude and adjusted odds ratios (non LERs only)

Food Groups (helpings per week)		Frequency		Crude OR		Adjusted OR [a]	
		Case (n)	Control (n)	OR	(95% CI)	OR	(95% CI)
Total Dairy	0 - 11.0	75	69	1.00	-	1.00	-
	11.5 - 17.5	86	102	0.78	(0.50-1.20)	0.95	(0.61-1.47)
	18.0 - 26.5	89	106	0.77	(0.50-1.19)	1.00	(0.65-1.55)
	> 26.5	109	94	1.07	(0.70-1.64)	1.08	(0.70-1.69)
				Score test for linear trend: p = 0.62 [b],0.949[c]			
Milk	0 - 6.5	45	48	1.00	-	1.00	-
	7.0 - 12.0	114	125	0.97	(0.60-1.57)	0.97	(0.61-1.54)
	12.5 - 14.0	111	115	1.03	(0.63-1.67)	1.06	(0.69-1.61)
	> 14.0	89	83	1.14	(0.69-1.90)	1.10	(0.71-1.70)
				Score test for linear trend: p = 0.48 [b], 0.948[c]			
Cheese	0 - 1.0	82	90	1.00	-	1.00	-
	1.5 - 3.0	89	89	1.10	(0.72-1.67)	1.13	(0.73-1.75)
	3.5 - 6.0	94	109	0.95	(0.63-1.42)	0.78	(0.50-1.20)
	> 6.0	94	83	1.24	(0.82-1.89)	1.14	(0.73-1.78)
				Score test for linear trend: p = 0.47 [b], 0.267[c]			
Eggs	0 - 1.5	68	75	1.00	-	1.00	-
	2.0 - 3.0	99	123	0.89	(0.58-1.35)	1.13	(0.73-1.74)
	3.5 - 5.0	87	98	0.98	(0.63-1.52)	1.17	(0.76-1.80)
	> 5.0	105	75	1.54	(0.99-2.41)	1.67	(1.05-2.64)
				Score test for linear trend: p = 0.030 [b], 0.157[c]			
Total Meat	0 - 10.0	54	83	1.00	-	1.00	-
	10.5 - 15.0	98	108	1.39	(0.90-2.17)	1.06	(0.69-1.63)
	15.5 - 21.0	110	88	1.92	(1.23-3.01)	1.62	(1.05-2.51)
	> 21.0	97	92	1.62	(1.03-2.54)	1.43	(0.90-2.27)
				Score test for linear trend: p = 0.020 [b], 0.097[c]			
Red Meat	0 - 5.5	61	93	1.00	-	1.00	-
	6.0 - 8.5	81	81	1.52	(0.97-2.39)	1.52	(0.99-2.34)
	9.0 - 13.0	103	105	1.50	(0.98-2.29)	1.19	(0.77-1.85)
	> 13.0	114	92	1.89	(1.23-2.90)	1.98	(1.24-3.17)
				Score test for linear trend: p = 0.006 [b], 0.022[c]			

Cont.

Table 5.25, cont.: Crude and adjusted odds ratios (non LERs only)

Food Groups (helpings per week)		Frequency		Crude OR		Adjusted OR [a]	
		Case (n)	Control (n)	OR	(95% CI)	OR	(95% CI)
Processed Meat	0 - 3.0	76	98	1.00	-	1.00	-
	3.5 - 5.5	73	83	1.13	(0.73-1.75)	1.18	(0.77-1.82)
	6.0 - 9.0	111	90	1.59	(1.05-2.40)	1.40	(0.91-2.14)
	> 9.0	99	100	1.28	(0.85-1.92)	1.41	(0.89-2.22)
				Score test for linear trend: p = 0.11 [b], 0.382 [c]			
Fish	0 - 2.0	79	72	1.00	-	1.00	-
	2.5 - 4.5	83	102	0.74	(0.48-1.14)	0.88	(0.57-1.35)
	5.0 - 8.0	115	101	1.04	(0.68-1.57)	1.06	(0.69-1.65)
	> 8.0	82	96	0.78	(0.50-1.20)	0.68	(0.43-1.06)
				Score test for linear trend: p = 0.63 [b], 0.197 [c]			
Total Vegetables (excluding potatoes)	0 -16.5	88	69	1.00	-	1.00	-
	17.0 - 26.5	63	93	0.53	(0.34-0.84)	0.74	(0.48-1.15)
	27.0 - 42.5	109	103	0.83	(0.55-1.26)	1.05	(0.68-1.61)
	> 42.5	99	106	0.73	(0.48-1.11)	0.63	(0.40-0.99)
				Score test for linear trend: p = 0.52 [b], 0.075 [c]			
Total Whole Fruit	0 - 7.5	87	70	1.00	-	1.00	-
	8.0 - 13.5	71	98	0.58	(0.37-0.91)	0.96	(0.62-1.49)
	14.0 - 21.5	102	98	0.84	(0.55-1.28)	1.08	(0.69-1.68)
	> 21.5	99	105	0.76	(0.50-1.15)	0.99	(0.62-1.57)
				Score test for linear trend p = 0.56 [b], 0.963 [c]			
Soy Food	0	338	335	1.00	-	1.00	-
	≥ 1	21	36	0.58	(0.33-1.01)	0.84	(0.55-1.28)
				Score test for linear trend: p = 0.053 [b], 0.411 [c]			
Grilled Meat	0	77	80	1.00	-	1.00	-
	1-2	206	221	0.97	(0.67-1.40)	0.96	(0.65-1.42)
	3-4	62	57	1.13	(0.70-1.82)	1.05	(0.63-1.75)
	5+	14	13	1.12	(0.49-2.54)	1.00	(0.43-2.35)
				Score test for linear trend: p = 0.60 [b], 0.983 [c]			

Cont.

Table 5.25, cont.: Crude and adjusted odds ratios (non LERs only)

Food Groups (units per week)		Frequency		Crude OR		Adjusted OR [a]	
		Case (n)	Control (n)	OR	(95% CI)	OR	(95% CI)
Grilled Meat Score	0	77	80	1.00	-	1.00	-
	1	19	10	1.97	(0.86-4.55)	1.71	(0.71-4.10)
	2	93	106	0.91	(0.60-1.39)	0.85	(0.54-1.32)
	3	191	113	0.93	(0.61-1.40)	0.99	(0.63-1.53)
	4+	69	62	1.16	(0.73-1.84)	1.08	(0.66-1.78)
				Score test for linear trend: p = 0.97 [b], 0.545 [c]			
Alcohol Consumed	No	70	49	1.00	-	1.00	-
	Yes	289	322	0.67	(0.45-0.99)	0.64	(0.42-0.97)
				Score test for linear trend: p = 0.042 [b], 0.036 [c]			
Beer	No alcohol consumption	70	49	1.00	-	1.00	-
	Alcohol consumption other than beer	92	96	0.67	(0.42-1.07)	0.66	(0.40-1.07)
	1-2	54	57	0.66	(0.39-1.12)	0.64	(0.37-1.12)
	3-9	80	108	0.52	(0.32-0.83)	0.54	(0.33-0.90)
	10+	63	61	0.72	(0.43-1.20)	0.75	(0.43-1.30)
				Score test for linear trend: p = 0.09 [b], 0.190 [c]			
Wine	No alcohol consumption	70	49	1.00	-	1.00	-
	Alcohol consumption other than wine	110	132	0.58	(0.37-0.91)	0.56	(0.35-0.91)
	1-2	78	90	0.61	(0.38-0.98)	0.62	(0.37-1.03)
	3-9	84	66	0.89	(0.55-1.45)	0.98	(0.58-1.66)
	10+	17	34	0.35	(0.17-0.71)	0.37	(0.17-0.76)
				Score test for linear trend: p = 0.21 [b], 0.006 [c]			
Spirits	No alcohol consumption	70	49	1.00	-	1.00	-
	Alcohol consumption other than spirits	85	91	0.65	(0.41-1.05)	0.68	(0.41-1.12)
	1-2	68	71	0.67	(0.41-1.10)	0.66	(0.39-1.12)
	3-9	86	90	0.67	(0.42-1.07)	0.68	(0.41-1.12)
	10+	50	70	0.50	(0.30-0.84)	0.49	(0.28-0.85)
				Score test for linear trend: p = 0.027 [b], 0.161 [c]			

N.B.
[a] = ORs adjusted for: Age, total energy (using residual method), family history of PCa & BrCa, deprivation index, smoking, EI/BMR ratio.
[b] = crude ORs, [c] = adjusted ORs.

5.4.10 Food group analysis: Stratified by age group

As shown in Table 5.14, 310 of subjects were in the younger age group (≤ 65yrs), with the remaining 606 subjects in the older age group (> 65 yrs). The distribution of cases and controls varied significantly between age groups ($p < 0.001$), with more controls within the younger age group and more cases within the older age group.

Food group consumption by age group

No significant differences were observed for consumption of most food groups between age groups, with the exception of total meat, processed meat and alcohol types for which consumption was significantly higher in the younger age group, see Tables 5.26 and 5.27.

Table 5.26: Distribution of continuous food group variables, by age group

Food Groups (helpings per week)	Younger Age Group (n= 310)		Older Age Group (n=606)		Test for difference between age-groups
	Mean (s.d.)	Median (I-QR)	Mean (s.d.)	Median (I-QR)	Mann-Whitney U Test (p-value)
Total Dairy	20.41 (12.61)	17.50 (11.00-27.63)	19.90 (11.12)	17.75 (11.38-26.00)	0.94
Milk	13.00 (9.08)	14.00 (7.00-14.00)	12.07 (8.22)	10.00 (7.00-14.00)	0.19
Cheese	4.64 (5.46)	3.00 (1.00-6.00)	4.32 (4.06)	3.00 (1.00-6.00)	0.46
Eggs	4.13 (4.60)	3.00 (2.00-5.50)	3.79 (3.18)	3.00 (2.00-5.00)	0.74
Total Meat	17.41 (9.99)	15.50 (10.50-23.00)	15.91 (8.56)	14.50 (10.00-20.00)	0.046
Red Meat	9.96 (6.70)	9.00 (5.00-14.13)	9.89 (6.39)	9.00 (5.50-13.00)	0.91
Processed Meat	7.25 (5.45)	6.00 (3.00-10.63)	6.21 (4.83)	5.25 (3.00-8.00)	0.01
Fish	5.76 (4.64)	4.50 (2.50-8.00)	5.51 (4.63)	4.50 (2.00-7.50)	0.34
Total Vegetables (excluding potatoes)	33.57 (24.69)	26.50 (16.50-47.00)	32.43 (23.78)	28.00 (15.88-41.00)	0.57
Total Whole Fruit	16.32 (15.25)	12.75 (6.50-21.00)	17.20 (14.21)	14.50 (7.88-22.00)	0.13
Soy Food	0.09 (0.38)	0.00 (0.00-0.00)	0.11 (0.77)	0.00 (0.00-0.00)	0.22

N.B.
s.d. = Standard Deviation
I-QR = Inter-Quartile Range

Table 5.27: Distribution of categorical food group and alcohol type variables, by age group

Food Group (helpings per week)	Younger Age Group (% within Age Group)	Older Age Group (% within Age Group)
Grilled Meat:		
No grilled meat	66 (21.3%)	140 (23.1%)
1-2	181 (58.4%)	358 (59.1%)
3-4	49 (15.8%)	89 (14.7%)
5+	14 (4.5%)	19 (3.1%)
Total	***310 (100%)***	***606 (100%)***
	Chi-Square Test (p-value) = 0.666	
Grilled Meat Score:		
No grilled meat	66 (21.3%)	140 (23.1%)
1	12 (3.9%)	28 (4.6%)
2	82 (26.5%)	164 (27.1%)
3	92 (29.7%)	177 (29.2%)
4+	58 (18.7%)	97 (16.0%)
Total	***310 (100%)***	***606 (100%)***
	Chi-Square Test (p-value) = 0.828	

Cont.

Table 5.27, cont.: Distribution of categorical food group and alcohol type variables, by age group

Alcohol Type (units per week)	Younger Age Group (% within Age Group)	Older Age Group (% within Age Group)
Alcohol consumption:		
No	34 (11.0%)	123 (20.3%)
Yes	276 (89.0%)	483 (79.7%)
Total	***310 (100%)***	***606 (100%)***
	Chi-Square Test (p-value) <0.001	
Beer		
No alcohol consumption	34 (11.0%)	123 (20.3%)
Alcohol consumption other than beer	64 (20.6%)	180 (29.7%)
1-2 units	57 (18.4%)	88 (14.5%)
3-9 units	82 (26.5%)	140 (23.1%)
10+ units	73 (23.5%)	75 (12.4%)
Total	***310 (100%)***	***606 (100%)***
	Chi-Square Test (p-value) < 0.001	
Wine		
No alcohol consumption	34 (11.0%)	123 (20.3%)
Alcohol consumption other than wine	125 (40.3%)	192 (31.7%)
1-2 units	55 (17.7%)	145 (23.9%)
3-9 units	71 (22.9%)	109 (18.0%)
10+ units	25 (8.1%)	37 (6.1%)
Total	***310 (100%)***	***606 (100%)***
	Chi-Square Test (p-value) < 0.001	
Spirits		
No alcohol consumption	34 (11.0%)	123 (20.3%)
Alcohol consumption other than spirits	88 (28.4%)	138 (22.8%)
1-2 units	53 (17.1%)	115 (19.0%)
3-9 units	71 (22.9%)	148 (24.4%)
10+ units	64 (20.6%)	82 (13.5%)
Total	***310 (100%)***	***606 (100%)***
	Chi-Square Test (p-value) < 0.001	

Crude ORs, by age group

The effect of food group consumption on PCa risk was observed to vary between age groups, see Table 5.28. For the younger age group, positive associations with PCa risk were observed for all dairy and meat products, with the exception of fish and grilled meat for which no association was observed. Of these only total meat (OR 2.45, 95%CI 1.22-4.90) and red meat (OR 3.04, 95%CI 1.56-5.90) was significant. Whereas the majority of alcohol types were observed to inversely associated with PCa risk, however none of these associations were observed to be significant.

However, within the older age group, no association was observed for dairy products, as well as fruit and vegetables, with the exception of eggs which were observed to be significantly associated with PCa risk (OR 1.66, 95%CI 1.01-2.73), see Table 5.28. Most meat products were observed to be positively associated with PCa risk, although none were shown to be significant. Whereas all alcohol types were inversely associated with PCa risk, with both wine and spirits showing significant associations (OR 0.26, 95%CI 0.11-0.61, and OR 0.53, 95%CI 0.30-0.94, respectively), as was soy foods (OR 0.50, 95%CI 0.25-0.98).

Score test for trends

Within the younger group, a dose response effect was found for total meat and red meat only, with the crude ORs of these food groups being observed to increase significantly with higher intake categories, see Table 5.28. Whereas for the older age group, a dose response effect was found for eggs, processed meat, soy food and beer, with crude ORs being observed to increase significantly with higher intake categories of eggs and processed meat, and decrease significantly with higher intake categories of soy food and beer.

Adjusted ORs

The controlling of confounding variables, including the use of energy adjusted nutrient intakes (using the residual method), had a small effect on the observed ORs for food group consumption in both age groups, see Table 5.28.

Within the younger age group, controlling for confounding factors had little effect on the association between food group consumption and PCa risk, with the exception of total meat, whose positive association with PCa risk became non-significant, and vegetables and beer for which a non-significant inverse association with PCa risk were now observed. Red meat remained significantly positively associated with PCa risk (OR 3.73, 95%CI 1.70-8.15).

Within the older age group, again controlling for confounding factors had little effect on the association between food group consumption and PCa risk, with the exception of eggs and soy foods (whose associations with PCa risk became non-significant), red meat (for which no association was observed) and vegetables which became significantly inversely associated with PCa risk (OR 0.60, 95%CI 0.36-0.99).

Significant dose-response effects were observed for red meat ($p = 0.007$) within the younger age group only, and for alcohol consumption ($p = 0.048$) and wine ($p = 0.002$) within the older age group only.

Table 5.28: Crude and adjusted odds ratios by age group

Food Groups (helpings per week)		Age Group							
		Younger (≤ 65 years)				Older (> 65 years)			
		Crude OR		Adjusted OR [a]		Crude OR		Adjusted OR [a]	
		OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Total Dairy	0 - 11.0	1.00	-	1.00	-	1.00	-	1.00	-
	11.5 - 17.5	1.24	(0.65-2.37)	0.81	(0.39-1.69)	0.74	(0.47-1.16)	1.10	(0.68-1.80)
	18.0 - 26.5	0.65	(0.32-1.32)	1.02	(0.50-2.07)	0.91	(0.58-1.43)	0.91	(0.56-1.49)
	> 26.5	1.82	(0.96-3.47)	1.32	(0.67-2.60)	0.90	(0.57-1.42)	0.87	(0.52-1.45)
		Score test for linear trend: p = 0.21 [b], 0.611 [c]				Score test for linear trend: p = 0.89 [b], 0.786 [c]			
Milk	0 - 6.5	1.00	-	1.00	-	1.00	-	1.00	-
	7.0 - 12.0	0.60	(0.29-1.25)	1.12	(0.51-2.45)	1.13	(0.69-1.83)	1.11	(0.67-1.84)
	12.5 - 14.0	0.90	(0.43-1.88)	0.86	(0.42-1.79)	1.12	(0.68-1.86)	1.13	(0.69-1.85)
	> 14.0	1.31	(0.62-2.77)	1.55	(0.77-3.08)	1.09	(0.63-1.88)	0.96	(0.58-1.59)
		Score test for linear trend: p = 0.12 [b], 0.372 [c]				Score test for linear trend: p = 0.82 [b], 0.902 [c]			
Cheese	0 - 1.0	1.00	-	1.00	-	1.00	-	1.00	-
	1.5 - 3.0	0.76	(0.39-1.45)	0.72	(0.36-1.46)	1.23	(0.79-1.94)	1.31	(0.79-2.17)
	3.5 - 6.0	0.96	(0.50-1.83)	0.78	(0.38-1.60)	0.76	(0.49-1.19)	0.86	(0.53-1.41)
	> 6.0	1.47	(0.78-2.77)	1.21	(0.60-2.45)	1.08	(0.68-1.72)	0.78	(0.48-1.27)
		Score test for linear trend: p = 0.20 [b], 0.478 [c]				Score test for linear trend: p = 0.65 [b], 0.204 [c]			
Eggs	0 - 1.5	1.00	-	1.00	-	1.00	-	1.00	-
	2.0 - 3.0	0.93	(0.49-1.78)	1.17	(0.58-2.37)	0.97	(0.62-1.51)	0.94	(0.57-1.53)
	3.5 - 5.0	1.02	(0.51-2.03)	1.15	(0.54-2.42)	1.03	(0.65-1.64)	1.13	(0.70-1.83)
	> 5.0	1.57	(0.82-3.01)	1.40	(0.68-2.86)	1.66	(1.01-2.73)	1.41	(0.84-2.36)
		Score test for linear trend: p = 0.15 [b], 0.839 [c]				Score test for linear trend: p = 0.045 [b], 0.428 [c]			
Total Meat	0 - 10.0	1.00	-	1.00	-	1.00	-	1.00	-
	10.5 - 15.0	2.20	(1.07-4.50)	1.56	(0.74-3.26)	1.09	(0.71-1.67)	1.03	(0.63-1.68)
	15.5 - 21.0	2.73	(1.32-5.63)	2.12	(1.03-4.34)	1.57	(1.00-2.47)	1.24	(0.75-2.05)
	> 21.0	2.45	(1.22-4.90)	1.83	(0.89-3.77)	1.37	(0.85-2.21)	1.30	(0.78-2.18)
		Score test for linear trend: p = 0.011 [b], 0.194 [c]				Score test for linear trend: p = 0.07 [b], 0.677 [c]			
Red Meat	0 - 5.5	1.00	-	1.00	-	1.00	-	1.00	-
	6.0 - 8.5	2.15	(1.06-4.38)	1.48	(0.73-3.00)	1.28	(0.81-2.02)	1.06	(0.64-1.74)
	9.0 - 13.0	2.37	(1.20-4.76)	2.23	(1.08-4.61)	1.13	(0.73-1.74)	0.79	(0.48-1.31)
	> 13.0	3.04	(1.56-5.90)	3.73	(1.70-8.15)	1.55	(0.97-2.48)	1.13	(0.68-1.88)
		Score test for linear trend: p = 0.001 [b], 0.007 [c]				Score test for linear trend: p = 0.12 [b], 0.520 [c]			

Cont.

Table 5.28, cont.: Crude and adjusted odds ratios by age group

Food Groups (helpings per week)		Age Group							
		Younger (≤ 65 years)				Older (> 65 years)			
		Crude OR		Adjusted OR [a]		Crude OR		Adjusted ORa	
		OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Processed Meat	0 - 3.0	1.00	-	1.00	-	1.00	-	1.00	-
	3.5 - 5.5	1.27	(0.63-2.53)	1.20	(0.57-2.50)	0.94	(0.60-1.46)	1.26	(0.78-2.05)
	6.0 - 9.0	1.76	(0.91-3.42)	1.23	(0.59-2.53)	1.46	(0.95-2.25)	1.37	(0.84-2.23)
	> 9.0	1.22	(0.66-2.26)	1.00	(0.49-2.05)	1.45	(0.91-2.32)	1.65	(0.99-2.75)
		Score test for linear trend: p = 0.41 [b], 0.906 [c]				Score test for linear trend: p = 0.03 [b], 0.268 [c]			
Fish	0 - 2.0	1.00	-	1.00	-	1.00	-	1.00	-
	2.5 - 4.5	0.68	(0.35-1.31)	1.10	(0.52-2.32)	1.14	(0.73-1.78)	0.96	(0.59-1.56)
	5.0 - 8.0	1.17	(0.61-2.24)	1.14	(0.56-2.29)	1.35	(0.89-2.09)	1.26	(0.76-2.07)
	> 8.0	0.99	(0.50-1.94)	0.91	(0.44-1.89)	1.02	(0.63-1.63)	0.78	(0.48-1.27)
		Score test for linear trend: p = 0.58 [b], 0.930 [c]				Score test for linear trend: p = 0.63 [b], 0.298 [c]			
Total Vegetables (excluding potatoes)	0 -16.5	1.00	-	1.00	-	1.00	-	1.00	-
	17.0 - 26.5	0.59	(0.30-1.16)	0.81	(0.40-1.65)	0.86	(0.54-1.37)	0.61	(0.37-0.99)
	27.0 - 42.5	1.34	(0.68-2.61)	1.50	(0.75-3.03)	0.85	(0.55-1.30)	0.84	(0.51-1.38)
	> 42.5	0.92	(0.50-1.72)	0.73	(0.34-1.56)	0.94	(0.60-1.47)	0.60	(0.36-0.99)
		Score test for linear trend: p = 0.64 [b], 0.197 [c]				Score test for linear trend: p = 0.71 [b], 0.109 [c]			
Total whole Fruit	0 - 7.5	1.00	-	1.00	-	1.00	-	1.00	-
	8.0 - 13.5	0.65	(0.34-1.23)	0.79	(0.40-1.56)	0.73	(0.46-1.17)	0.98	(0.59-1.62)
	14.0 - 21.5	0.59	(0.31-1.12)	0.59	(0.27-1.30)	1.18	(0.75-1.84)	1.28	(0.78-2.12)
	> 21.5	0.74	(0.40-1.40)	0.73	(0.34-1.53)	1.03	(0.66-1.62)	1.21	(0.73-2.02)
		Score test for linear trend: p = 0.28 [b], 0.624 [c]				Score test for linear trend: p = 0.44 [b], 0.633 [c]			
Soy Food	0	1.00	-	1.00	-	1.00	-	1.00	-
	≥ 1	0.79	(0.34-1.82)	0.92	(0.43-1.95)	0.50	(0.25-0.98)	0.71	(0.41-1.21)
		Score test for linear trend: p = 0.57 [b], 0.823 [c]				Score test for linear trend: p = 0.039 [b], 0.206 [c]			
Grilled meat	0	1.00	-	1.00	-	1.00	-	1.00	-
	1-2	1.35	(0.74-2.46)	1.24	(0.65-2.38)	1.08	(0.73-1.60)	1.14	(0.75-1.75)
	3-4	1.90	(0.87-4.12)	1.54	(0.65-3.68)	1.17	(0.69-2.00)	1.22	(0.68-2.21)
	5+	1.19	(0.35-4.02)	1.22	(0.31-4.79)	1.11	(0.42-2.91)	1.32	(0.46-3.74)
		Score test for linear trend: p = 0.22 [b], 0.668 [c]				Score test for linear trend: p = 0.59 [b], 0.953 [c]			

Cont.

Table 5.28, cont.: Crude and adjusted odds ratios by age group

Food group type (helpings / units per week)		Age Group							
		Younger (≤ 65 years)				Older (> 65 years)			
		Crude OR		Adjusted OR [a]		Crude OR		Adjusted OR [a]	
		OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Grilled Meat score	0	1.00	-	1.00	-	1.00	-	1.00	-
	1	2.14	(0.61-7.59)	1.85	(0.46-7.41)	1.55	(0.67-3.55)	2.38	(0.90-6.28)
	2	1.17	(0.59-2.34)	1.08	(0.51-2.27)	1.13	(0.72-1.78)	1.14	(0.70-1.86)
	3	1.44	(0.74-2.82)	1.38	(0.67-2.86)	0.97	(0.62-1.51)	1.00	(0.61-1.63)
	4+	1.74	(0.83-3.66)	1.40	(0.61-3.22)	1.20	(0.72-2.03)	1.37	(0.76-2.44)
		Score test for linear trend: p = 0.16 [b], 0.717 [c]				Score test for linear trend: p = 0.84 [b], 0.404 [c]			
Alcohol consumption	No	1.00	-	1.00	-	1.00	-	1.00	-
	Yes	0.67	(0.33-1.37)	0.47	(0.21-1.06)	0.71	(0.46-1.06)	0.65	(0.42-1.01)
		Score test for linear trend: p = 0.27 [b], 0.150 [c]				Score test for linear trend: p = 0.10 [b], 0.048 [c]			
Beer	No alcohol consumption	1.00	-	1.00	-	1.00	-	1.00	-
	Alcohol consumption other than beer	0.41	(0.17-1.00)	0.32	(0.12-0.85)	0.81	(0.51-1.29)	0.76	(0.46-1.26)
	1-2	0.82	(0.35-1.93)	0.55	(0.21-1.43)	0.74	(0.43-1.29)	0.64	(0.35-1.18)
	3-9	0.58	(0.26-1.33)	0.38	(0.15-0.95)	0.65	(0.40-1.06)	0.57	(0.33-0.98)
	10+	0.98	(0.43-2.23)	0.73	(0.29-1.83)	0.59	(0.33-1.05)	0.55	(0.29-1.04)
		Score test for linear trend: p = 0.37 [b], 0.075 [c]				Score test for linear trend: p = 0.036 [b], 0.184 [c]			
Wine	No alcohol consumption	1.00	-	1.00	-	1.00	-	1.00	-
	Alcohol consumption other than wine	0.63	(0.29-1.37)	0.41	(0.17-0.99)	0.64	(0.40-1.01)	0.59	(0.36-0.98)
	1-2	0.42	(0.17-1.06)	0.31	(0.11-0.86)	0.82	(0.51-1.34)	0.72	(0.42-1.22)
	3-9	0.92	(0.40-2.10)	0.68	(0.27-1.73)	0.97	(0.57-1.64)	0.96	(0.54-1.73)
	10+	0.88	(0.31-2.52)	0.64	(0.20-2.05)	0.26	(0.11-0.61)	0.21	(0.08-0.52)
		Score test for linear trend: p = 0.64 [b], 0.105 [c]				Score test for linear trend: p = 0.17 [b], 0.002 [c]			
Spirits	No alcohol consumption	1.00	-	1.00	-	1.00	-	1.00	-
	Alcohol consumption other than spirits	0.71	(0.32-1.58)	0.55	(0.22-1.35)	0.63	(0.38-1.03)	0.57	(0.33-0.97)
	1-2	0.58	(0.24-1.41)	0.39	(0.15-1.07)	0.95	(0.57-1.60)	0.86	(0.49-1.50)
	3-9	0.69	(0.30-1.59)	0.51	(0.20-1.27)	0.75	(0.46-1.21)	0.69	(0.41-1.17)
	10+	0.68	(0.29-1.58)	0.41	(0.15-1.07)	0.53	(0.30-0.94)	0.49	(0.26-0.91)
		Score test for linear trend: p = 0.51 [b], 0.577 [c]				Score test for linear trend: p = 0.12 [b], 0.087 [c]			

N.B.
[a] = ORs adjusted for: Age, total energy, family history of PCa & BrCa, deprivation index, smoking, EI/BMR ratio.
[b] = crude ORs, [c] = adjusted ORs.

5.5 Logistic Regression Analysis - the final model

In order to investigate the overall effect of important dietary factors observed to be significantly associated with PCa risk, the variables for these dietary factors were added into a model along with the potential confounding factors. The final model included:

- Protein
- Cholesterol
- Alcohol
- Selenium
- Red meat
- Vegetables
- Age
- Family history of PCa and BRCa
- Carstairs Deprivation Index
- Smoking
- EI:BMR ratio

Of the six important dietary factors observed to significantly effect PCa risk, only alcohol and red meat consumption continued to have significant inverse (OR 0.63, 95%CI 0.41-0.96) and positive (OR 1.66, 95%CI 1.03-2.70) associations with PCa risk, respectively, see Table 5.29. It should also be noted that the ORs for these dietary factors remained at the same magnitude as when adjusted for confounding variables only. Selenium also continued to have an inverse association with PCa risk, however this association was only shown to be significant for the second highest category. Whereas, the positive association between cholesterol intake and PCa risk, with a magnitude similar to that when only confounding factors were adjusted for, was observed to be non-significant, as was the inverse association observed with vegetable consumption.

Table 5.29: Adjusted ORs for important dietary factors - Full model

		Adjusted OR [a]	
		OR	(95%CI)
Protein (g)	0 - 74.7	1.00	-
	74.7 - 92.1	0.90	(0.59-1.37)
	92.1 - 112.7	0.82	(0.52-1.30)
	> 112.7	0.77	(0.47-1.27)
Cholesterol (mg)	0 - 242	1.00	-
	242 - 326	0.93	(0.60-1.43)
	326 - 450	1.25	(0.81-1.94)
	>450	1.51	(0.95-2.41)
Alcohol (g)	0 - 3.4	1.00	-
	3.4 - 9.9	0.78	(0.53-1.16)
	9.9 - 21.6	0.69	(0.46-1.03)
	>21.6	0.63	(0.41-0.96)
Selenium (μg)	0 - 56	1.00	-
	56 - 73	0.87	(0.58-1.30)
	73 - 94	0.62	(0.41-0.96)
	>94	0.90	(0.58-1.40)
Red meat (helpings per week)	0 - 5.5	1.00	-
	6.0 - 8.5	1.28	(0.85-1.93)
	9.0 - 13.0	1.24	(0.79-1.93)
	>13.0	1.66	(1.03-2.70)
Vegetables (helpings per week)	0 - 16.5	1.00	-
	17.0 - 26.5	0.71	(0.47-1.07)
	27.0 - 42.5	1.20	(0.78-1.81)
	>42.5	0.78	(0.50-1.21)

[a] = Adjusted for age, EI (residual method), family history of PCa and BrCa, Carstairs Deprivation Index, Smoking and EI:BMR ratio.

5.6 Adjusted ORs, using the multivariate analysis model

Given the strong intercorrelation between EI and most nutrients and food groups, in particular fats and high fat food groups such as meat, it is possible that adjusting for EI using the residual method may have caused the effect of nutrient intake to be over controlled for. This possibility is discussed in further detail in section 6.2 of the Discussion Chapter. Adjusted ORs were therefore recalculated using the multi-variate model method of adjusting for EI (i.e. putting EI into the final model along with the other confounders). For nutrient intake, an increase in both magnitude and significance was observed in ORs for total fat (OR 2.17, 95%CI 0.99-4.80), MUFA (OR 2.38, 95%CI1.11-5.11), cholesterol (OR 2.19, 95%CI 1.27-3.78) and alcohol (OR 0.62, 95%CI 0.41-0.94). See Table 5.30. Whereas for food groups, a slight increase in both magnitude and significance was observed in ORs for red meat (OR 1,79, 95%CI 1.14-2.82) and soy foods (OR 0.52, 95%CI 0.30-0.91). See Table 5.31.

Table 5.30: Adjusted ORs for nutrient intake, using the multiple regression model method for EI adjustment.

Nutrient Variable		Frequency		Adjusted OR[a]	
		Case (n)	Control (n)	OR	(95% CI)
Protein (g)	0 - 74.7	92	121	1.00	-
	74.7 - 92.1	104	124	0.87	(0.53-1.43)
	92.1 - 112.7	104	118	0.87	(0.48-1.55)
	> 112.7	133	120	1.03	(0.52-2.05)
Total Fat (g)	0 - 65.3	73	121	1.00	-
	65.3 - 84.9	113	121	1.74	(1.03-2.95)
	84.9 - 109.6	112	121	1.84	(0.97-3.50)
	> 109.6	135	120	2.17	(0.99-4.80)
Saturated Fat (g)	0 - 25.3	83	123	1.00	-
	25.3 - 34.0	97	119	1.11	(0.69-1.77)
	34.0 - 46.3	127	121	1.45	(0.85-2.47)
	> 46.3	126	120	1.31	(0.70-2.46)
MUFA (g)	0 - 22.8	73	121	1.00	-
	22.8 - 29.9	117	124	1.77	(1.05-2.96)
	29.9 - 38.3	110	119	1.81	(0.96-3.39)
	> 38.3	133	119	2.38	(1.11-5.11)
PUFA (g)	0 - 9.7	90	123	1.00	-
	9.7 - 13.3	110	119	1.49	(0.93-2.37)
	13.3 - 17.8	124	121	1.31	(0.80-2.16)
	> 17.8	109	120	0.95	(0.54-1.69)
Cholesterol (mg)	0 - 242	71	121	1.00	-
	242 - 326	92	122	1.16	(0.74-1.82)
	326 - 450	129	120	1.83	(1.14-2.93)
	> 450	141	120	2.19	(1.27-3.78)
Alcohol (g)	0 - 3.4	129	122	1.00	-
	3.4 - 9.9	112	120	0.81	(0.55-1.19)
	9.9 - 21.6	102	122	0.76	(0.51-1.12)
	> 21.6	90	119	0.62	(0.41-0.94)

Cont.

Table 5.30, Cont.: Adjusted ORs for nutrient intake, using the multiple regression model method for EI adjustment.

Nutrient Variable		Frequency		Adjusted OR [a]	
		Case (n)	Control (n)	OR	(95% CI)
Calcium (mg)	0 - 812	84	121	1.00	-
	812 - 1039	104	121	1.14	(0.73-1.78)
	1039 - 1321	118	121	1.23	(0.75-2.01)
	> 1321	127	120	1.31	(0.76-2.27)
Selenium (μg)	0 - 56	102	121	1.00	-
	56 - 73	103	122	0.81	(0.53-1.25)
	73 - 94	105	122	0.78	(0.49-1.24)
	> 94	123	118	0.76	(0.46-1.24)
Retinol (μg)	0 - 348	86	121	1.00	-
	348 - 571	124	121	1.43	(0.94-2.19)
	571 - 838	98	121	1.00	(0.63-1.57)
	> 838	125	120	1.36	(0.86-2.17)
Carotene (μg)	0 - 1308	117	121	1.00	-
	1308 - 2187	103	121	0.79	(0.54-1.18)
	2187 - 3447	95	121	0.74	(0.49-1.11)
	> 3447	118	120	0.85	(0.56-1.30)
Vitamin E (μg)	0 - 4.89	82	121	1.00	-
	4.89 - 7.27	131	121	1.52	(0.98-2.35)
	7.27 - 10.56	103	121	1.14	(0.70-1.86)
	> 10.56	117	120	1.18	(0.72-1.93)
Vitamin C (mg)	0 - 62.5	103	121	1.00	-
	62.5 - 90.5	92	121	0.92	(0.61-1.40)
	90.5 - 134.7	126	121	1.07	(0.70-1.62)
	> 134.7	112	120	1.07	(0.68-1.68)
Isoflavones (μg)	0 - 581.1	95	121	1.00	-
	581.1 - 1050.9	100	121	0.98	(0.65-1.48)
	1050.9 - 1982.8	112	121	1.09	(0.72-1.65)
	> 1982.8	126	120	1.20	(0.79-1.83)

N.B.
MUFA = Mono unsaturated Fat
PUFA = Poly unsaturated Fat
EI = Energy Intake
[a] = Adjusted for Age, EI (multiple regression model method), Family History of PCa and BrCa, Deprivation Index, Smoking and EI/BMR Ratio.

Table 5.31: Adjusted ORs for food group intake, using the multiple regression model method for EI adjustment.

Food Groups (helpings per week)		Frequency		Adjusted OR [a]	
		Case (n)	Control (n)	OR	(95% CI)
Total Dairy	0 - 11.0	111	119	1.00	-
	11.5 - 17.5	104	127	0.82	(0.55-1.23)
	18.0 - 26.5	100	126	0.76	(0.51-1.14)
	> 26.5	118	111	0.99	(0.65-1.50)
Milk	0 - 6.5	65	74	1.00	-
	7.0 - 12.0	148	179	1.02	(0.66-1.57)
	12.5 - 14.0	122	133	1.07	(0.69-1.69)
	> 14.0	98	97	1.14	(0.70-1.83)
Cheese	0 - 1.0	113	128	1.00	-
	1.5 - 3.0	112	118	0.95	(0.64-1.41)
	3.5 - 6.0	102	137	0.74	(0.50-1.10)
	> 6.0	106	100	0.98	(0.65-1.49)
Eggs	0 - 1.5	93	116	1.00	-
	2.0 - 3.0	124	158	0.78	(0.53-1.15)
	3.5 - 5.0	100	118	0.94	(0.62-1.42)
	> 5.0	116	91	1.50	(0.95-2.28)
Total Meat	0 - 10.0	91	141	1.00	-
	10.5 - 15.0	116	134	1.34	(0.90-2.00)
	15.5 - 21.0	123	104	1.89	(1.24-2.89)
	> 21.0	103	104	1.49	(0.93-2.39)
Red Meat	0 - 5.5	94	151	1.00	-
	6.0 - 8.5	101	104	1.44	(0.96-2.17)
	9.0 - 13.0	116	126	1.41	(0.94-2.12)
	> 13.0	122	102	1.79	(1.14-2.82)
Processed Meat	0 - 3.0	113	150	1.00	-
	3.5 - 5.5	88	113	1.06	(0.71-1.58)
	6.0 - 9.0	127	108	1.49	(1.01-2.21)
	> 9.0	105	112	1.22	(0.80-1.88)

Cont.

Table 5.31, Cont.: Adjusted ORs for food group intake, using the multiple regression model method for EI adjustment.

Food Groups (helpings per week)		Frequency		Adjusted OR [a]	
		Case (n)	Control (n)	OR	(95% CI)
Fish	0 - 2.0	107	125	1.00	-
	2.5 - 4.5	105	132	0.97	(0.65-1.44)
	5.0 - 8.0	133	121	1.20	(0.80-1.79)
	> 8.0	88	105	0.81	(0.52-1.26)
Total Vegetables (excluding potatoes)	0 -16.5	124	125	1.00	-
	17.0 - 26.5	85	118	0.70	(0.47-1.06)
	27.0 - 42.5	117	120	0.87	(0.58-1.30)
	> 42.5	107	120	0.71	(0.46-1.09)
Total Whole Fruit	0 - 7.5	120	121	1.00	-
	8.0 - 13.5	88	125	0.60	(0.40-0.90)
	14.0 - 21.5	113	118	0.91	(0.61-1.35)
	> 21.5	112	119	0.88	(0.58-1.35)
Soy Food	0	410	440	1.00	-
	≥ 1	23	43	0.52	(0.30-0.91)

N.B.
Adjusted ORs for grilled meat, grilled meat score, alcohol consumption and wine / beer / spirit consumption were omitted from the table as the original adjusted ORs were calculated using the multiple regression model method, (due to the categorical nature of the data).
[a] = ORs adjusted for: Age, total energy (using residual method), family history of PCa & BrCa, deprivation index, smoking, EI/BMR ratio.
[b] = crude ORs. [c] = adjusted ORs.

6 . Chapter 6: Discussion

6.1 Discussion of results

The findings of this study suggest that several nutrients and food groups may be important factors associated with PCa risk. The findings for each individual á priori nutrient and food group will be discussed in turn according to whether the hypotheses were accepted or rejected, a summary of the hypotheses can be found in the aims and objectives section of the Methodology Chapter. The discussion of these findings in relation to previous studies are presented in Section 6.3.

6.1.1 Accepted Hypotheses

The hypotheses for the following à priori nutrients were accepted due to strong and consistent significant associations with PCa risk being observed throughout the analysis, thereby inferring that these nutrients are important factors associated with PCa risk.

Cholesterol

Out of all the components of fat, cholesterol was the only one in which a consistent significant association was observed, thereby allowing for the hypothesis that high cholesterol intake is associated with an increased risk of PCa to be accepted. Subjects whose cholesterol intake was greater than 450mg/day were shown to be 50% more likely to be diagnosed with PCa than those whose intake was less than 242mg/day. Average cholesterol intake was 350mg/day, similar to that reported in Scottish men age 16-64 yrs[53].

A significant adjusted OR for the highest cholesterol intake category was observed, adjusted OR 1.57 (95%CI 1.04-2.37), the omission of LERs had little effect on this association. This significant positive association with PCa was confirmed by the log likelihood ratio test showing cholesterol intake to have a significant effect on PCa and also the observed significant positive dose-response effect. However, when other important significant dietary factors were adjusted for, this association became borderline non-significant. This could be explained by the presence of red meat

consumption in the model, a dietary factor observed to be both strongly associated with PCa risk and highly correlated with cholesterol, see next paragraph. Further analysis stratifying by age group showed significant crude ORs continuing to be observed in both age groups, ORs 2.01 (95%CI 1.05-3.82) and 1.99 (95%CI 1.22-3.23) for younger and older age groups respectively. However, adjusting for confounding factors caused these associations to become non-significant, even though the magnitude of the association remained similar, especially in the younger age group.

Close examination of the association between cholesterol and other dietary and confounding factors showed that cholesterol intake was strongly positively correlated with protein, retinol and meat products, the Carstairs deprivation index and smoking status, in addition to energy intake, the EI / BMR ratio and total fat and its other constituents. These associations were expected as meat products are an important source of cholesterol, in addition to other fats, protein and retinol; hence the association with these nutrients. The association with Carstairs deprivation index and smoking status and cholesterol was also expected as high consumption of meat products and fried foods are far more prevalent within lower social classes[44], as is the prevalence of smokers.

Red Meat

Out of all the meat food groups, red meat consumption was the only one in which a consistent significant positive association with PCa risk was observed, thereby allowing for the hypothesis that high red meat consumption is associated with an increased risk of PCa to be accepted. Subjects whose red meat consumption was greater than thirteen servings a week were shown to be over 60% more likely to be diagnosed with PCa than those who consumed less than five and a half servings of red meat per week. Furthermore, the risk was even greater in younger men where younger subjects whose red meat consumption was in the highest category being nearly four times as likely to be diagnosed with PCa. The average consumption of red meat was nine servings a week.

A significant adjusted OR for the highest red meat consumption category was observed, adjusted OR 1.64 (95%CI 1.09-2.48). The omission of LERs had little effect on this association, as did adjusting for other important significant dietary factors. This positive association was confirmed by the log likelihood ratio test showing red meat consumption to have a significant effect on PCa and also by the observed significant positive dose-response effect. Further analysis stratifying by age group showed the significant adjusted ORs to become stronger within the younger age group, adjusted OR 3.73 (95%CI 1.70-8.15).

Close examination of the association between red meat and other dietary and confounding factors showed that red meat intake was strongly positively correlated with EI, fats and protein as well as other meat products. These associations were expected, as red meat is an important source of these nutrients.

Protein

High protein intake was shown to have a significant positive association with PCa risk for younger subjects, thereby allowing for the hypothesis that protein intake is associated with an increased risk of PCa to be accepted within the younger age group. Younger subjects whose protein intake was greater than 112.7g/day were shown to be over twice as likely to be diagnosed with PCa than those who intake was less than 74.7g/day. The average intake of protein was 93.3g/day.

For all subjects, a significant crude OR for the highest protein intake category was observed, OR 1.46 (95%CI 1.01-2.11), as was a significant positive dose-response effect. However, adjusting for confounding variables made the OR for protein intake non-significant, as did the omission of LERs. However, further analysis stratifying by age group observed the association between protein intake and PCa risk to become stronger within the younger age group, adjusted OR 2.34 (95%CI 1.13-4.87).

Close examination of the association between protein and other dietary and confounding factors showed that protein intake was strongly positively correlated with cholesterol, selenium and meat products, in addition to EI and the EI / BMR

ratio. These associations were expected as meat products are important sources of protein, in addition to cholesterol, hence the association with this nutrient.

Vegetables

High vegetable consumption was shown to have a significant inverse association with PCa risk, thereby allowing for the hypothesis that vegetable consumption is associated with a protective effect against PCa to be accepted. Subjects whose vegetable consumption was greater than 42.5 portions per week were shown to be 40% less likely to be diagnosed with PCa than those who consumed less then 16.5 portions per week. The average consumption of vegetables was 27.5 portions a week.

A significant adjusted OR for the highest vegetable consumption category was observed, adjusted OR 0.62 (95%CI 0.41-0.93), the omission of LERs had little effect on this association. However, when other important significant dietary factors were adjusted for, this association became non-significant. Further analysis stratifying by age group showed significant adjusted ORs continuing to be observed within the older age group, adjusted OR 0.60 (95%CI 0.36-0.99).

Close examination of the association between vegetable consumption and other dietary and confounding factors showed that vegetable consumption was strongly positively correlated with fruit, fish, PUFA, selenium, carotene, vitamin E and vitamin C, and negatively correlated with fats (with the exception of PUFA) the Carstairs deprivation index and smoking. Most of these associations were expected as vegetables are an important source of many of these nutrients, hence the association. Vegetable consumption is also associated with healthy eating habits which include high intake of fish and unsaturated fats and which is more prevalent within higher social classes and amongst non-smokers.

Selenium

High selenium intake was shown to have a significant inverse association with PCa risk within older subjects, thereby allowing for the hypothesis that selenium intake is associated with a protective effect against PCa to be accepted within the older age group. Older subjects whose selenium intake was greater than 94μg were shown to

be nearly half less likely to be diagnosed with PCa than those whose selenium intake was less than 56μg. The average intake of selenium was 74.5μg per day.

For all subjects, the results suggested an inverse association between selenium intake and PCa risk. As although the adjusted OR for the highest selenium intake category was observed to be non-significant (OR 0.88, 95%CI 0.59-1.29), a significant adjusted OR for the 2nd highest intake was observed (OR 0.67, 95%CI 0.45-0.99), adjusting for other important significant dietary factors had little effect on this association. However, further analysis stratifying by age group observed the association between selenium intake and PCa risk to become both stronger and significant within the older age group, adjusted OR 0.61 (95%CI 0.37-0.99). It should also be noted that within the younger age group a significant positive crude association was observed (OR 2.07, 95%CI 1.08-3.97), however this association became non-significant when confounding factors were adjusted for.

Close examination of the association between selenium and other nutrients, food groups and confounding factors showed that selenium intake was strongly positively correlated with PUFA, protein, fish and vegetables, in addition to EI and the EI : BMR ratio. These associations were expected, as meat products are an important source of selenium, as are vegetables, hence the association with these nutrients and food groups. The co-variation between selenium and protein and red meat could explain why a positive association with PCa risk was observed within the younger age group.

Alcohol

Alcohol consumption was consistently observed to be significantly inversely associated with PCa risk, for both pure alcohol intake, consumption of alcohol versus no consumption and by alcohol type, thereby causing the hypothesis that alcohol is associated with an increase in PCa risk to be rejected. Subjects whose pure alcohol intake was in the highest category (greater than 21.6g/day, the equivalent of 2.5 units) were shown to be at least 30% less likely to be diagnosed with PCa than those in the lowest intake category (less than 3.4g/day). This reduction in PCa risk was even stronger for wine and spirit consumption. The average intake of pure alcohol

was 9.05g/day (just over one unit per day), with 82.9% of subjects reporting to consume alcohol.

For pure alcohol intake, a significant adjusted OR for the highest alcohol intake category was observed, adjusted OR 0.66 (95%CI, 0.44-0.99). However the omission of LERs made this association non-significant, whereas adjusting for other important significant dietary factors had little effect on this association. Similar associations were also observed for alcohol consumption (versus non-consumption) (adjusted OR 0.62, 95%CI 0.42-0.90) and for wine and spirit consumption (adjusted ORs 0.38, 95%CI 0.19-0.74 and 0.48, 95%CI 0.29-0.79, respectively), the omission of LERs had little effect. These inverse associations with PCa were also reinforced by the presence of a significant dose-response effect for both wine and spirits. Further analysis stratifying by age group showed significant adjusted ORs continuing to be observed in the older age group, in particular for pure alcohol intake and wine consumption whose inverse associations with PCa risk became even stronger (adjusted ORs 0.54, 95%CI 0.32-0.89 and 0.21, 95%CI 0.08-0.52 respectively). The association between spirits and PCa risk for the older age group remained similar (adjusted OR 0.49, 95%CI 0.26-0.91). Within the younger age group, inverse associations between alcohol and PCa were also observed, however these were found to be non-significant.

Close examination of the association between alcohol consumption and dietary and confounding factors showed that pure alcohol intake was weakly inversely correlated with most nutrients, strong positive associations with alcohol type were also observed as expected. Age was observed to be significantly inversely associated with pure alcohol intake, though this association was not strong. No strong correlations with other dietary and confounding factors were observed for alcohol types either, with the exception of an inverse association between wine consumption and the Carstairs Deprivation Index. The lack of strong associations between alcohol consumption and other nutrients, food groups and confounding variables was surprising, in particular the lack of association with energy intake. There was however a general pattern towards 'healthy eating' habits and lower deprivation with

increased wine consumption and 'unhealthy eating' habits including increased fat and meat consumption, with increased beer consumption.

6.1.2 Rejected hypotheses

Both vitamin C and isoflavone intakes were observed to have no association with PCa risk, with both crude and adjusted ORs for these nutrients being close to equilibrium. Therefore, the hypotheses that intake for vitamin C and isoflavones are associated with a protective effect against PCa were rejected.

Within the food groups, all dairy products (except eggs), fish and fruit were observed to have no association with PCa risk with both crude and significant ORs for these food groups being close to equilibrium. Therefore, the hypotheses that intake for dairy products and fish, and fruit are associated with an increase and decrease in PCa risk respectively were rejected.

For the remaining nutrients and food groups, although the hypotheses for these were rejected due to the lack of consistent statistically significant associations with PCa risk, the ORs observed for these dietary factors suggest that some association may exist.

High intakes of total fat, saturated fat, MUFA and retinol were observed to have positive associations with PCa. Significant crude ORs were observed for these nutrients, as was a significant positive dose-response effect for each fat intake variable. However, adjusting for confounding variables, in particular the use of the energy-adjusted fat intakes, made these ORs non-significant.

Within the food groups, high consumption of eggs and total meat were observed to have positive associations with PCa risk. Significant crude ORs were observed for these food groups, as were significant positive dose-response effects. However, adjusting for confounding variables, in particular the use of the energy-adjusted intakes, made these ORs non-significant. Positive ORs were also observed for processed meat and the grilled meat score, however these were found to be non-significant.

High intakes of PUFA, calcium, carotenes and vitamin E were suggested to have a protective effect against PCa. As although crude ORs for these nutrients were either observed to be positive, though non-significant, or showed no association, adjusting for confounding factors revealed an inverse, though non-significant, association with PCa risk.

Within the food groups, soy products and beer consumption were suggested to have a protective effect against PCa. Significant crude ORs were observed for soy products, however adjusting for confounding variables made the OR non-significant. For beer consumption, inverse, though non-significant, associations were observed for both crude and adjusted ORs within the highest consumption category. However, both crude and adjusted ORs for the second highest consumption category observed a significant inverse association (adjusted OR 0.54, 95%CI 0.35-0.85), suggesting that moderate beer consumption (3-9 units per week) also had a protective effect against PCa.

6.2 Reasons behind the observed associations: Caveats and problems

In interpreting these findings, it is important to consider how much of the observed association between these dietary factors and PCa risk may have been affected by other factors before concluding that these associations are a true causal relationship. These considerations include whether the observed associations were affected by bias, confounding or could be due to chance.

The design of this study and the methods used in the selection and recruitment of subjects and data collection allowed for potential bias and confounding to be limited. The use of hospital records from all the major hospitals to ascertain all new cases of PCa, and also the use of health board and GP lists as a sampling frame to select controls at random, ensured that not only were all newly diagnosed cases of PCa within the defined population identified, but also that the controls came from this same population, thereby limiting selection bias. However, many subjects refused to take part in the study or did not respond to the invitation, leading to an overall response rate (proportion of subjects agreeing to participate within the total number of eligible subjects contacted) of 67%, this is slightly lower than the response rate considered acceptable by Bowling[266] (75%). It is possible that bias may have been introduced into the study as the response rate was shown to differ significantly across status, with a higher number of cases agreeing to participate compared to controls. Also, subjects from the Borders Health Board were far more likely to participate than those from the Greater Glasgow Health Board, as were younger subjects and those with lower levels of deprivation. It is therefore possible that controls who agreed to participate were more likely to be a subset of potential controls interested in health and therefore likely to consume "healthy" diets high in vegetables and low in fats. This is supported by the lower response rates for controls within high deprivation categories, where high fat and low vegetable consumption is more prevalent.

The non-participation of Greater Glasgow controls was reduced as far as possible by asking the appropriate GP to contact the potential control rather than using direct contact which may have made the potential control less likely to respond than if it had been sent by someone he knew and trusted. The contacting of Lothian GPs and

controls via Lothian Health Board also helped to reduce non-participation for the same reasons. The use of reminder letters also helped in keeping the non-response rate low.

The use of a FFQ which was self-completed, in addition to the blinding of data managers and technicians to the case / control status, allowed for observer bias to be minimised. However recall bias, in which cases may have recalled their diet differently to controls, may well have effected the observed associations. This is a major caveat for all case-control studies in which information on exposure is collected after the disease of interest has been diagnosed. Certain nutrients, including β-carotene, selenium and isoflavones were especially prone to this bias and this maybe a reason for the lack of statistically significant inverse associations with PCa for these nutrients. These nutrients have all recently been featured in the media as being protective against PCa and its progression, thereby causing many older men especially those diagnosed with PCa to increase their intake of foods such as tomatoes and soy products which are high in these nutrients. This anecdotal evidence was confirmed by the presence of notes written on the FFQs by cases advising of a change in diet to include more of these foods, especially soy milk. To combat this, the FFQ included a question regarding recent diet changes, which would have hopefully picked up any post-diagnosis diet changes, however this question was usually mistaken to be about weight reducing dietary changes rather than for specific foods. Further potential for misclassification of nutrient intake was reduced by using an FFQ and food tables that have been validated within the population under study. The use of the new comprehensive and validated Isoflavone Database[71] in particular, allowed for accurate estimations of isoflavone intake. However, as discussed in Chapter 2, no dietary assessment method is 100% accurate, although any potential misclassification of dietary intake is likely to be non-differential, thus leading to a bias towards an underestimation of risk.

Regarding potential confounding problems, the majority of confounding factors were controlled for at the analysis stage. Age was also controlled for by age-frequency matching population controls to cases, although the addition of BPH controls which were not age-frequency matched diluted this controlling effect. Age was therefore

included as a confounding variable in addition to stratifying the analysis by older and younger age groups. EI was adjusted for by using energy-adjusted dietary intakes, therefore allowing for the study of the association for each dietary variable outwith the effect of EI. This is especially important as EI was observed to have a significant positive association with PCa risk. However, it is possible that adjusting for EI using the Residual Method may cause dietary factors to be over controlled for, particularly for nutrients and food groups containing large amounts of energy such as fats. This point is discussed in more detail in Section 6.3.1. Indeed, when the adjusted ORs were recalculated using the multi-variate model method of adjusting for EI, the association was observed to increase in both magnitude and significance for a number of dietary factors including: total fat, MUFA, cholesterol, alcohol, red meat and soy foods. However, as the residual method of adjusting for EI is considered the 'Gold Standard', emphasis is still given to the findings using the residual method of EI adjustment.

Although this study examined and controlled for several potential confounding factors, the residual confounding of unknown factors for which data was not collected for must not be ruled out.

In order to protect against the subject misclassification, all cases were pathologically confirmed as having PCa. In addition, the use of BPH controls ensured that at least a large proportion of controls were confirmed as not having asymptomatic PCa. The use of BPH controls could introduce selection bias if BPH is associated with PCa risk, however, to date no evidence for this association has been observed[267]. However, this study was limited in that information relating to the mode of detection of PCa, in particular PSA screening, was not available, nor was information regarding the stage and grade of PCa. It is highly likely that a proportion of cases were detected through PSA testing of asymptomatic men. This may lead to bias if any associations between diet and PCa risk are related to the mode of detection, for example, it could be assumed that men who have a PSA test are more likely to be health conscious and consume a healthier diet high in vegetables and low in meat and fat. The lack of PCa stage and grade information could also produce bias leading to an underestimation of risk if the risk patterns of less aggressive and/or incidental PCa

cases detected by PSA testing were more similar to those risk patterns of the controls.

It is possible that several of the observed significant findings could be due to chance as a result of multiple testing. The use of 20+ dietary factors increased the likelihood of at least one spurious result to be observed as significant at the 0.05 level. However, the use of only á priori dietary factors for which evidence of an association with PCa had been reported in previous studies, and also that p-values far below the 0.05 level were observed for the majority of significant ORs (p-values not shown) in addition to further analyses (such as the log likelihood ratio test) confirming the significant association, meant that the presence of a spurious result was unlikely.

In conclusion, the combined strength of the design and methodologies as discussed above produced a study that was robust enough to detect any true associations between dietary factors and PCa risk. However, care must still be taken in the interpretation of the results due to residual confounding, responder bias and potential misclassification caused by the lack of information regarding PCa stage / grade and detection method and also from the diet assessment method used.

6.3 Discussion of dietary factors in relation to previous studies

In general, the findings of this study are similar to those of the studies reviewed in Chapter 3. These findings, in their own right, also add to the overall evidence in the field of nutritional cancer epidemiology by providing estimations of PCa risk for dietary factors using a robust methodology in a high risk population not studied before. This next section will discuss those dietary factors reported to have a significant association with PCa risk in further detail, including a comparison with other studies.

6.3.1 Fat

The observed lack of significant associations between fat intake and PCa risk (with the exception of cholesterol) when confounding factors, in particular EI, were adjusted for, were similar to the findings of the majority of previous studies that have examined this association such as Andersson et al[131] whose large Swedish case-control study reported no significant association between PCa risk and total fat, saturated fat, MUFA and PUFA and Schuurman et al[93] whose nested case-control study (taken from a large cohort of 58,279 Dutch men) also reported no significant association between PCa risk and fat and its components. By contrast, the observed significant positive effect of cholesterol on PCa risk, has not been reported in any previous studies investigating cholesterol. However, to date only two case-control studies have reported on the association between PCa and cholesterol intake[131;135].

It should also be noted that (as with other previous studies which reported crude relative risks, such as Andersson et al[131]) total fat, saturated fat and MUFA were shown to have a crude significant positive effect on PCa risk. These associations continued to be statistically significant for total fat, MUFA and cholesterol, when EI was adjusted for by including EI in the multivariate models rather than by using the Residual Method. As fat intake was highly correlated with EI (rho = 0.92, $p < 0.001$), due mainly to the high proportion of EI coming from fat, it could be conceivable that the use the Residual Method to calculate energy-adjusted intakes may cause fat intake to be over controlled for. If this is indeed the case, the use of the Energy Density Method or multivariate analysis to control for EI as a proxy for total food

intake would be more appropriate. It could also be suggested that although fat and its components (apart from cholesterol) has been shown not have a direct effect on PCa risk, within the public health context high fat intake could still be considered as an important risk factor. As the total gross effect of fat intake (including the associated risk from EI) on PCa risk will lead a significant increased risk of PCa in those men consuming high amounts of fat.

It should also be noted that attributable risk estimates suggest that approximately 20-25 % of PCa incidence among Caucasian-Americans and African-Americans, and 5-10% among Asian-Americans maybe due to high levels of saturated fat intake[10;268].

6.3.2 Protein and red meat

The observed significant positive associations between protein and red meat consumption and PCa risk when confounding factors were adjusted for are similar to the findings of several of previous studies, such as Chan et al[171] and Hayes et al[128] whose large case-control studies reported significant positive associations with both total meat and red meat consumption, and also Le Marchand et al[168] whose large cohort study reported a significant positive association with beef consumption. Only one case-control study examined the association of meat products stratifying for age group[161], however direct comparisons were difficult to make as the age cut-off used was different (< 70 years) and red meat consumption was not reported.

The observed lack of association between PCa risk and retinol intake and meat doneness, a proxy for heterocyclic amine and polycyclic aromatic hydrocarbon intake, suggests that the fat component of meat (in particular cholesterol and possibly saturated fat) is the underlying factor behind the association with meat consumption. This is further emphasised by the attenuation of the association between cholesterol consumption and PCa risk when red meat and protein consumpion, along with other important dietary factors, were adjusted for.

6.3.3 Vegetables and associated nutrients

The observed significant inverse association between vegetable consumption and PCa risk, in particular when confounding factors were adjusted for, are also similar

to the findings from previous studies that have examined this relationship, such as Cohen et al[207] and Kolonel et al[208] whose large case-control studies reported significant inverse associations with vegetable intake, in particular cruciferous vegetables and carrots. No previous studies have examined vegetable intake stratified by age-group, making it impossible to compare the continuing significant inverse association with vegetable consumption within the older age group.

The only plant-based nutrient to be significantly associated with PCa risk was selenium, this association was only shown to be significant within the older age group. The lack of previous studies investigating selenium intake makes comparisons difficult, however findings of a significant inverse relationship from several studies investigating serum and toenail concentrations of selenium in addition to the NTPC trial[188] are confirmed by this study.

Selenium and possibly carotenes (for which an inverse, though non-significant, association was observed), maybe the underlying factors behind vegetable consumption. However the protective effect of high vegetable consumption could also just be a proxy for a general healthy diet and lifestyle.

The inverse association reported between soyfoods and PCa risk, although non-significant when adjusted for confounding factors, is an important finding and suggests a protective effect against PCa that has been reported by several previous studies such as Kolonel et al[208], Lee et al[214] and Jacobsen et al[212] all of which were large studies conducted in populations known for their high consumption of soy foods. The lack of a statistically significant association in this study may be due to the low consumption of soy foods reported in the study population (only 7% of subjects reported to consume soy foods). The association between soy food consumption and PCa risk may also have been underestimated due to responder bias caused by cases changing their post diagnosis diet to include phyto-oestrogen rich soy foods.

6.3.4 Alcohol consumption

The observed significant inverse association between alcohol consumption and PCa risk, is not supported by the majority of previous studies examining alcohol intake, thereby adding to the inconclusive evidence of the effect of alcohol consumption on PCa. This is not surprising given the considerable variation in study design, study population and methodologies as discussed in Chapter 3. For example this study used non-drinkers of any alcohol as the reference category for alcohol type consumption, unlike most previous studies that used non-drinkers of the relevant alcohol type. This reference category was used due to the observed significant association with overall alcohol consumption and also the observation that non-drinkers of one alcohol type were likely to be drinkers of another, thereby making the non-drinkers of the relevant alcohol type as the reference category ineffective. The cut-points for consumption categories also differed from those in previous studies. It would be very interesting to conduct a meta-analysis using the original data from these previous studies in order to regulate reference categories and other methodological variations.

The reported consistent inverse associations, even when LERs were omitted (thereby controlling for any misclassification bias from controls underestimating alcohol consumption) and confounding factors were adjusted for, suggest that alcohol consumption has a true protective effect against prostate cancer. The large variation in alcohol consumption within Scottish men caused by the high daily consumption of alcohol, as discussed in Chapter 2, allowed for the association between PCa and alcohol consumption to be examined accurately, unlike for many of the previous studies which were undertaken in populations, such as the US and the Netherlands, where alcohol consumption is lower. However, the scarcity of data for high alcohol consumption meant that the highest consumption categories for alcohol type had to be combined, therefore making it difficult to examine the effect of high consumption of individual alcohol types on PCa risk.

This reported protective effect is supported by the presence of a potential biomechanism in which alcohol consumption effects androgen serum levels, which in turn are linked to prostate growth and development and most possibly PCa

genesis. Nevertheless it is still possible that the reported findings may have been affected by other methodological factors, in particular recall bias caused by cases recalling their alcohol consumption differently to controls.

6.4 The Public Health context

The evidence from this study suggests that in order to reduce risk of PCa, and thereby reducing incidence of PCa, consumption of red meat and fat should be reduced and the consumption of vegetables should be increased to at least six portions per day. If the findings of this study regarding the association between alcohol consumption and PCa risk are indeed true, the consumption of at least two and a half units of alcohol per day may also reduce PCa risk. Although the findings suggest that alcohol consumption both at and above this level is protective against PCa, it is probably more appropriate to keep to the suggested consumption at the lower range. This is a moderate level of consumption and is below the recommended maximum daily amount of three to four units for men. However, the public health implications of the protective effect of alcohol consumption against PCa risk are complex. Increased alcohol consumption is associated with an increased risk of several diseases such as liver disease, stroke and some cancers, thus any recommendation regarding alcohol consumption will need to be carefully examined regarding both the potential benefits and risks of increased alcohol consumption. This has been done successfully with the recommendations for red wine consumption to protect against heart disease.

These suggestions for reducing PCa risk, with exception of alcohol, are similar to those of the Eating for Health: A Diet Action Plan for Scotland[269], published by the Scottish Office in 1996, which recognized the detrimental effect on health a poor and unhealthy diet can have and suggested several recommendations on improving the Scottish diet. These included:

- The average intake of fruit and vegetables to double to more than 400 grams a day by 2005.
- The average intake of total fat to reduce from 40.7% to no more then 35% of food energy by 2005.
- The average intake of saturated fats to reduce from 16.6% to no more than 11% of food energy by 2005.

These are targets are very challenging, especially given the Scottish population's affection for high fat / high meat consumption and their dislike for healthy food[270]. It is very unlikely that they will be met solely by providing dietary education and advice or from the increased intake of dietary supplements. The Diet Action Plan for Scotland[269] has therefore recommended further key steps to tackle this, such as shaping consumer tastes to make healthier choices and to improve access to healthy food in particular in low income areas; ensuring that food producers, manufacturers and retailers supply, develop and market healthier products and by collaborating with health services and local authorities on health promotion and education, such as the '5-a-Day' campaign to increase fruit and vegetable consumption and the new 'Choose Life, Choose Healthy Living' advice line and web-site set up by HEBS. It also recognizes that dietary improvement is not achievable without tackling poverty and deprivation that underlines so much of Scotland's poor dietary and nutritional status.

6.5 Further study

The findings of this study are of great interest, however each of the dietary factors observed to be associated with PCa risk, in particular alcohol consumption and cholesterol, as well as the effect that they may have on advanced PCa and the interaction with age, require further study. These investigations should not only be in the form of epidemiological and intervention studies but also in experimental and animal model studies that will allow us greater understanding of the biological mechanisms involved. Several biological and methodological issues are discussed in this thesis and should be considered carefully when undertaking these future investigations, including the complex nature of diet, study design and diet assessment methodologies.

A new field of investigation, combining the fields of nutritional and genetic epidemiology, is that of the interaction between diet and genetics. Diet-gene interactions are of particular importance as they may explain the inconsistencies within the findings for dietary factors that cannot be explained by differences methods alone. It is possible that genetic factors relevant to the metabolism and function of nutrients and hormones (e.g. the Vitamin D Receptor gene and Androgen Receptor gene) and to carcinogen activation /elimination (e.g. Glutathione-S-transferases genes), may influence susceptibility to the effect of dietary factors on PCa.

Another important area of nutritional epidemiology is the study of effect of diet in early life. As PCa is a slowly progressing disease, which probably begins decades prior to diagnosis and may possibly be influenced by exposures during puberty and adolescence[3], the study of pre-adult diet and its effect on PCa risk is also an important line of future investigation.

6.6 Conclusion

The findings of this thesis add to the overall evidence of an association between PCa risk and diet. These findings are especially important, given that the study was conducted in a high PCa risk population never studied before and used a robust methodology that included a validated diet assessment method.

In summary, this thesis supports the hypotheses that high vegetable consumption and selenium intake (in older men only) are protective against PCa, and that high red meat consumption, in particular for men aged 50 -65 years, is associated with an increased risk of PCa. In addition, the findings that high cholesterol intake and increased alcohol consumption are associated with an increased and reduced risk of PCa respectively, are relatively novel compared to previous studies and therefore should be investigated further.

These findings are of particular interest with regards to health promotion amongst Scottish men. If healthy eating targets (such as the increase of fruit and vegetable consumption and the reduction in meat and fat consumption) are made, it could lead to a considerable reduction in PCa incidence and mortality in addition to other diseases such a heart disease at which these targets are aimed.

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8 . Appendices

8.1 Protocol for selection of controls from Glasgow GP Practice List

The essential principle was that a sampling frame was established in which a pool of at least ten potential controls was used as a source for random sampling of five (primary control plus four replacements) potential controls. This pool was a list of all male patients whose dates of birth fall within the birth month/year of the required control. The procedure for randomly selecting potential controls from this pool was as follows:

1. Male patients whose date of birth was within the required birth month / year were selected to the pool of potential controls. Checks were made that there were at least ten patients for each required primary control. If this requirement was not met, patients whose date of birth was within the birth month/years either side of the original birth month/year were included in the pool of potential controls, until the requirement was achieved. The number of potential controls within the pool was counted (N).

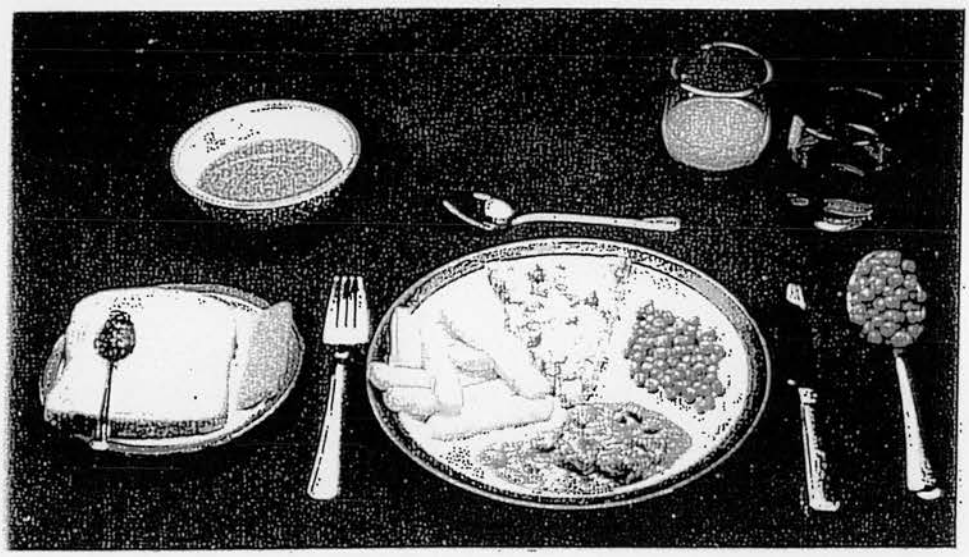
2. With the use of a set of random numbers between 0 and 1 (r), the number of potential controls (N) was multiplied by the next random number on the list (N x r), the resulting number was rounded up to the nearest integer number (M), this was then used to select the M^{th} patient on the list as the primary control. If this number = 0, the calculation was repeated using the next random number. The name, address and date of birth of the selected potential control was noted on the selected controls form and the selected control was removed from the list. This step was repeated five times in order to select the five potential controls (primary control plus four replacements) required.

8.2 SCG-FFQ and FFQ information sheet

Aberdeen Food Frequency Questionnaire (version 6.3)

Examples of food measures

The photograph shows the measures of amounts of food which are used in the questionnaire. Clockwise from the top right of the picture, these are:



Orange juice (in glass)	*½ medium glassful*
Blackcurrant drink (in glass)	*1 medium glassful*
Peas (in spoon)	*1 tablespoon*
Peas (on dinner plate)	*1 tablespoon*
Chips (on dinner plate)	*¼ plate*
Stewed beef (on dinner plate)	*2 tablespoons*
Pizza (on dinner plate)	*1 slice*
Bread (on side plate)	*1 slice*
Margarine (on bread)	*a thin layer*
Jam (on side plate)	*1 teaspoon*
Cheese (on side plate)	*1 oz (25g) or a match-box sized piece.*
Tomato soup (in soup bowl)	*1 small bowlful*

To help you estimate the amounts of different foods, keep this photograph beside you as you complete the questionnaire.

Please return the photograph with your completed questionnaire

19974

Study Number | | | | | | |

Aberdeen Food Frequency Questionnaire

Version 6.31

© Aberdeen FFQ Group, 1999

This questionnaire consists of a list of 150 foods, divided into 20 food groups. We would like you to describe how much of each food on the list you have eaten in the **last 2-3 months**.

If you didn't eat a food, or ate it less than once a month, please circle '**R**' (rarely or never).

For foods you ate on average once a month or more often, we would like to know two things:
- the amount of the food you usually ate on a day you had the food
- the number of days in a week you usually ate the food

Please try to indicate foods you eat at home and foods you eat at work or in restaurants or cafes. The amount of each food should be described in measures such as tablespoon, slice etc. The measures are pictured on a colour photograph enclosed with this questionnaire.

Please use black or blue pen.

Example:

If in the last 2-3 months you ate 4 slices of bread most days, an apple most weekdays, half a plate of chips once a week, 3 scoops of ice-cream once or twice a month, but never had carrots, you should circle the measures and numbers of days a week like this:

	Measure	Measures per day	Number of days per week
Bread	1 slice	1 2 3 (4) 5+	R M 1 2 3 4 5 6 (7)
Apple	1 medium fruit	(1) 2 3 4 5+	R M 1 2 3 4 (5) 6 7
Chips	¼ plate	1 (2) 3 4 5+	R M (1) 2 3 4 5 6 7
Ice-cream	1 scoop	1 2 (3) 4 5+	R (M) 1 2 3 4 5 6 7
Carrots	1 tablespoon	1 2 3 4 5+	(R) M 1 2 3 4 5 6 7

Please note:
- **5+** means five or more measures per day
- **R** means rarely or never. If you circle R you do not have to circle a number of measures a day
- **M** means you ate the food once or twice a month

Any foods which you usually eat which are not in the list can be added in section 20 at the end.

Please remember that we need you to give a response to every question on this form.
If you rarely or never ate a food, please don't forget to circle (R)

19974

1. Bread

Which of the following kinds of bread do you usually eat? Please tick one or more types:

i) White ___ ***ii) Brown ___*** ***iii) Wholemeal ___***

	Measure	Measures per day					Number of days per week							
a) Bread (including toast & sandwiches)	1 medium slice	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
b) Bread roll	1 roll	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
c) Croissants, butteries	1 roll	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
d) Other breads (pitta, naan, etc.)	1 pitta or ½ naan	1	2	3	4	5+	R	M	1	2	3	4	5	6	7

2. Breakfast Cereals

	Measure	Measures per day					Number of days per week							
a) Cornflakes, Special K, Rice Krispies etc.	1small bowl	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
b) Bran Flakes, Sultana Bran, All Bran etc.	1small bowl	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
c) Shredded Wheat, Weetabix etc.	1 biscuit	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
d) Coco Pops, Frosties, Sugar Puffs, Crunchy Cornflakes etc.	1small bowl	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
e) Muesli (all types)	1small bowl	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
f) Porridge and Ready Brek	1small bowl	1	2	3	4	5+	R	M	1	2	3	4	5	6	7

3. Milk *(including milk on cereals and in drinks, but not milk in cooked foods)*

	Measure	Measures per day					Number of days per week							
a) Full fat milk	¼ pint	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
b) Semi-skimmed milk	¼ pint	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
c) Skimmed milk	¼ pint	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
d) Dried milk or creamer	1 teaspoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7

Please check that you have circled a response on every line before going to the next page.

4. Cream and Yogurt

	Measure	Measures per day	Number of days per week
a) Low fat yogurt (plain or fruit)	1 pot (5 fl oz)	1 2 3 4 5+	R M 1 2 3 4 5 6 7
b) Full fat yogurt (e.g. Greek)	1 pot (5 fl oz)	1 2 3 4 5+	R M 1 2 3 4 5 6 7
c) Low calorie yogurt (natural or fruit)	1 pot (5 fl oz)	1 2 3 4 5+	R M 1 2 3 4 5 6 7
d) Fromage frais (plain or fruit)	1 pot (5 fl oz)	1 2 3 4 5+	R M 1 2 3 4 5 6 7
e) Cream	1 tablespoon	1 2 3 4 5+	R M 1 2 3 4 5 6 7

5. Cheese

	Measure	Measures per day	Number of days per week
a) Full fat hard cheese (e.g. Cheddar, Gruyere, Wensleydale, Gouda)	1oz (25g) or a matchbox-sized piece	1 2 3 4 5+	R M 1 2 3 4 5 6 7
b) Medium fat cheese (e.g. Edam, Brie, Feta, Camembert, cheese spreads)	1oz (25g) or a matchbox-sized piece	1 2 3 4 5+	R M 1 2 3 4 5 6 7
c) Full fat cream cheese (e.g. Philadelphia, Danish Blue, Boursin Lymeswold)	1 tablespoon or 1oz (25g)	1 2 3 4 5+	R M 1 2 3 4 5 6 7
d) Low fat cheese (e.g. low fat cream cheese, reduced fat hard cheese)	1 tablespoon or 1oz (25g)	1 2 3 4 5+	R M 1 2 3 4 5 6 7
e) Cottage cheese (all types)	1 tablespoon	1 2 3 4 5+	R M 1 2 3 4 5 6 7

6. Eggs

	Measure	Measures per day	Number of days per week
a) Boiled or poached eggs	1egg	1 2 3 4 5+	R M 1 2 3 4 5 6 7
b) Fried eggs	1egg	1 2 3 4 5+	R M 1 2 3 4 5 6 7
c) Scambled eggs or omelette	1egg	1 2 3 4 5+	R M 1 2 3 4 5 6 7

Please check that you have circled a response on every line before going to the next page.

7. Meats *(excluding meat substitutes e.g. Quorn or soya)*

		Measure	Measure per day					Number of days per week							
a)	Mince or meat sauce e.g. bolognese	2 tablespoons	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
b)	Sausages (beef, pork and frankfurters)	1sausage	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
c)	Burgers (all types)	1 burger	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
d)	Beef (roast, grilled, casseroled or fried)	2 tablespoons, 2 slices or 1 steak	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
e)	Pork or lamb (roast, grilled, casseroled or fried)	2 tablespoons, 2 slices or 1 chop	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
f)	Chicken or turkey (roast, grilled, casseroled or fried)	1 wing or thigh, ½ breast or 2 slices	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
g)	Bacon or gammon	1slice	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
h)	Liver, liver sausage or liver pate	1serving	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
i)	Haggis, black pudding	2 tablespoons	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
j)	Meat or chicken pies, pasties, sausage roll	1 pie or 1 roll	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
k)	Cold meats (e.g. ham, corned beef, chicken roll)	1slice	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
l)	Salami or continental sausage	1slice	1	2	3	4	5+	R	M	1	2	3	4	5	6	7

m) How many times a week do you have **fried or grilled** red meat (steaks, chops, bacon, sausages or burgers)?

Zero ___ ***1-2*** ___ ***3-4*** ___ ***5+*** ___

n) Do you normally have these meats:

i) lightly browned ___ ***ii) medium browned*** ___ ***iii) well browned*** ___ ?

8. Fish

		Measure	Measures per day					Number of days per week							
a)	Fish fingers	1finger	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
b)	Fried white fish (e.g. haddock, cod or plaice)	1small fillet	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
c)	Grilled, poached or baked white fish	1small fillet	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
d)	Smoked white fish	1small fillet	1	2	3	4	5+	R	M	1	2	3	4	5	6	7

Please check that you have circled a response on every line before going to the next page.

	Measure	Measures per day					Number of days per week							
e) Fried oily fish (e.g. salmon, herrings, or mackerel)	1small fillet	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
f) Grilled, poached, baked or pickled oily fish	1small fillet	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
g) Smoked oily fish (kipper, mackerel or salmon)	1 small fillet or slice	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
h) Fish cakes, fish pie	1 cake or 2 tablespoons	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
i) Tinned sardines	2 sardines	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
j) Tinned tuna	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
k) Scampi, prawns, crab etc.	1 tablespoon (shelled)	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
l) Mussels, oysters, cockles, scallops	1 tablespoon (shelled)	1	2	3	4	5+	R	M	1	2	3	4	5	6	7

9. Potatoes, Rice and Pasta

	Measure	Measures per day					Number of days per week							
a) Boiled or baked potatoes	1 medium or ½ large	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
b) Mashed potatoes	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
c) Oven chips	¼ plate	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
d) Home-cooked chips	¼ plate	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
e) Chips from a chip shop or restaurant	¼ plate	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
f) Roast or fried potatoes	¼ plate	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
g) White rice	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
h) Brown rice	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
i) Pasta (all types)	¼ plate	1	2	3	4	5+	R	M	1	2	3	4	5	6	7

10. Savoury foods, Soups and Sauces

	Measure	Measures per day					Number of days per week							
a) Pizza	½ an 8 inch or 1 slice	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
b) Quiche or savoury flan	1 medium slice	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
c) Savoury pancakes	1 pancake	1	2	3	4	5+	R	M	1	2	3	4	5	6	7

Please check that you have circled a response on every line before going to the next page.

	Measure	Measures per day					Number of days per week							
d) Baked beans	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
e) Nut roast, nut burgers or vegetable burgers	1 slice or 1 burger	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
f) Quorn products (all types)	1 tablespoon, 1 slice or 1 sausage	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
g) Soya beans, TVP, Tofu or soya meat substitute	1 tablespoon or 1 sausage	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
h) Other beans (kidney, butter, chick peas)	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
i) Lentils (excluding soup)	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
j) Soups (home-made)	1small bowl	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
k) Soups (tinned)	1small bowl	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
l) Soups (dried or instant)	1small bowl or mug	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
m) Gravy	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
n) Tomato-based sauces (e.g for pasta)	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
o) Other savoury sauces (white, cheese etc.)	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
p) Bottled sauces (e.g. ketchup)	½ tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
q) Salad cream, mayonnaise	1 teaspoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
r) Oil & vinegar dressing	1 teaspoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
s) Pickled vegtables or chutneys	1 teaspoon or 1 pickle	1	2	3	4	5+	R	M	1	2	3	4	5	6	7

*11. **Vegetables** (including fresh, frozen and tinned vegetables)*

a) How many servings of vegetables (excluding potatoes) do you have each day? 0 1 2 3 4 5+

	Measure	Measures per day					Number of days per week							
b) Tinned vegetables (all types)	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
c) Peas or green beans	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
d) Carrots	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
e) Cabbage (all kinds)	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7

Please check that you have circled a response on every line before going to the next page.

	Measure	Measures per day					Number of days per week							
f) Brussels sprouts	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
g) Broccoli	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
h) Spinach or spring greens	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
i) Leeks or courgettes	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
j) Cauliflower or swede (neeps) or turnip	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
k) Sweetcorn	1 tablespoon or 1 small piece	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
l) Onions	1 tablespoon or ½ onion	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
m) Tomatoes	½ medium or 2 cherry tomatoes	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
n) Sweet peppers	¼ pepper	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
o) Other salad veg. (lettuce, cucumber etc)	2 leaves or 4 slices	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
p) Potato salad	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
q) Coleslaw or other veg. salads in dressing	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7

12. ***Fruit*** *(including fresh, cooked, frozen and tinned fruits)*

a) How many servings of fruit (excluding fruit juice) do you usually have each day? 0 1 2 3 4 5+

	Measure	Measures per day					Number of days per week							
b) Tinned fruit (all kinds)	1 tablespoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
c) Apples	1medium apple	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
d) Bananas	1medium banana	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
e) Oranges (all kinds) or grapefruit	1small or ½ large fruit	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
f) Pears	1medium pear	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
g) Peaches, nectarines	1medium fruit	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
h) Kiwi fruit	1 fruit	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
i) Dried fruit (raisins, dates, figs etc.)	1 tablespoon or 1 oz (25g)	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
j) All other fruit (grapes, strawberries, melon, plums etc.)	1 tablespoon or 1 slice	1	2	3	4	5+	R	M	1	2	3	4	5	6	7

Please check that you have circled a response on every line before going to the next page.

13. Puddings

	Measure	Measures per day					Number of days per week							
a) Milk-based puddings (e.g. rice, semolina)	1small bowl	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
b) Sponge puddings (steamed, syrup, jam etc)	1small bowl	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
c) Fruit-based puddings (pies, tarts, crumbles)	1 pie, 1 slice or 2 tablespoons	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
d) Mousse, blancmange, trifle, meringue	2 tablespoon or 1 meringue	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
e) Custard or other sweet sauces	2 tablespoons	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
f) Ice cream (all kinds)	1 scoop	1	2	3	4	5+	R	M	1	2	3	4	5	6	7

14. Chocolates, Sweets, Nuts and Crisps

	Measure	Measures per day					Number of days per week							
a) Chocolate bars (e.g. Mars, Dairy Milk)	1bar or 2oz (50g)	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
b) Chocolate sweets, toffees or fudge	1 sweet	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
c) Boiled sweets, mints	1 sweet	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
d) Fruit gums, pastilles, jellies or chewy sweets	1 sweet	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
e) Salted nuts (peanuts, cashews etc.)	1small packet or 1 oz (25g)	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
f) Unsalted nuts	1small packet or 1 oz (25g)	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
g) Crisps	1 small bag	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
h) Other savoury snacks	1 small bag	1	2	3	4	5+	R	M	1	2	3	4	5	6	7

15. Biscuits

	Measure	Measures per day					Number of days per week							
a) Plain (e.g. Rich Tea, digesive)	1 biscuit	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
b) Sweet (e.g. ginger, custard creams)	1 biscuit	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
c) Shortbread	1 biscuit	1	2	3	4	5+	R	M	1	2	3	4	5	6	7

Please check that you have circled a response on every line before going to the next page.

	Measure	Measures per day					Number of days per week							
d) Chocolate coated biscuits	1 biscuit	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
e) Savoury biscuits (crackers, crispbreads)	1 biscuit	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
f) Oatcakes	1 biscuit	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
g) Cereal bars, flapjacks	1 bar	1	2	3	4	5+	R	M	1	2	3	4	5	6	7

16. Cakes

	Measure	Measures per day					Number of days per week							
a) Plain cakes (sponge madeira, ginger etc.)	1 medium slice	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
b) Fruit cakes (all kinds)	1 medium slice	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
c) Rich cakes (e.g. cream, chocolate, cheesecake)	1 medium slice	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
d) Pastries or other iced cakes	1 cake or 1 pastry	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
e) Pancakes or scones	1 pancake or 1 scone	1	2	3	4	5+	R	M	1	2	3	4	5	6	7

17. Sugar and spreads

	Measure	Measures per day					Number of days per week							
a) Table sugar (in drinks & on cereals or deserts)	1 teaspoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
b) Jam, honey, marmalade etc.	1 teaspoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
c) Yeast or meat extract (Marmite, Bovril etc.)	½ teaspoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
d) Peanut butter or chocolate spread	1 teaspoon	1	2	3	4	5+	R	M	1	2	3	4	5	6	7

e) What kind of butter or margarine do you usually spread on bread? Please give as much detail as you can, including brand name(s) or shop name and variety if possible

_____

_____

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f) How much do you normally spread on one slice of bread? (Please tick your answer)

1. none ___ ***2. a scrape*** ___ ***3. a thin layer*** ___ ***4. a thick layer*** ___

g) What type(s) of fat or oil do you usually use for home frying? Please give as much detail as you can, including brand name(s) or shop name and variety if possible

_____

_____

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Please check that you have circled a response on every line before going to the next page.

18. Beverages and Soft Drinks

a) How many cups or mugs of tea or coffee do you usually drink each day?

i)	Regular tea (taken with milk)	cups/mugs
ii)	Regular tea (taken without milk)	cups/mugs
iii)	Herbal, fruit or deceffeninated tea	cups/mugs
iv)	Instant coffee (regular)	cups/mugs
v)	Filter, jug, espresso or other brewed fresh coffee	cups/mugs
vi)	Decaffeinated coffee (instant or brewed)	cups/mugs

	Measure	Measures per day					Number of days per week							
b) Pure fruit juice (orange, apple, etc.)	½ medium glass	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
c) Tomato juice	½ medium glass	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
d) Blackcurrant squash (e.g. Ribena)	1 medium glass	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
e) Other fruit squash	1 medium glass	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
f) Low calorie fizzy drinks (Cola, lemonade etc.)	1 can	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
g) Regular fizzy drinks	1 can	1	2	3	4	5+	R	M	1	2	3	4	5	6	7

19. Alcoholic Drinks

a) Have you had any alcoholic drinks in the last 2-3 months? ***yes*** ___ ***no*** ___

If no, please go to section 20.

If yes, please circle the number of measures you have had in an **average week**. Please try to allow for weeks in which you had very few alcoholic drinks and for weeks in which you had more than usual.

For example, if you had a pint of beer each day, you should circle 10-14 measures per week. If you had two glasses of wine each weekend you should circle 1-2 measures per week.

Please check that you have circled a response on every line before going to the next page.

19974

Drink	Measure	Number of measures per week								
b) Low alcohol beer or lager	1/2 pint	0	1-2	3-4	5-9	10-14	15-19	20-29	30-39	40+
c) Beer (Export) or stout (e.g. Guinness)	1/2 pint	0	1-2	3-4	5-9	10-14	15-19	20-29	30-39	40+
d) Lager or Pilsner-type beer	1/2 pint	0	1-2	3-4	5-9	10-14	15-19	20-29	30-39	40+
e) Wine	1 wine glass	0	1-2	3-4	5-9	10-14	15-19	20-29	30-39	40+
f) Sherry, port etc.	1 sherry glass	0	1-2	3-4	5-9	10-14	15-19	20-29	30-39	40+
g) Spirits or liqueurs	1 pub measure	0	1-2	3-4	5-9	10-14	15-19	20-29	30-39	40+
h) Alcopops (Hooch etc.)	1bottle	0	1-2	3-4	5-9	10-14	15-19	20-29	30-39	40+

i) If you have wine, is it usually red or white? ***mainly red*** ___ ***mainly white*** ___ ***both red & white*** ___

20. Other Foods

Office Use Only Data Entered? yes no

Please use the space below to describe any foods which you have eaten regularly in the last 2-3 months which you have not already included on the questionnaire.

Food	Measure	Measures per day					Number of days per week								
a) _____	_____	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
b) _____	_____	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
c) _____	_____	1	2	3	4	5+	R	M	1	2	3	4	5	6	7
d) _____	_____	1	2	3	4	5+	R	M	1	2	3	4	5	6	7

21. Vitamin, Mineral and Food Supplements

a) Have you taken any vitamin, mineral or food supplements (e.g. bran, iron tablets, fish oil capsules, or multi-vitamin pills) in the last 2-3 months?

yes ___ ***no*** ___ If No, please go to section 22

b) If Yes, please give the type of supplement (e.g. multivitamins, cod liver oil), the amount you take per week, and as much information as possible on e.g. brand name, strength and ingredients (as given on the label or packet)

Type	Amount per week	Brand name, strength and ingredients
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Please check that you have circled a response on every line before going to the next page.

22. Dietary Restrictions

Have you excluded any of the following foods from your diet in the last 2-3 months?

a) Red Meat (beef, pork, lamb etc.) *yes* ___ *no* ___

b) Poultry (chicken, turkey etc.) *yes* ___ *no* ___

c) Fish *yes* ___ *no* ___

d) Eggs *yes* ___ *no* ___

e) Milk and milk products (including cheese and yogurt) *yes* ___ *no* ___

f) Other Dietary Restrictions ? *yes* ___ *no* ___

If yes, please specify: _____

g) For how long have you excluded these foods? ☐☐ years ☐☐ months

23. Special Diets

a) Have you been on a weight reducing diet in the last 2-3 months? *yes* ___ *no* ___

b) Have you been on any other special diet in the last 2-3 months? *yes* ___ *no* ___

If yes, please give details _____

24. General Information

a) Your date of birth ☐☐ day ☐☐ month ☐☐☐☐ year

b) Your age ☐☐ years

c) Your sex *male* ___ *female* ___

d) Your current weight ☐☐ st ☐☐ lb **or** ☐☐☐ kg

e) Your height ☐☐ ft ☐☐ in **or** ☐☐☐ cm

f) Are you currently a *smoker* ___ *ex-smoker* ___ *non-smoker* ___ ?

g) Date of completing the questionnaire: ☐☐ day ☐☐ month ☐☐☐☐ year

Please check that you have circled a response on every line before going to the next page.

19974

h) How many brothers do you have? ☐☐

i) How old are they (or were they when they died)?

☐☐ ☐☐ ☐☐ ☐☐ ☐☐

j) How many uncles (brothers of your mother or father) do you have? ☐☐

k) How old are they (or were they when they died)?

Mother's brothers: ☐☐ ☐☐ ☐☐ ☐☐ ☐☐

Father's brothers: ☐☐ ☐☐ ☐☐ ☐☐ ☐☐

l) How old is your father (or was he when he died)? ☐☐

m) Have any of these male relatives had prostate problems which were or may have been due to a cancer? ***yes*** ___ ***no*** ___

If yes: 1) how many were definitely due to a cancer? ☐☐

2) how many others may have been? ☐☐

n) How many sisters do you have? ☐☐

o) How old are they (or were they when they died)?

☐☐ ☐☐ ☐☐ ☐☐ ☐☐

p) How many aunts (sisters of your mother or father) do you have? ☐☐

q) How old are they (or were they when they died)?

Mother's sisters: ☐☐ ☐☐ ☐☐ ☐☐ ☐☐

Father's sisters: ☐☐ ☐☐ ☐☐ ☐☐ ☐☐

r) How old is your mother (or was she when she died)? ☐☐

s) Have any of these female relatives had breast problems which were or may have been due to a cancer? ***yes*** ___ ***no*** ___

If yes: 1) how many were definitely due to a cancer? ☐☐

2) how many others may have been? ☐☐

Thank-you for your help in completing this questionnaire.

All information provided on this questionnaire will be treated in strictest confidence.

8.3 Additional nutrient analysis results

Table 8.1: Distribution of all nutrient intakes by status

Nutrient Daily Intake Variables	Cases (n=437)		Controls (Population and BPH controls) (n=483)		Test for difference between Cases and Controls	
	Mean (s.d.)	Median (I-QR)	Mean (s.d.)	Median (I-QR)	T-test (p-value)	Mann-Whitney U Test (p-value)
Total Energy (kJ)	10584 (3344)	10165 (8369-12370)	10127 (3349)	9684 (7874-11757)	0.04	0.02
Protein (g)	100.69 (33.07)	96.10 (78.15-118.85)	96.34 (33.77)	92.10 (74.70-112.70)	0.05	0.03
Carbohydrate (g)	308.62 (103.10)	295.80 (239.65-368.35)	295.10 (103.91)	283.40 (224.20-344.40)	0.05	0.02
Total Fat (g)	95.95 (35.77)	91.30 (72.75-116.30)	90.51 (35.66)	84.90 (65.30-109.60)	0.02	0.007
Saturated Fat (g)	39.36 (16.71)	37.00 (27.55-48.15)	36.67 (15.83)	34.00 (25.30-46.30)	0.01	0.01
MUFA (g)	33.32 (12.34)	31.20 (25.50-40.60)	31.50 (12.71)	29.90 (22.80-38.30)	0.03	0.006
PUFA (g)	14.83 (6.29)	13.90 (10.50-17.90)	14.39 (6.51)	13.30 (9.70-17.80)	0.30	0.14
Cholesterol (mg)	401 (194)	368 (277-486)	362 (173)	326 (242-450)	0.002	<0.001
Total Sugar (g)	141.96 (61.90)	132.40 (100.35-171.20)	131.90 (58.17)	121.70 (92.70-157.50)	0.01	0.005
Starch (g)	169.68 (58.78)	162.90 (129.55-203.10)	165.38 (58.65)	157.10 (123.40-202.70)	0.27	0.19
Fibre (g)	20.18 (8.45)	18.70 (14.40-24.50)	19.78 (7.98)	18.40 (14.20-24.20)	0.46	0.51
Alcohol (g)	13.2 (15.1)	7.9 (1.8-20.3)	14.4 (14.6)	9.9 (3.4-21.6)	0.23	0.06
Sodium (mg)	3509 (1195)	3400 (2672-4199)	3366 (1174)	3192 (2579-3996)	0.07	0.04
Potassium (mg)	4230 (1439)	3920 (3283-5055)	4085 (1401)	3872 (3162-4728)	0.12	0.14
Calcium (mg)	1143 (400)	1110 (859-1373)	1101 (411)	1039 (812-1321)	0.12	0.04
Magnesium (mg)	386 (126)	359 (298-457)	375 (119)	361 (288-441)	0.15	0.25
Phosphorous (mg)	1765 (547)	1703 (1391-2061)	1694 (564)	1640 (1295-1958)	0.05	0.02
Iron (mg)	14.93 (5.17)	14.51 (11.15-17.60)	14.47 (4.93)	13.58 (11.09-17.05)	0.17	0.17
Copper (mg)	1.58 (0.61)	1.47 (1.17-1.83)	1.53 (0.57)	1.43 (1.14-1.78)	0.22	0.27
Zinc (mg)	12.53 (4.27)	12.09 (9.58-14.82)	12.00 (4.27)	11.49 (8.99-14.19)	0.06	0.04
Chloride (mg)	5372 (1811)	5218 (4135-6450)	5160 (1750)	4862 (3992-6052)	0.07	0.05
Manganese (mg)	4.63 (1.89)	4.45 (3.47-5.47)	4.57 (1.84)	4.34 (3.47-5.46)	0.63	0.46
Selenium (μg)	83 (45)	75 (58-98)	78 (33)	73 (56-94)	0.06	0.25

Cont.

Table 8.1, cont.: Distribution of all nutrient intakes by status

Nutrient Daily Intake Variables	Cases (n=437)		Controls (Population and BPH controls) (n=483)		Test for difference between Cases and Controls	
	Mean (s.d.)	Median (I-QR)	Mean (s.d.)	Median (I-QR)	T-test (p-value)	Mann-Whitney U Test (p-value)
Iodine (μg)	190 (92)	173 (130-229)	176 (80)	161 (121-213)	0.02	0.02
Retinol (μg)	759 (647)	582 (390-910)	701 (568)	571 (348-838)	0.15	0.15
Carotene (μg)	2690 (2156)	2143 (1185-3614)	2742 (2224)	2187 (1308-3447)	0.72	0.75
Vitamin D (μg)	4.00 (2.33)	3.63 (2.29-5.16)	3.94 (3.01)	3.14 (2.21-4.75)	0.76	0.09
Vitamin E (μg)	8.70 (4.86)	7.31 (5.35-10.97)	8.34 (4.63)	7.27 (4.89-10.56)	0.25	0.30
Vitamin C (mg)	110.4 (67.1)	97.2 (65.2-136.5)	104.7 (61.2)	90.5 (62.5-134.7)	0.18	0.19
Thiamine (mg)	2.19 (0.82)	2.08 (1.63-2.56)	2.14 (0.92)	2.00 (1.58-2.48)	0.32	0.16
Riboflavin (mg)	2.26 (0.78)	2.19 (1.69-2.73)	2.15 (0.78)	2.07 (1.62-2.52)	0.05	0.02
Niacin (mg)	23.67 (8.57)	22.44 (17.47-28.16)	23.17 (8.38)	21.99 (17.22-27.65)	0.37	0.52
Potential Niacin (mg)	21.05 (6.89)	20.01 (16.23-24.71)	20.15 (6.94)	19.30 (15.47-23.45)	0.05	0.03
Vitamin B6 (mg)	2.80 (1.03)	2.61 (2.08-3.37)	2.71 (0.98)	2.55 (2.02-3.23)	0.15	0.24
Vitamin B12 (μg)	7.21 (3.62)	6.56 (4.64-8.96)	6.95 (4.24)	5.89 (4.42-8.48)	0.32	0.04
Folic Acid (μg)	332 (118)	307 (244-402)	321 (111)	310 (246-377)	0.15	0.35
Pantothenic Acid (mg)	10.13 (8.86)	7.21 (5.60-10.45)	9.97 (8.60)	7.05 (5.47-10.79)	0.78	0.31
Biotin (ug)	53.09 (18.23)	51.70 (41.50-60.80)	51.61 (18.88)	49.00 (39.30-59.20)	0.23	0.05
Isoflavone (μg)	1975.87 (2455.09)	1143.20 (636.75-2444.50)	1835.72 (2828.21)	1050.90 (581.10-1982.80)	0.42	0.10
Isoflavone (with manual calculations) (μg)	2131.85 (3439.51)	1143.20 (636.75-2444.50)	1922.58 (3560.56)	1050.90 (581.10-2001.40)	0.37	0.11

N.B.
s.d. = Standard Deviation
I-QR = Inter-Quartile Range
MUFA = Mono Unsaturated Fat
PUFA = Poly Unsaturated Fat
Carotene = Carotene Equivalent
Vitamin E = α-Tocopherol Equivalent
Potential Niacin = Niacin from Tryptophan
Isoflavone = Daidzein and Genistein

Table 8.2: Correlation coefficients for nutrient intake

Correlations

			Energy (kJ)	Protein (g)	Total Fat (g)	Saturated Fat (g)	Mono Unsaturated Fat (g)	Poly Unsaturated Fat (g)	Cholesterol (mg)	Alcohol (g)	Calcium (mg)	Selenium (ug)	Retinol (ug)	Carotene Equivalent (ug)	Vitamin E (alpha tocopherol equivalent) (ug)	Vitamin C (mg)	Isoflavone (ug)
Spearman's rho	Energy (kJ)	Correlation Coefficient	1.000	.882**	.917**	.838**	.904**	.769**	.730**	.170**	.734**	.670**	.541**	.419**	.622**	.511**	.392**
		Sig. (2-tailed)	.	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Protein (g)	Correlation Coefficient	.882**	1.000	.823**	.721**	.825**	.733**	.750**	.125**	.739**	.729**	.481**	.461**	.540**	.471**	.291**
		Sig. (2-tailed)	.000	.	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Total Fat (g)	Correlation Coefficient	.917**	.823**	1.000	.947**	.984**	.768**	.823**	.071*	.683**	.621**	.651**	.345**	.582**	.329**	.382**
		Sig. (2-tailed)	.000	.000	.	.000	.000	.000	.000	.031	.000	.000	.000	.000	.000	.000	.000
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Saturated Fat (g)	Correlation Coefficient	.838**	.721**	.947**	1.000	.907**	.556**	.819**	.044	.665**	.495**	.690**	.269**	.398**	.256**	.322**
		Sig. (2-tailed)	.000	.000	.000	.	.000	.000	.000	.182	.000	.000	.000	.000	.000	.000	.000
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Mono Unsaturated Fat (g)	Correlation Coefficient	.904**	.825**	.984**	.907**	1.000	.777**	.826**	.085**	.654**	.621**	.620**	.337**	.574**	.317**	.376**
		Sig. (2-tailed)	.000	.000	.000	.000	.	.000	.000	.010	.000	.000	.000	.000	.000	.000	.000
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Poly Unsaturated Fat (g)	Correlation Coefficient	.769**	.733**	.768**	.556**	.777**	1.000	.521**	.107**	.523**	.673**	.375**	.403**	.852**	.398**	.400**
		Sig. (2-tailed)	.000	.000	.000	.000	.000	.	.000	.001	.000	.000	.000	.000	.000	.000	.000
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Cholesterol (mg)	Correlation Coefficient	.730**	.750**	.823**	.819**	.826**	.521**	1.000	.079*	.564**	.511**	.654**	.279**	.334**	.196**	.232**
		Sig. (2-tailed)	.000	.000	.000	.000	.000	.000	.	.017	.000	.000	.000	.000	.000	.000	.000
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Alcohol (g)	Correlation Coefficient	.170**	.125**	.071*	.044	.085**	.107**	.079*	1.000	-.015	.128**	.090**	.122**	.048	.083*	-.062
		Sig. (2-tailed)	.000	.000	.031	.182	.010	.001	.017	.	.643	.000	.006	.000	.143	.012	.060
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Calcium (mg)	Correlation Coefficient	.734**	.739**	.683**	.665**	.654**	.523**	.564**	-.015	1.000	.478**	.475**	.323**	.441**	.388**	.303**
		Sig. (2-tailed)	.000	.000	.000	.000	.000	.000	.000	.643	.	.000	.000	.000	.000	.000	.000
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Selenium (ug)	Correlation Coefficient	.670**	.729**	.621**	.495**	.621**	.673**	.511**	.128**	.478**	1.000	.339**	.418**	.507**	.408**	.332**
		Sig. (2-tailed)	.000	.000	.000	.000	.000	.000	.000	.000	.000	.	.000	.000	.000	.000	.000
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Retinol (ug)	Correlation Coefficient	.541**	.481**	.651**	.690**	.620**	.375**	.654**	.090**	.475**	.339**	1.000	.339**	.283**	.130**	.202**
		Sig. (2-tailed)	.000	.000	.000	.000	.000	.000	.000	.006	.000	.000	.	.000	.000	.000	.000
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Carotene Equivalent (ug)	Correlation Coefficient	.419**	.461**	.345**	.269**	.337**	.403**	.279**	.122**	.323**	.418**	.339**	1.000	.378**	.541**	.155**
		Sig. (2-tailed)	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.	.000	.000	.000
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Vitamin E (alpha tocopherol equivalent) (ug)	Correlation Coefficient	.622**	.540**	.582**	.398**	.574**	.852**	.334**	.048	.441**	.507**	.283**	.378**	1.000	.455**	.324**
		Sig. (2-tailed)	.000	.000	.000	.000	.000	.000	.000	.143	.000	.000	.000	.000	.	.000	.000
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Vitamin C (mg)	Correlation Coefficient	.511**	.471**	.329**	.256**	.317**	.398**	.196**	.083*	.388**	.408**	.130**	.541**	.455**	1.000	.151**
		Sig. (2-tailed)	.000	.000	.000	.000	.000	.000	.000	.012	.000	.000	.000	.000	.000	.	.000
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Isoflavone (ug)	Correlation Coefficient	.392**	.291**	.382**	.322**	.376**	.400**	.232**	-.062	.303**	.332**	.202**	.155**	.324**	.151**	1.000
		Sig. (2-tailed)	.000	.000	.000	.000	.000	.000	.000	.060	.000	.000	.000	.000	.000	.000	.
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916

**. Correlation is significant at the .01 level (2-tailed).

*. Correlation is significant at the .05 level (2-tailed).

Table 8.3: Crude and adjusted ORs for all nutrient intakes

Nutrient Variable		Frequency		Crude Odds Ratio		Adjusted Odds Ratio [a]	
		Case (n)	Control (n)	OR	(95% CI)	OR	(95% CI)
Total Energy (kJ)	0 - 7874	87	121	1.00	-		
	7874 - 9684	105	121	1.21	(0.82-1.77)		
	9684 - 11757	106	121	1.22	(0.83-1.78)		
	> 11757	135	120	1.56	(1.08-2.27)		
				Score test for linear trend [b], p = 0.022			
Protein (g)	0 - 74.7	92	121	1.00	-	1.00	-
	74.7 - 92.1	104	124	1.10	(0.76-1.61)	0.99	(0.67-1.46)
	92.1 - 112.7	104	118	1.16	(0.79-1.69)	0.91	(0.61-1.36)
	> 112.7	133	120	1.46	(1.01-2.11)	1.00	(0.67-1.48)
				Score test for linear trend [b], p = 0.042			
Carbohydrates (g)	0 - 224.2	82	121	1.00	-	1.00	-
	224.2 - 283.4	127	121	1.55	(1.06-2.26)	1.59	(1.07-2.37)
	283.4 - 344.4	85	121	1.04	(0.70-1.54)	1.35	(0.90-2.02)
	> 344.4	139	120	1.71	(1.17-2.49)	1.05	(0.69-1.60)
				Score test for linear trend [b], p = 0.040			
Total Fat (g)	0 - 65.3	73	121	1.00	-	1.00	-
	65.3 - 84.9	113	121	1.55	(1.05-2.29)	1.11	(0.75-1.64)
	84.9 - 109.6	112	121	1.53	(1.04-2.27)	1.11	(0.75-1.65)
	> 109.6	135	120	1.86	(1.27-2.74)	1.10	(0.74-1.65)
				Score test for linear trend [b], p = 0.003			
Saturated Fat (g)	0 - 25.3	83	123	1.00	-	1.00	-
	25.3 - 34.0	97	119	1.21	(0.82-1.78)	1.03	(0.69-1.54)
	34.0 - 46.3	127	121	1.56	(1.07-2.27)	1.03	(0.69-1.54)
	> 46.3	126	120	1.56	(1.07-2.27)	1.15	(0.77-1.72)
				Score test for linear trend [b], p = 0.009			
MUFA (g)	0 - 22.8	73	121	1.0	-	1.00	-
	22.8 - 29.9	117	124	1.56	(1.06-2.30)	1.17	(0.79-1.75)
	29.9 - 38.3	110	119	1.53	(1.04-2.27)	1.21	(0.81-1.81)
	> 38.3	133	119	1.85	(1.26-2.73)	1.25	(0.83-1.87)
				Score test for linear trend [b], p = 0.004			
PUFA (g)	0 - 9.7	90	123	1.00	-	1.00	-
	9.7 - 13.3	110	119	1.26	(0.87-1.84)	0.88	(0.60-1.30)
	13.3 - 17.8	124	121	1.40	(0.97-2.03)	1.01	(0.69-1.49)
	> 17.8	109	120	1.24	(0.85-1.81)	0.86	(0.57-1.28)
				Score test for linear trend [b], p = 0.221			

Table 8.3, cont.: Crude and adjusted ORs for all nutrient intakes

Nutrient Variable		Frequency		Crude Odds Ratio		Adjusted Odds Ratio [a]	
		Case (n)	Control (n)	OR	(95% CI)	OR	(95% CI)
Cholesterol (mg)	0 - 242	71	121	1.00	-	1.00	-
	242 - 326	92	122	1.29	(0.86-1.92)	0.95	(0.63-1.43)
	326 - 450	129	120	1.83	(1.24-2.70)	1.26	(0.85-1.88)
	> 450	141	120	2.00	(1.36-2.95)	1.57	(1.04-2.37)
				Score test for linear trend [b], p = 0.0001			
Total Sugar (g)	0 - 92.7	83	121	1.00	-	1.00	-
	92.7 - 121.7	106	121	1.28	(0.87-1.87)	1.30	(0.87-1.95)
	121.7 - 157.5	106	121	1.28	(0.87-1.87)	1.06	(0.69-1.61)
	> 157.5	138	120	1.68	(1.15-2.44)	1.57	(1.05-2.34)
				Score test for linear trend [b], p = 0.009			
Fibre (g)	0 - 14.2	103	121	1.00	-	1.00	-
	14.2 - 18.4	106	121	1.03	(0.71-1.49)	0.82	(0.55-1.22)
	18.4 - 24.2	109	124	1.03	(0.71-1.49)	1.11	(0.75-1.65)
	> 24.2	115	117	1.15	(0.80-1.67)	0.78	(0.52-1.18)
				Score test for linear trend [b], p = 0.462			
Alcohol (g)	0 - 3.4	129	122	1.00	-	1.00	-
	3.4 - 9.9	112	120	0.88	(0.62-1.26)	0.80	(0.55-1.17)
	9.9 - 21.6	102	122	0.79	(0.55-1.14)	0.72	(0.49-1.07)
	> 21.6	90	119	0.72	(0.49-1.04)	0.66	(0.44-0.99)
				Score test for linear trend [b], p = 0.060			
Sodium (mg)	0 - 2579	92	121	1.00	-	1.00	-
	2579 - 3192	95	121	1.03	(0.70-1.51)	0.94	(0.63-1.40)
	3192 - 3996	117	121	1.27	(0.88-1.85)	0.87	(0.59-1.30)
	> 3996	129	120	1.41	(0.98-2.05)	0.93	(0.63-1.38)
				Score test for linear trend [b], p = 0.035			
Calcium (mg)	0 - 812	84	121	1.00	-	1.00	-
	812 - 1039	104	121	1.24	(0.84-1.82)	1.15	(0.77-1.71)
	1039 - 1321	118	121	1.40	(0.96-2.05)	1.33	(0.90-1.97)
	> 1321	127	120	1.52	(1.05-2.22)	0.81	(0.54-1.23)
				Score test for linear trend [b], p = 0.022			
Phosphorus (mg)	0 - 1295	77	121	1.00	-	1.00	-
	1295 - 1640	115	121	1.49	(1.02-2.20)	1.34	(0.90-1.98)
	1640 - 1958	106	121	1.38	(0.93-2.03)	1.13	(0.76-1.69)
	> 1958	135	120	1.77	(1.21-2.59)	1.03	(0.69-1.54)
				Score test for linear trend [b], p = 0.008			

Table 8.3, cont.: Crude and adjusted ORs for all nutrient intakes

Nutrient Variable		Frequency		Crude Odds Ratio		Adjusted Odds Ratio [a]	
		Case (n)	Control (n)	OR	(95% CI)	OR	(95% CI)
Zinc (mg)	0 - 8.99	88	121	1.00	-	1.00	-
	8.99 - 11.49	105	121	1.19	(0.82-1.74)	0.88	(0.59-1.30)
	11.49 - 14.19	115	121	1.31	(0.90-1.90)	0.99	(0.67-1.46)
	> 14.19	125	120	1.43	(0.99-2.08)	0.90	(0.60-1.32)
				Score test for linear trend [b], p = 0.053			
Chloride (mg)	0 - 3992	94	121	1.00	-	1.00	-
	3992 - 4862	92	121	0.98	(0.67-1.44)	1.21	(0.82-1.79)
	4862 - 6052	115	121	1.22	(0.84-1.77)	0.83	(0.55-1.24)
	> 4862	132	120	1.42	(0.98-2.04)	0.97	(0.65-1.43)
				Score test for linear trend [b], p = 0.030			
Selenium (µg)	0 - 56	102	121	1.00	-	1.00	-
	56 - 73	103	122	1.00	(0.69-1.45)	0.92	(0.62-1.35)
	73 - 94	105	122	1.02	(0.70-1.48)	0.67	(0.45-0.99)
	> 94	123	118	1.24	(0.86-1.78)	0.88	(0.59-1.29)
				Score test for linear trend [b], p = 0.257			
Iodine (µg)	0 - 121	90	121	1.00	-	1.00	-
	121 - 161	103	122	1.14	(0.77-1.66)	1.57	(1.06-2.34)
	161 - 213	106	120	1.19	(0.81-1.73)	1.20	(0.79-1.81)
	> 213	134	120	1.50	(1.04-2.17)	1.29	(0.86-1.94)
				Score test for linear trend [b], p = 0.030			
Retinol (µg)	0 - 348	86	121	1.00	-	1.00	-
	348 - 571	124	121	1.44	(0.99-2.10)	1.11	(0.75-1.65)
	571 - 838	98	121	1.14	(0.78-1.67)	0.94	(0.63-1.40)
	> 838	125	120	1.47	(1.01-2.13)	1.21	(0.82-1.80)
				Score test for linear trend [b], p = 0.141			
Carotene (µg)	0 - 1308	117	121	1.00	-	1.00	-
	1308 - 2187	103	121	0.88	(0.61-1.27)	0.73	(0.49-1.07)
	2187 - 3447	95	121	0.81	(0.56-1.18)	0.77	(0.52-1.13)
	> 3447	118	120	1.02	(0.71-1.46)	0.76	(0.51-1.14)
				Score test for linear trend [b], p = 0.972			
Vitamin D (µg)	0 - 2.21	99	121	1.00	-	1.00	-
	2.21 - 3.14	81	123	0.80	(0.55-1.19)	0.97	(0.65-1.44)
	3.14 - 4.75	126	119	1.30	(0.90-1.87)	1.07	(0.72-1.58)
	> 4.75	127	120	1.29	(0.90-1.86)	1.02	(0.69-1.52)
				Score test for linear trend [b], p = 0.036			

Table 8.3, cont.: Crude and adjusted ORs for all nutrient intakes

Nutrient Variable		Frequency		Crude Odds Ratio		Adjusted Odds Ratio [a]	
		Case (n)	Control (n)	OR	(95% CI)	OR	(95% CI)
Vitamin E (μg)	0 - 4.89	82	121	1.00	-	1.00	-
	4.89 - 7.27	131	121	1.60	(1.10-2.33)	0.92	(0.62-1.37)
	7.27 - 10.56	103	121	1.26	(0.85-1.85)	1.07	(0.72-1.57)
	> 10.56	117	120	1.44	(0.98-2.11)	0.86	(0.57-1.28)
				Score test for linear trend [b], p =0.206			
Vitamin C (mg)	0 - 62.5	103	121	1.00	-	1.00	-
	62.5 - 90.5	92	121	0.89	(0.61-1.30)	1.13	(0.76-1.69)
	90.5 - 134.7	126	121	1.22	(0.85-1.76)	1.12	(0.75-1.67)
	> 134.7	112	120	1.10	(0.76-1.58)	1.18	(0.79-1.78)
				Score test for linear trend [b], p = 0.320			
Riboflavin (mg)	0 - 1.62	92	121	1.00	-	1.00	-
	1.62 - 2.07	104	122	1.12	(0.77-1.64)	1.21	(0.81-1.80)
	2.07 - 2.52	104	123	1.11	(0.76-1.62)	1.20	(0.81-1.77)
	> 2.52	133	117	1.50	(1.03-2.16)	1.10	(0.74-1.64)
				Score test for linear trend [b], p = 0.039			
Potential Niacin (mg)	0 - 15.47	92	121	1.00	-	1.00	-
	15.47 - 19.30	102	121	1.11	(0.76-1.62)	0.91	(0.62-1.36)
	19.30 - 23.45	102	121	1.11	(0.76-1.62)	0.90	(0.61-1.34)
	> 23.45	137	120	1.50	(1.04-2.17)	1.02	(0.69-1.52)
				Score test for linear trend [b], p = 0.033			
Vitamin B12 (μg)	0 - 4.42	99	121	1.00	-	1.00	-
	4.42 - 5.89	83	121	0.84	(0.57-1.23)	0.99	(0.66-1.47)
	5.89 - 8.48	130	121	1.31	(0.91-1.89)	1.25	(0.85-1.84)
	> 8.48	121	120	1.23	(0.85-1.78)	1.10	(0.74-1.63)
				Score test for linear trend [b], p = 0.072			
Biotin (ug)	0 - 39.3	87	121	1.00	-	1.00	-
	39.3 - 49.0	105	121	1.21	(0.82-1.77)	1.12	(0.75-1.66)
	49.0 - 59.2	118	122	1.35	(0.92-1.96)	1.12	(0.76-1.66)
	> 59.2	123	119	1.44	(0.99-2.09)	1.03	(0.69-1.53)
				Score test for linear trend [b], p = 0.048			

Table 8.3, cont.: Crude and adjusted ORs for all nutrient intakes

Nutrient Variable		Frequency		Crude Odds Ratio		Adjusted Odds Ratio [a]	
		Case (n)	Control (n)	OR	(95% CI)	OR	(95% CI)
Isoflavones (µg)	0 - 581.1	95	121	1.00	-	1.00	-
	581.1 - 1050.9	100	121	1.05	(0.72-1.54)	1.12	(0.76-1.67)
	1050.9 - 1982.8	112	121	1.18	(0.81-1.71)	1.11	(0.75-1.65)
	> 1982.8	126	120	1.34	(0.93-1.93)	1.18	(0.79-1.75)
				Score test for linear trend [b], p = 0.094			
Isoflavones (with manual calculations) (µg)	0 - 581.1	95	121	1.00	-	1.00	-
	581.1 - 1050.9	100	121	1.05	(0.72-1.54)	1.14	(0.77-1.70)
	1050.9 - 1982.8	112	120	1.19	(0.82-1.73)	1.13	(0.76-1.67)
	> 1982.8	126	121	1.33	(0.92-1.92)	1.18	(0.79-1.75)
				Score test for linear trend [b], p = 0.100			

N.B.
MUFA = Mono unsaturated Fat
PUFA = Poly unsaturated Fat
EI = Energy Intake
[a] = Adjusted for EI (residual method), Family History of PCa and BrCa, Deprivation Index, Smoking and EI/BMR Ratio.
[b] = Crude ORs only.

Table 8.4: Crude ORs for confounding variables

Nutrient Variable		Frequency		Crude OR	
		Case (n)	Control (n)	OR	(95% CI)
Age (years)	50 - 62	88	120	1.00	-
	63 - 66	99	121	1.12	(0.76-1.64)
	67 - 69	73	122	0.82	(0.55-1.22)
	70 - 74	173	120	1.97	(1.36-2.83)
				Score test for linear trend, p < 0.001	
Family history	No family history of PCa or BrCa	298	387	1.00	-
	Family history of PCa	60	38	2.05	(1.32-3.17)
	Family history of BrCa	58	48	1.56	(1.03-2.37)
	Family history of PCa and BrCa	17	10	2.21	(0.99-4.91)
				Score test for linear trend, p < 0.001	
Carstairs deprivation index	1	69	66	1.00	-
	2	64	73	0.84	(0.52-1.35)
	3	97	103	0.90	(0.58-1.40)
	4	75	93	0.77	(0.49-1.21)
	5	54	69	0.75	(0.46-1.23)
	6	31	33	0.90	(0.49-1.63)
	7	37	35	1.01	(0.57-1.79)
				Score test for linear trend, p = 0.724	
Smoking status	Non Smoker	175	229	1.00	-
	Ex Smoker	174	168	1.36	(1.01-1.81)
	Smoker	76	79	1.26	(0.87-1.83)
				Score test for linear trend, p = 0.10	
EI: BMR ratio	< 1.17	79	116	1.0	-
	1.17 - 1.45	106	117	1.33	(0.90-1.96)
	1.46 - 1.78	98	117	1.23	(0.83-1.82)
	> 1.78	138	116	1.75	(1.19-2.56)
				Score test for linear trend , p = 0.008	

N.B. PCa = prostate cancer, BrCa = breast cancer

Table 8.5: Correlation coefficients for food groups

Correlations

			Total Dairy	Milk	Cheese	Eggs	Total meat	Red meat	Fish	Processed Meat	Soy Foods	Total Vegetables	Total Fruit	Beer	Wine	Spirits	Grilled meat	Grilled Meat Score
Spearman's rho	Total Dairy	Correlation Coefficient	1.000	.787**	.493**	.087**	.093**	.062	.085**	.097**	.037	.113**	.068*	.041	.057	-.067*	.099**	.102**
		Sig. (2-tailed)	.	.000	.000	.009	.005	.060	.010	.003	.259	.001	.039	.214	.084	.044	.003	.002
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Milk	Correlation Coefficient	.787**	1.000	.137**	.065*	.074*	.056	.006	.082*	.000	.006	-.017	-.024	-.082*	-.082*	.101**	.116**
		Sig. (2-tailed)	.000	.	.000	.048	.025	.089	.846	.013	.997	.866	.614	.465	.013	.013	.002	.000
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Cheese	Correlation Coefficient	.493**	.137**	1.000	.154**	.161**	.141**	.161**	.154**	.039	.166**	.076*	.163**	.159**	.070*	.077*	.047
		Sig. (2-tailed)	.000	.000	.	.000	.000	.000	.000	.000	.238	.000	.021	.000	.000	.034	.020	.152
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Eggs	Correlation Coefficient	.087**	.065*	.154**	1.000	.333**	.394**	.088**	.277**	-.048	.032	-.060	.189**	-.130**	.106**	.262**	.239**
		Sig. (2-tailed)	.009	.048	.000	.	.000	.000	.008	.000	.144	.338	.068	.000	.000	.001	.000	.000
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Total meat	Correlation Coefficient	.093**	.074*	.161**	.333**	1.000	.853**	.212**	.797**	-.114**	.250**	.056	.222**	-.023	.149**	.363**	.314**
		Sig. (2-tailed)	.005	.025	.000	.000	.	.000	.000	.000	.001	.000	.088	.000	.494	.000	.000	.000
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Red meat	Correlation Coefficient	.062	.056	.141**	.394**	.853**	1.000	.132**	.564**	-.126**	.156**	-.020	.221**	-.077*	.152**	.430**	.377**
		Sig. (2-tailed)	.060	.089	.000	.000	.000	.	.000	.000	.000	.000	.538	.000	.019	.000	.000	.000
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Fish	Correlation Coefficient	.085**	.006	.161**	.088**	.212**	.132**	1.000	.139**	.087**	.403**	.236**	.113**	.206**	.120**	.033	.027
		Sig. (2-tailed)	.010	.846	.000	.008	.000	.000	.	.000	.009	.000	.000	.001	.000	.000	.312	.421
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Processed Meat	Correlation Coefficient	.097**	.082*	.154**	.277**	.797**	.564**	.139**	1.000	-.055	.127**	.007	.221**	-.069*	.108**	.303**	.281**
		Sig. (2-tailed)	.003	.013	.000	.000	.000	.000	.000	.	.098	.000	.824	.000	.037	.001	.000	.000
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Soy Foods	Correlation Coefficient	.037	.000	.039	-.048	-.114**	-.126**	.087**	-.055	1.000	.094**	.072*	-.038	.027	-.073*	-.108**	-.066*
		Sig. (2-tailed)	.259	.997	.238	.144	.001	.000	.009	.098	.	.004	.030	.252	.414	.027	.001	.045
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Total Vegetables (excluding potatoes)	Correlation Coefficient	.113**	.006	.166**	.032	.250**	.156**	.403**	.127**	.094**	1.000	.439**	.117**	.184**	.090**	.011	.001
		Sig. (2-tailed)	.001	.866	.000	.338	.000	.000	.000	.000	.004	.	.000	.000	.000	.007	.748	.984
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Total Fruit	Correlation Coefficient	.068*	-.017	.076*	-.060	.056	-.020	.236**	.007	.072*	.439**	1.000	-.021	.111**	-.042	-.123**	-.099**
		Sig. (2-tailed)	.039	.614	.021	.068	.088	.538	.000	.824	.030	.000	.	.531	.001	.208	.000	.003
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Beer	Correlation Coefficient	.041	-.024	.163**	.189**	.222**	.221**	.113**	.221**	-.038	.117**	-.021	1.000	.092**	.265**	.116**	.106**
		Sig. (2-tailed)	.214	.465	.000	.000	.000	.000	.001	.000	.252	.000	.531	.	.005	.000	.000	.001
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Wine	Correlation Coefficient	.057	-.082*	.159**	-.130**	-.023	-.077*	.206**	-.069*	.027	.184**	.111**	.092**	1.000	.197**	-.034	-.075*
		Sig. (2-tailed)	.084	.013	.000	.000	.494	.019	.000	.037	.414	.000	.001	.005	.	.000	.309	.023
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Spirits	Correlation Coefficient	-.067*	-.082*	.070*	.106**	.149**	.152**	.120**	.108**	-.073*	.090**	-.042	.265**	.197**	1.000	.143**	.101**
		Sig. (2-tailed)	.044	.013	.034	.001	.000	.000	.000	.001	.027	.007	.208	.000	.000	.	.000	.002
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Grilled meat	Correlation Coefficient	.099**	.101**	.077*	.262**	.363**	.430**	.033	.303**	-.108**	.011	-.123**	.116**	-.034	.143**	1.000	.897**
		Sig. (2-tailed)	.003	.002	.020	.000	.000	.000	.312	.000	.001	.748	.000	.000	.309	.000	.	.000
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
	Grilled Meat Score	Correlation Coefficient	.102**	.116**	.047	.239**	.314**	.377**	.027	.281**	-.066*	.001	-.099**	.106**	-.075*	.101**	.897**	1.000
		Sig. (2-tailed)	.002	.000	.152	.000	.000	.000	.421	.000	.045	.984	.003	.001	.023	.002	.000	.
		N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916

**. Correlation is significant at the .01 level (2-tailed).

*. Correlation is significant at the .05 level (2-tailed).

Table 8.6.: Correlations between food groups and nutrient intake

		Total Dairy	Milk	Cheese	Eggs	Total meat	Red meat	Processed Meat	Fish	Grilled Meat	Grilled Meat Score	Soy Foods	Total Vegetables	Total Fruit	Alcohol consumption	Beer	Wine	Spirits
Energy (kJ)	Rho	**.346**	**.250**	**.309**	**.296**	**.544**	**.499**	**.412**	**.373**	**.177**	**.159**	.019	**.450**	**.337**	**.090**	**.196**	.010	**.110**
	P value	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.566	.000	.000	.007	.000	.760	.001
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Protein (g)	Rho	**.398**	**.313**	**.325**	**.340**	**.688**	**.622**	**.458**	**.478**	**.199**	**.184**	-.007	**.482**	**.274**	**.077**	**.182**	-.019	**.087**
	P value	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.822	.000	.000	.019	.000	.565	.008
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Total Fat (g)	Rho	**.348**	**.247**	**.371**	**.384**	**.578**	**.564**	**.446**	**.322**	**.232**	**.210**	.029	**.322**	**.174**	.055	**.133**	-.038	.064
	P value	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.381	.000	.000	.097	.000	.252	.052
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Saturated Fat (g)	Rho	**.389**	**.285**	**.395**	**.366**	**.516**	**.523**	**.395**	**.206**	**.241**	**.214**	-.020	**.215**	**.118**	.035	**.102**	-.057	.050
	P value	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.551	.000	.000	.296	.002	.085	.130
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
MUFA (g)	Rho	**.311**	**.221**	**.343**	**.404**	**.607**	**.594**	**.472**	**.334**	**.249**	**.224**	.032	**.322**	**.167**	.056	**.147**	-.033	**.077**
	P value	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.327	.000	.000	.089	.000	.319	.019
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
PUFA (g)	Rho	**.205**	**.107**	**.270**	**.238**	**.475**	**.394**	**.378**	**.462**	**.118**	**.110**	**.110**	**.468**	**.244**	**.094**	**.142**	.044	**.070**
	P value	.000	.001	.000	.000	.000	.000	.000	.000	.000	.001	.001	.000	.000	.004	.000	.181	.035
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Cholesterol (mg)	Rho	**.272**	**.209**	**.297**	**.712**	**.619**	**.639**	**.441**	**.263**	**.279**	**.242**	-.063	**.199**	**.073**	.026	**.159**	**-.109**	**.071**
	P value	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.058	.000	.028	.424	.000	.001	.031
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Alcohol (g)	Rho	.047	-.053	**.178**	**.119**	**.185**	**.162**	**.151**	**.199**	**.156**	**.099**	**-.071**	**.163**	-.011	**.644**	**.607**	**.517**	**.634**
	P value	.156	.107	.000	.000	.000	.000	.000	.000	.000	.003	.032	.000	.747	.000	.000	.000	.000
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916

Table 8.6, cont.: Correlations between food groups and nutrient intake

		Total Dairy	Milk	Cheese	Eggs	Total meat	Red meat	Processed Meat	Fish	Grilled Meat	Grilled Meat Score	Soy Foods	Total Vegetables	Total Fruit	Alcohol consumption	Beer	Wine	Spirits
Calcium (mg)	Rho	**.749**	**.660**	**.417**	**.226**	**.305**	**.262**	**.270**	**.259**	**.136**	**.144**	.057	**.312**	**.243**	-.008	**.074**	-.064	-.054
	P value	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.087	.000	.000	.820	.025	.054	.102
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Selenium (ug)	Rho	**.212**	**.129**	**.249**	**.240**	**.409**	**.360**	**.273**	**.589**	**.109**	**.108**	**.107**	**.467**	**.260**	**.118**	**.140**	**.072**	**.099**
	P value	.000	.000	.000	.000	.000	.000	.000	.000	.001	.001	.001	.000	.000	.000	.000	.029	.003
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Retinol (ug)	Rho	**.345**	**.235**	**.314**	**.356**	**.377**	**.420**	**.299**	**.199**	**.200**	**.176**	-.038	**.105**	.005	.055	**.093**	-.012	.043
	P value	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.247	.001	.884	.099	.005	.715	.196
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Carotene Equivalent (ug)	Rho	**.155**	.037	**.168**	**.089**	**.271**	**.218**	**.152**	**.370**	**.067**	.062	.065	**.789**	**.356**	**.142**	**.099**	**.152**	.045
	P value	.000	.262	.000	.007	.000	.000	.000	.000	.044	.059	.050	.000	.000	.000	.003	.000	.171
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Vitamin E (ug)	Rho	**.189**	.086	**.225**	**.131**	**.291**	**.198**	**.238**	**.323**	.031	.033	**.108**	**.450**	**.364**	.044	**.071**	.051	-.003
	P value	.000	.009	.000	.000	.000	.000	.000	.000	.347	.315	.001	.000	.000	.183	.031	.124	.930
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Vitamin C (mg)	Rho	**.191**	**.066**	**.171**	-.009	**.189**	**.105**	**.097**	**.342**	-.010	-.005	**.093**	**.681**	**.726**	**.081**	**.066**	**.174**	.012
	P value	.000	.046	.000	.779	.000	.001	.003	.000	.758	.878	.005	.000	.000	.014	.047	.000	.710
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916
Isoflavone (ug)	Rho	**.143**	**.107**	**.100**	.019	**.122**	**.101**	**.130**	**.104**	.007	.043	**.285**	**.127**	**.084**	.010	.023	.029	**-.090**
	P value	.000	.001	.003	.576	.000	.002	.000	.002	.827	.191	.000	.000	.011	.767	.491	.380	.006
	N	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916	916

Significant correlation coefficients ($p < 0.05$) are highlighted in **bold**

8.4 Subject Correspondance

8.4.1 Study Summaries:

SS1: Study summary for health professionals

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Cancer, Inherited Susceptibility and Diet

STUDY SUMMARY

AIM

To investigate associations between diet, inherited susceptibility and clinically important prostate cancer.

DESIGN AND HYPOTHESES

An epidemiological case-control study will compare (a) recent diet (b) diet during adolescence and (c) polymorphic variants of the androgen receptor gene in cases of prostate cancer (stage ≥ T2, Gleason score ≥4) and controls. Particular attention will be focused on dietary fat and dietary phyto-estrogens.

SETTING

Greater Glasgow, Lothian and Borders Health Board regions.

SUBJECTS

Men with prostate cancer aged 50-74 years and resident in one of the study areas diagnosed (for the first time) from 1/04/98 and controls of the same age (i) selected randomly from GP and/or Health Board lists, (ii) with benign prostate hyperplasia, and (iii) with incidental prostate cancer diagnosed at least 5 years ago.

Men are ineligible if mentally unable to complete a food frequency questionnaire and ineligible as controls (i), (ii) if they have had a diagnosis of prostate cancer.

DATA AND PROCEDURES

Epidemiological data will be collected by self-completed food frequency questionnaires (FFQ) which have previously been validated in Scotland. In addition, a 20ml venepuncture blood sample will be collected from consenting subjects. Serum will be analysed to quantify phyto-estrogen content. 5-α-reductase activity will also be measured in serum from controls to test for association with phyto-estrogen content. Polymorphic repeats lengths of sequences CAG and GGC in the androgen receptor gene will be compared in cases of controls.

For further details, copies of the protocol or discussion, please contact Professor Freda Alexander, Dr Caroline Bolton-Smith, Dr Fouad Habib or Dr Mike Morton at:

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Cardiovascular Epidemiology Unit
University of Dundee
Ninewells Hospital & Medical School
Dundee DD1 9SY

Dr Fouad Habib
University of Edinburgh
Department of Oncology
Western General Hospital
Crewe Road
Edinburgh EH4 2XU

Dr Mike Morton
Bioclinical Services International
Units 1-3
Willowbrook Laboratories
Crickhowell Road
St Mellons, Cardiff CF3 OEF

SS2: Study summary for subjects

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Cancer, Inherited Susceptibility and Diet

STUDY SUMMARY

AIM

The aim of this study is to investigate dietary factors which we believe may, in some instances, increase and in others, decrease risk of prostate cancer occurring or progressing. In order to do this, we need information from people with prostate cancer to compare with similar information from people without it.

WHAT DOES IT INVOLVE?

If you are willing to take part, it will involve you completing a simple questionnaire about your diet. This can be completed at home and generally takes a little under an hour; it can be returned in a prepaid envelope. All information will be treated confidentially and no individuals will be identified in published results.

WHY SHOULD I HELP?

If we knew why people developed prostate cancer, then attempts could be made to prevent it. To do this, we need information from people like yourselves.

WHO IS INCLUDED?

Up to 600 men with prostate cancer and the same number without the disease, resident mainly in the Lothians, Greater Glasgow and the Borders, but including some from the rest of Scotland.

WILL THERE BE ANYTHING ELSE?

People who complete the questionnaire will be asked if they are willing to provide a small sample of blood which will normally be collected at a routine hospital visit (those with prostate cancer) or at your GP practice. This will be very useful to us but if you do not wish to do this, then you are under no obligation to do so. We should still like you to complete the questionnaire.

The same people will be asked for their consent for us to check hospital notes (those with prostate cancer) and GP notes (others – to check treatment for prostate disease).

WHAT IF I DO NOT WANT TO TAKE PART?

Just let us know and we will not bother you again. This will have no affect on your future health care.

IF I HAVE ANY QUESTIONS WHOM DO I ASK?

The Senior Scientists responsible for this study are:

Professor Freda Alexander
Department of Public Health Sciences
University of Edinburgh
Medical School
Teviot Place
Edinburgh EH8 9AG

Dr Caroline Bolton-Smith
Cardiovascular Epidemiology Unit
University of Dundee
Ninewells Hospital & Medical School
Dundee DD1 9SY

SS3: Study summary for cases: Analysis of blood samples

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Disease, Inherited Susceptibility and Diet

We know little about the causes of prostate tumours but we do know that the disease is under hormonal control and that risk is much less for men living in countries like China and Japan than those in countries like Scotland. These two pieces of information suggest that:

Diet with high levels of substances similar to the female hormone estrogen may protect against prostate tumours. Soy products contain large amounts of these `phyto-estrogens`.

Inherited factors may influence risk.

Some genes occur naturally in alternative (healthy) forms with different frequencies for Western and Oriental men. Scientists believe that one or more of these may be an inherited influence on risk of prostate tumours.

The questionnaire will have asked about your consumption of substances containing phyto-estrogens but we should like to check the results by measuring phyto-estrogens in your circulation. This is one reason why a blood sample will assist our research.

The second reason is that we should like to compare the genes mentioned above in men with and without prostate disease. To do this, genetic material (DNA) will, with your consent, be extracted and examined for the genes it contains.

We therefore invite you to help us further in our research by donating a sample of blood. We are collecting such samples from people who have had prostate tumours (like yourself) and from other men of similar age who have not. If you agree, then a small amount (20ml, which is about 3 teaspoonsful) of blood will be collected from an arm vein. It can be collected when you are having blood taken at the hospital for routine follow-up checks. It will be posted to Cardiff and the Western General Hospital in Edinburgh for analysis in specialist laboratories. These laboratories will store the samples securely and destroy them when the study is completed.

Genetic information from this study will not be made available either to subjects in the study or to any third party.

When our results are published it will not be possible to identify any individual participant.

Dr Freda Alexander
Department of Public Health Sciences
University of Edinburgh
Medical School
Teviot Place, Edinburgh EH8 9AG

Dr Fouad Habib
University of Edinburgh
Department of Oncology
Western General Hospital
Crewe Road
Edinburgh EH4 2XU

Dr Michael Morton
Bioclinical Services International
Units 1-3
Willowbrook Laboratories
Crickhowell Road
St Mellons, Cardiff CF3 OEF

SS4: Study summary for controls: Analysis of blood samples

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Cancer, Inherited Susceptibility and Diet

We know little about the causes of prostate cancer but we do know that the disease is under hormonal control and that risk is much less for men living in countries like China and Japan than those in countries like Scotland. These two pieces of information suggest that:

Diet with high levels of substances similar to the female hormone estrogen may protect against prostate cancer. Soy products contain large amounts of these `phyto-estrogens`.

Inherited factors may influence risk.

Some genes occur naturally in alternative (healthy) forms with different frequencies for Western and Oriental men. Scientists believe that one or more of these may be an inherited influence or risk on prostate cancer.

The questionnaire will have asked about your consumption of substances containing phyto-estrogens but we should like to check the results by measuring phyto-estrogens in your circulation. This is one reason why a blood sample will assist our research. We should also like to measure certain hormones believed to influence prostate cancer to see whether their levels are changed by phyto-estrogens.

The second reason why a blood sample would assist us is that we should like to compare the genes mentioned above in men with and without prostate disease. To do this, genetic material (DNA) will, with your consent, be extracted and examined for the genes it contains.

We therefore invite you to help us further in our research by donating a sample of blood. We are collecting such samples from people who have had prostate cancer and from other men of similar age who have not (like yourself). If you agree, then a small amount (20ml, which is about 3 teaspoonsful) of blood will be collected from an arm vein. It can be collected when you are having blood taken at the hospital for routine follow-up checks. It will be posted to the Tenovus laboratory in Cardiff and the Western General Hospital in Edinburgh for analysis in specialist laboratories. These laboratories will store the samples securely and destroy them when the study is completed.

Genetic information from this study will not be made available either to subjects in the study or to any third party.

When our results are published it will not be possible to identify any individual participant.

Professor Freda Alexander
Department of Public Health Sciences
University of Edinburgh
Medical School
Teviot Place
Edinburgh EH8 9AG

Dr Fouad Habib
University of Edinburgh
Department of Oncology
Western General Hospital
Crewe Road
Edinburgh EH4 2XU

Dr Michael Morton
Bioclincal Services International
Units 1-3
Willowbrook Laboratories
Crickhowell Road
St Mellons, Cardiff CF3 OEF

8.4.2 Case Correspondence

CA01: Approach to treating consultant

«TREATING_CONSULTANT»
«TREATING_HOSP»
«CONSADDRESS1»
«CONSADDRESS2»
«CONSADDRESS3»

<<DATE>>

Dear «TREATING_CONSULTANT»

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Cancer, Inherited Susceptibility and Diet

Re: «FIRST_NAME» «LAST_NAME»: Date of birth: «DOB»: Unit No: «UNIT_NO»

PCANDIET is in a case control study of prostate cancer in adults in the south of Scotland (see Study Summary). With your permission, we would like to approach the patient named above. The study would involve the patient completing a food frequency questionnaire and, with the patients' consent, a blood sample being drawn by my nurse or your phlebotomist.

I would be grateful if you would complete and return the enclosed form stating whether or not you are willing for us to contact this patient.

This study has the approval of the relevant ethical committee(s).

If you have any other comments or wish to know more of this study, please contact me personally at this address.

Thanking you for your assistance.

Yours sincerely

Freda Alexander

Professor of Cancer Epidemiology

Enc. SS1, CA01R, SAE

CA01R: Treating consultant reply / consent form

Study No:«STUDY_NO»

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Cancer, Inherited Susceptibility and Diet

Re: «FIRST_NAME» «LAST_NAME»: Date of birth: «DOB»

*I give my permission for you to ask the above to participate in the named study and for you to view the relevant hospital notes, subject to the consent of the patient.

*I wish to make the approach to this patient myself.

*This patient is ineligible (diagnosed earlier than 1/04/98 or mentally incapable of completing the questionnaire).

*I do not wish this patient to be approached (but he is eligible).

Signed.....Date.....

Patient's home address:

.....
.....

GP Name and address:

.....
.....

Any personal/family circumstances of relevance: .....
.....

***Delete whichever is not applicable**

Please return this form in the enclosed addressed, prepaid envelope.

CA02: Approach to case

Mr «FIRST_NAME» «LAST_NAME»
«ADDRESS_LINE_1»
«ADDRESS_LINE_2»
«ADDRESS_LINE_3»

<<DATE>>

Dear Mr «LAST_NAME»

We are conducting a survey in your area to investigate possible causes of prostate cancer and your Consultant, «TREATING_CONSULTANT», has given permission for us to invite you to be included in our study.

If you will agree to help us in this research, it would involve you completing a diet questionnaire which will take 2hour -12 hours. The information will be regarded as strictly confidential and will be seen only by myself and other members of the research team. We would also wish to review your confidential medical records at «TREATING_HOSP».

People who complete the food frequency questionnaires will also be asked if they are willing to provide a blood sample. You are, of course, free to decline this part of the study.

Your decision to participate in this study or not to participate, will have no influence on your treatment. If you do participate you are, of course, free to change your mind and withdraw at any time.

This study has been approved by the following ethical committees:

Borders Health Board, Glasgow Royal Infirmary, Lothian Health Board, Stobhill NHS Trust, Southern General, Glasgow and the West Glasgow Hospitals NHS Trust.

I enclose a form and self addressed, prepaid envelope and I would be very grateful if you would complete and return this to me.

Thank you for your time.

Yours sincerely

Freda Alexander

Professor of Epidemiology

Encs: SS2, CA02R, SAE

CA02R: Case reply / consent form

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Cancer, Inherited Susceptibility and Diet

Mr «FIRST_NAME» «LAST_NAME»

*I am willing to take part in the above study. Please send me a diet questionnaire.

I am willing/not willing* for you to inform my GP that I am taking part in this study (it is a normal courtesy for us to do this).

*I am willing/not willing for you to check my medical records at «TREATING_HOSP»

*I am not willing to take part in this study.

SIGNATURE: ..... DATE: .....

Title: Mr Other

My telephone number is..... (Home)

My telephone number is..... (Work)

***Delete whichever is not applicable**

CA03: FFQ cover letter to case

Mr «FIRST_NAME» «LAST_NAME»
«ADDRESS_LINE_1»
«ADDRESS_LINE_2»
«ADDRESS_LINE_3»

<<DATE>>

Dear Mr «LAST_NAME»

Thank you for agreeing to take part in our study.

I am enclosing a food questionnaire. If you have any difficulty in completing it, please telephone my assistant, Morag Leitch (Freephone number 0800 783 5281).

Thank you for helping us.

Yours sincerely

Freda Alexander

Professor of Epidemiology

Enc. Food frequency questionnaire, information sheet

CA04: Information letter to GP, re: case approach

Dr «GP»
«GPADDRESS1»
«GPADDRESS2»
«GPADDRESS_3»
«POSTCODE»

27 May 2005

Dear Dr «GPSAL»

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Cancer, Inherited Susceptibility and Diet

Re: Name: «FIRST_NAME» «LAST_NAME»: Date of birth: «DOB»

Your patient has been approached, with the consent of the treating consultant, and has agreed to take part in this study.

He will be completing a food frequency questionnaire and will possibly be providing a small venepuncture blood sample for analyses of serum phyto-estrogens.

Yours sincerely

Freda Alexander

Professor of Cancer Epidemiology

Enc: SS1

CA05: Request for blood sample from case

Mr «FIRST_NAME» «LAST_NAME»
«ADDRESS_LINE_1»
«ADDRESS_LINE_2»
«ADDRESS_LINE_3»

27 May 2005

Dear Mr «LAST_NAME»

Thank you very much for sending me the completed dietary questionnaire. This will be very helpful for our research.

As I indicated in the information sheet I sent you initially, we are asking everyone who, like yourself, has completed the questionnaire if they will help us further by providing a small blood sample. I am enclosing an information sheet. If you are willing to provide a sample then it can be collected next time you go to the clinic for a check up.

Please return the form to me to indicate whether or not you wish to take part in this extra part of the study.

Whatever, your choice, please accept my thanks for your help.

The study will continue for two years and we shall not have any results available until the end of 2001. If you wish to contact the office then, we shall send you a summary of our results.

Yours sincerely

Freda Alexander

Professor of Epidemiology

Encs. CA05R, SS3, SAE

CA05R: Case reply / consent for blood sample

Study No. «STUDY_NO»

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Disease, Inherited Susceptibility and Diet

Mr «FIRST_NAME» «LAST_NAME»

*I am willing to provide a blood sample for research purposes. I have read the information sheet (SS3). *[In this case, we shall send you the necessary bottles].*

*I am not willing to provide a blood sample.

Signed: _____ Date:_____

My next appointment is: _____

***Please delete whichever is not applicable.**

Please return this form using the prepaid envelope.

CA06: Blood sample cover letter to case

Mr «FIRST_NAME» «LAST_NAME»
«ADDRESS_LINE_1»
«ADDRESS_LINE_2»
«ADDRESS_LINE_3»

<<DATE>>

Dear Mr «LAST_NAME»

Thank you for returning the form we sent you. I am now writing to send you the bottles and boxes for the collection of the blood sample.

Please take these to the clinic on your next visit. You will need to show them the copy of the consent form you have signed.

Without your help and that of the other participants, this study would have not been possible.

We are very grateful to you.

Yours sincerely

Freda Alexander

Professor of Epidemiology

Enc. Copy of consent form, blood boxes

8.4.3 BPH Control Correspondence

BPH01: Approach to treating consultant

«TREATING_CONSULTANT»
«TREATING_HOSP»
«CONSADDRESS1»
«CONSADDRESS2»
«CONSADDRESS3»

<<DATE>>

Dear «TREATING_CONSULTANT»

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Cancer, Inherited Susceptibility and Diet

Re: «FIRST_NAME» «LAST_NAME»: Date of birth: «DOB»: Unit No: «UNIT_NO»

PCANDIET is in a case control study of prostate cancer in adults in the south of Scotland (see Study Summary). With your permission, we would like to approach the patient named above. The study would involve the patient completing a food frequency questionnaire and, with the patients' consent, a blood sample being drawn by my nurse or at their GP surgery.

I would be grateful if you would complete and return the enclosed form stating whether or not you are willing for us to contact this patient.

This study has the approval of the relevant ethical committee(s).

If you have any other comments or wish to know more of this study, please contact me personally at this address.

Thanking you for your assistance.

Yours sincerely

Freda Alexander

Professor of Cancer Epidemiology

Enc. SS1, BPH01R, SAE

BPH01R: Treating consultant reply / consent form

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Cancer, Inherited Susceptibility and Diet

Re: «FIRST_NAME» «LAST_NAME» Date of birth: «DOB»

*I give my permission for you to ask the above to participate in the named study.

*I wish to make the approach to this patient myself.

*This patient is ineligible (diagnosed earlier than 1998 or mentally incapable of completing the questionnaire).

*I do not wish this patient to be approached (but he is eligible).

Signed..... Date.....

Patient's home address:

.....

.....

GP Name and address:

.....

.....

Any personal/family circumstances of relevance: .....

.....

*Delete whichever is not applicable

Please return this form in the enclosed addressed, prepaid envelope.

BPH02: Approach to potential BPH control

Mr «FIRST_NAME» «LAST_NAME»
«ADDRESS_LINE_1»
«ADDRESS_LINE_2»
«ADDRESS_LINE_3»

<<DATE>>

Dear Mr «LAST_NAME»

We are conducting a survey in your area to investigate possible causes of prostate cancer. We shall compare men WITH and WITHOUT prostate cancer. You have recently been treated for BENIGN prostate disease and we should like to include you in the comparison group. Your consultant, «TREATING_CONSULTANT», has given me permission to approach you to invite you to take part in this important study.

If you will agree to help us in this research, it would involve you completing a diet questionnaire which will take 2hour -12 hours. The information will be regarded as strictly confidential and will be seen only by myself and other members of the research team. Your decision whether to participate will not affect your future health care in any way.

People who complete the diet questionnaire will also be asked if they are willing to provide a blood sample. You are, of course, free to decline this part of the study.

This study has been approved by the following ethical committees:

Borders Health Board, Glasgow Royal Infirmary, Lothian Health Board, Stobhill NHS Trust, Southern General, Glasgow and the West Glasgow Hospitals NHS Trust.

I enclose a form and self addressed, prepaid envelope and I would be very grateful if you would complete and return this to me.

Thank you for your time.

Yours sincerely

Freda Alexander

Professor of Cancer Epidemiology

Enc. SS2, Reply Form BPH02R, SAE.

BPH02R: BPH control reply / consent form

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Cancer, Inherited Susceptibility and Diet

Mr «FIRST_NAME» «LAST_NAME»

*I am willing to take part in the above study. Please send me a diet questionnaire.

I am willing/not willing* for you to inform my GP that I am taking part in this study (it is a normal courtesy for us to do this).

*I am not willing to take part in this study.

SIGNATURE: ..... DATE: .....

Title: Mr Other

My telephone number is..... (Home)

My telephone number is..... (Work)

***Delete whichever is not applicable**

BPH03: FFQ cover letter to BPH control

Mr «FIRST_NAME» «LAST_NAME»
«ADDRESS_LINE_1»
«ADDRESS_LINE_2»
«ADDRESS_LINE_3»

<<DATE>>

Dear Mr «LAST_NAME»

Thank you for agreeing to take part in our study.

I am enclosing a food questionnaire. If you have any difficulty in completing it, please telephone my assistant, Morag Leitch (Freephone number 0800 783 5281).

Thank you for helping us.

Yours sincerely

Freda Alexander

Professor of Epidemiology

Enc. Food frequency questionnaire, information sheet

BPH04: Information letter to GP, re: case approach / approach to collect blood

Dr «GP»
«GPADDRESS1»
«GPADDRESS2»
«GPADDRESS_3»
«POSTCODE»

<<DATE>>

Dear Dr «GPSAL»

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Cancer, Inherited Susceptibility and Diet

Re: Name: «FIRST_NAME» «LAST_NAME»: Date of birth: «DOB»

Your patient has been approached, with the consent of the treating consultant, and has agreed to take part in this study.

He will be completing a food frequency questionnaire and will possibly be providing a small venepuncture blood sample for Serum and DNA analysis, in which case this patient may ask for you to collect a blood sample from him. We hope you will agree that your practice collects the sample; our funding includes a payment of £10 for this.

If you are not willing for your practice to collect the blood sample please let me know by returning the enclosed form.

Thanking you for your assistance.

Yours sincerely

Freda Alexander

Professor of Cancer Epidemiology

Enc. SS1, BPH04R, SAE

BPH04R: GP refusal form re: blood collection

Study No. «STUDY_NO»

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Cancer, Inherited Susceptibility and Diet

RE: «FIRST_NAME» «LAST_NAME» Date of Birth: «DOB»

I regret that I am not able to have the blood sample from the above-mentioned patient collected by my staff.

BPH05: Request for blood sample from BPH control

Mr «FIRST_NAME» «LAST_NAME»
«ADDRESS_LINE_1»
«ADDRESS_LINE_2»
«ADDRESS_LINE_3»

<<DATE>>

Dear Mr «LAST_NAME»

Thank you very much for sending me the completed dietary questionnaire. This will be very helpful for our research.

As I indicated in the information sheet I sent you initially, we are asking everyone who, like yourself, has completed the questionnaire if they will help us further by providing a small blood sample. I am enclosing an information sheet. If you are willing to provide a sample, we hope your GP will be willing to have it collected at their practice. If not, it can be collected by my research nurse who will contact you to arrange a visit in your home at a mutually convenient time.

Please return the form to me to indicate whether or not you wish to take part in this extra part of the study.

Whatever your choice, please accept my thanks for your help.

The study will continue for two years and we shall not have any results available until the end of 2001. If you wish to contact the office then, we shall send you a summary of our results.

Yours sincerely

Freda Alexander

Professor of Cancer Epidemiology

Enc. BPH05R, SS4, SAE

BPH05R: Consent for blood sample from BPH control

Study No. «STUDY_NO»

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Disease, Inherited Susceptibility and Diet

Mr «FIRST_NAME» «LAST_NAME»

*I am willing to provide a blood sample for research purposes. I have read the information sheet (SS4BPH). *[In this case, we shall send you the necessary bottles].*

*I am not willing to provide a blood sample.

Signed..... Date.....

***Please delete whichever is not applicable.**

Please return this form using the prepaid envelope.

BPH06: Blood sample cover letter for BPH control

Mr «FIRST_NAME» «LAST_NAME»
«ADDRESS_LINE_1»
«ADDRESS_LINE_2»
«ADDRESS_LINE_3»

<DATE>>

Dear Mr «LAST_NAME»

Thank you for returning the form we sent you. I am now writing to send you the necessary bottle and box for the collection of the blood sample.

We hope that the sample can be collected at your GP practice. If your practice has a nurse you should ask for an appointment with her. If not, then please ask your GP for an appointment but make it clear that this is a 'non-urgent' appointment. When you go to the surgery, you should take the bottle and box. You will need to show a copy of the consent form you have signed. Please take this second copy of information sheet SS4 to your GP practice.

If this is not convenient for your GP, then please telephone our FREEPHONE number: 0800-783-5281 and my research nurse will contact you to arrange a time when she will collect the sample.

Without your help and that of the other participants, this study would have not been possible.

We are very grateful to you.

Yours sincerely

Freda Alexander

Professor of Epidemiology

Enc. Copy of Consent form, SS4BPH, Box

8.4.4 Population Control - Glasgow GP Correspondence:

CT01G1: Approach to Glasgow GP re: permission to use practice list

Dr «Gpinitials» «GPSurname»
«PRACADDR1»
«PRACADDR2»
«PRACADDR3»

<<DATE>>

Dear Dr «GPSurname»

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Cancer, Inherited Susceptibility and Diet

PCANDIET is a case control study of Prostate Cancer in men in the south of Scotland (see Study Summary). With your permission, we would like to select from your patient list, or that of one of your partners, «Total_requested_inc_spares» patient(s) (plus 4 potential replacements for each selected patient) as CONTROLS. With your consent, we would approach these patients (or, if you prefer, provide you with a letter of approach to send to them yourself). The study would involve the patient completing a food frequency questionnaire. Possibly also, with the patient's further consent, a venepuncture blood sample would be drawn, either by my research nurse or your practice nurse. For this second part of the study, our funding includes making a payment of £10 to practices.

I would be grateful if you would complete and return the enclosed form, stating whether or not you are willing for us to use your patient list for the selection of controls.

If you agree to participate, we will contact you or the appropriate contact person, in order to arrange a suitable time for a researcher to visit your practice to select the controls.

This study has the approval of the relevant ethical committees.

If you have any other comments or wish to know more of this study, please contact me personally at this address.

Thanking you for your assistance.

Yours sincerely

Freda Alexander

Professor of Cancer Epidemiology

Encs. SS1 CT01G1R, SAE.

CT01G1R: GP consent form, re: use of practice list

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Cancer, Inherited Susceptibility and Diet

Dr «Gpinitials» «GPSurname» «PRACADDR1»

I give* / do not give* my permission to select patients from my patient list.

Please contact myself* / Practice Manager* / other contact person* to arrange a visit.

Name of contact person:.....

Telephone no. of contact person:.....

Signed..... Date.....

If permission given, I would*/would not* be prepared to have a blood sample collected by my staff.

*Delete whichever is not applicable

Please return this form in the enclosed addressed, prepaid envelope.

CT01G2: Confirmation of visit

«CONTACT_TITLE» «CONTACT_1ST_NAME» «CONTACT_SURNAME»
«PRACADDR1»
«PRACADDR2»
«PRACADDR3»

<<DATE>>

Dear «CONTACT_TITLE» «CONTACT_SURNAME»

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Cancer, Inherited Susceptibility and Diet.

Following our telephone conversation this morning, I am enclosing a copy of our study summary for your information.

A research nurse and myself will visit you on «VISIT_DT» at «VISIT_TIME» as arranged. We plan to select from Dr «GPSurname»'s patient list: «Total_requested_inc_spares» male patient(s), plus 4 potential replacements for each primary subject, between the ages of 50 to 74 years as CONTROLS for our case-control study.

We will be randomly selecting each control set from patients having a specific month/year of birth. The simplest method for this would be if you could give us a printout for all males aged 50 to 74 years on the patient list, with their name, address and date of birth. If necessary, a manual selection can be arranged. Following selection, we will leave forms for GP consent, to be returned to us prior to approaching the patient(s).

Dr «GPSurname» may prefer to contact the selected patient(s) theirself; if so, I would be most grateful if we could have several sheets of your practice's headed paper, in order to prepare these approach letters for Dr «GPSurname» to sign. I realise that this is a further task for a busy practice, but we have found that some GPs prefer to avoid their patients receiving letters from us before they have consented to participate. For your information I attach a copy of the letter and reply form.

Thanking you for your assistance.

Yours Sincerely

Charlotte Heald

Epidemiologist for PCANDIET Study

cc Professor Freda Alexander

Encs. SS1, copy of CT02G, copy of CT02R

CT01G3: Approach to GP re: consent to approach control

Dr «Gpinitials» «GPSurname»
«PRACADDR1»
«PRACADDR2»
«PRACADDR3»

«VISIT_DT»

Dear Dr «GPSurname»

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Cancer, Inherited Susceptibility and Diet

Thank you for allowing my researcher to select the potential subjects listed below from your patient list.

Now, as indicated previously, I am asking for your consent to approach the first patient from the list as a CONTROL. In order to streamline things, and to prevent unnecessary correspondence, I would also be grateful if you would give consent to approach appropriate replacement subjects as well. Please note that these replacements will only be approached if the previous choice is: Ineligible, you do not which him to be approached or he refuses to take part in the study.

Selected patient: ..... DOB: .....
1st Replacement: ..... DOB: .....
2nd Replacement: ..... DOB: .....
3rd Replacement: ..... DOB: .....
4th Replacement: ..... DOB: .....

As mentioned before in our previous letter, the study will involve the patient completing a food frequency and possibly also, with the patient's further consent, a venepuncture blood sample being drawn.

I would be grateful if you would complete and return the enclosed forms stating whether or not you are willing for us to contact these patients.

You may prefer to contact the selected patient(s) yourself; if so, I would be most grateful if we could have several sheets of your practice's headed paper, in order to prepare these approach letters for you to sign. I realise that this is a further task for a busy practice, but we have found that some GPs prefer to avoid their patients receiving letters from us before they have consented to participate. For your information I attach a copy of the letter and reply form.

If you have any other comments or wish to know more of this study, please contact me personally at this address.

Yours sincerely

Freda Alexander

Professor of Cancer Epidemiology

Enc. CT01G3R, copy of CT02G(a) & CT02R, SAE

CT01G3R: GP Consent form, re: control approach

Practice No: .....
Study No: .....

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Cancer, Inherited Susceptibility and Diet

** Please delete whichever is not applicable:*

1. Selection of ONE CONTROL subject .

Name DoB Address Tel. No.	....	This patient is eligible / ineligible* (because of mental incapacity or previous diagnosis of prostate cancer). *If ineligible, ignore next question.* I give / do not give* my permission for you to ask this patient to participate in PCANDIET.

2. Selection of 1st potiential replacement.

Name DoB Address Tel. No.	....	This patient is eligible / ineligible* (because of mental incapacity or previous diagnosis of prostate cancer). *If ineligible, ignore next question.* I give / do not give* my permission for you to ask this patient to participate in PCANDIET.

3. Selection of 2nd potiential replacement.

Name DoB Address Tel. No.	....	This patient is eligible / ineligible* (because of mental incapacity or previous diagnosis of prostate cancer). *If ineligible, ignore next question.* I give / do not give* my permission for you to ask this patient to participate in PCANDIET.

Please turn over.

** Please delete whichever is not applicable:*

4. Selection of 3rd potiential replacement.

Name	This patient is eligible / ineligible* (because of mental incapacity or previous diagnosis of prostate cancer).
DoB	
Address	
.....	*If ineligible, ignore next question.*
Tel. No.	I give / do not give* my permission for you to ask this patient to participate in PCANDIET.

5. Selection of 4th potiential replacement.

Name	This patient is eligible / ineligible* (because of mental incapacity or previous diagnosis of prostate cancer).
DoB	
Address	
.....	*If ineligible, ignore next question.*
Tel. No.	I give / do not give* my permission for you to ask this patient to participate in PCANDIET.

Please sign below and print name:

Signed: ..... Date: .....

Name: .....

Are any of these patients currently receiving therapy by finasteride or other drug for benign prostatic hyperplasia. If so, please give number and drug name(s).

.....

.....

Any personal/family circumstances of relevance:

.....

.....

Please return this form in the enclosed addressed, prepaid envelope.

CT01: Approach to GP (Lothian & Borders Health Boards)

«GP»
«GPADDRESS1»
«GPADDRESS2»
«GPADDRESS_3»
«POSTCODE»

<<DATE>>

Dear Dr «GPSAL»

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Cancer, Inherited Susceptibility and Diet

Re: «FIRST_NAME» «LAST_NAME» Date of Birth: «DOB»

PCANDIET is a case control study of Prostate Cancer in adults in the South of Scotland (see Study Summary). With your permission, we would like to approach the patient named above as a CONTROL. His name has been randomly selected from your health board's computerised lists. The study would involve the patient completing a food frequency questionnaire and possibly, with the patient's further consent, a venepuncture blood sample being drawn. For this second part of the study we hope that you will agree that your practice collects the sample; our funding includes making a payment of £10 to you for this.

I would be grateful if you would complete and return the enclosed form stating whether or not you are willing for us to contact this patient.

This study has the approval of the relevant ethical committee(s).

If you have any other comments or wish to know more about this study, please contact me personally at this address.

Thanking you for your assistance.

Yours sincerely

Freda Alexander

Professor of Cancer Epidemiology

Encs. SS1, CT01R, SAE

CT01R: GP reply / consent form

Study No. «STUDY_NO»

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Cancer, Inherited Susceptibility and Diet

Re: «FIRST_NAME» «LAST_NAME» Date of Birth: «DOB»

* I give my permission for you to ask the above to participate in the named study.

* I wish to make the approach to this patient myself [if so, PCANDIET will send you the literature for the patient].

* This patient is ineligible (because of mental incapacity or previous diagnosis of prostate cancer).

* I do not wish this patient to be approached (but I believe him to be eligible).

Signed ..... Date .....

If the patient agrees to participate, then I **would / would not*** be prepared to have a blood sample collected by my staff.

Is this patient currently receiving therapy by finasteride or other drug for benign prostatic hyperplasia. If so, please give drug names(s).

.....

Any personal / family circumstances of relevance: .....

.....

***DELETE WHICH EVER IS NOT APPLICABLE**

Please return this form in the enclosed addressed prepaid envelope.

CT02: Approach to population control

Mr «FIRST_NAME» «LAST_NAME»
«ADDRESS_LINE_1»
«ADDRESS_LINE_2»
«ADDRESS_LINE_3»

<<DATE>>

Dear Mr «LAST_NAME»

We are conducting a survey in your area to investigate possible causes of prostate cancer. You have been RANDOMLY selected from a list of men registered with GPs in your area. We need information from people like yourselves to help us to interpret the data from people with this disease. Your GP, «GP», has given me permission to approach you to invite you to take part in this important study.

If you will agree to help us in this research, it would involve you completing a diet questionnaire which will take ½hour - 1½hours. The information will be regarded as strictly confidential and will be seen only by myself and other members of the research team. Your decision whether to participate will not affect your future health care in any way.

People who complete the food frequency questionnaires will also be asked if they are willing to provide a blood sample. You are, of course, free to decline this part of the study.

This study has been approved by the following ethical committees:

Borders Health Board, Glasgow Royal Infirmary, Lothian Health Board, Stobhill NHS Trust, Southern General, Glasgow and the West Glasgow Hospitals NHS Trust.

I enclose a form and self addressed, prepaid envelope and I would be very grateful if you would complete and return this to me.

Thank you for your time.

Yours sincerely

Freda Alexander

Professor of Cancer Epidemiology

Enc. SS2, CT02R, SAE.

CT02R: Control reply / consent form

Study No. «STUDY_NO»

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Cancer, Inherited Susceptibility and Diet

«FIRST_NAME» «LAST_NAME»

*I am willing to take part in the above study. Please send me a diet questionnaire.

*I am not willing to take part in this study.

*I have never had prostate cancer diagnosed

SIGNATURE..... DATE.....

Title: Mr Other

My telephone number is..... (Home)

My telephone number is..... (Work)

***Delete whichever are not applicable**

CT03: FFQ cover letter to population control

Mr «FIRST_NAME» «LAST_NAME»
«ADDRESS_LINE_1»
«ADDRESS_LINE_2»
«ADDRESS_LINE_3»

<<DATE>>

Dear Mr «LAST_NAME»

Thank you for agreeing to take part in our study.

I am enclosing a food questionnaire. If you have any difficulty in completing it, please telephone my assistant, Morag Leitch (Freephone number 0800 783 5281).

Thank you for helping us.

Yours sincerely

Freda Alexander

Professor of Epidemiology

Enc. Food frequency questionnaire, information sheet

CT05: Request for blood sample from population control

Mr «FIRST_NAME» «LAST_NAME»
«ADDRESS_LINE_1»
«ADDRESS_LINE_2»
«ADDRESS_LINE_3»

<<DATE>>

Dear Mr «LAST_NAME»

Thank you very much for sending me the completed dietary questionnaire. This will be very helpful for our research.

As I indicated in the information sheet I sent you initially, we are asking everyone who, like yourself, has completed the questionnaire if they will help us further by providing a small blood sample. I am enclosing an information sheet. If you are willing to provide a sample, we hope your GP will be willing to have it collected at their practice. If not, it can be collected by my research nurse who will contact you to arrange a visit in your home at a mutually convenient time.

Please return the form to me to indicate whether or not you wish to take part in this extra part of the study.

Whatever your choice, please accept my thanks for your help.

The study will continue for two years and we shall not have any results available until the end of 2001. If you wish to contact the office then, we shall send you a summary of our results.

Yours sincerely

Freda Alexander

Professor of Cancer Epidemiology

Enc. CT05R, SS4, SAE

CT05R: consent for blood sample from control

Study No. «STUDY_NO»

PCANDIET: A Medical Research (Epidemiological) Study of Prostate Disease, Inherited Susceptibility and Diet

Mr «FIRST_NAME» «LAST_NAME»

*I am willing to provide a blood sample for research purposes. I have read the information sheet (SS4). *[In this case, we shall send you the necessary bottles].*

*I am not willing to provide a blood sample.

Signed..... Date.....

***Please delete whichever is not applicable.**

Please return this form using the prepaid envelope.

CT06: Blood sample cover letter to population control

Mr «FIRST_NAME» «LAST_NAME»
«ADDRESS_LINE_1»
«ADDRESS_LINE_2»
«ADDRESS_LINE_3»

<<DATE>>

Dear Mr «LAST_NAME»

Thank you for returning the form we sent you. I am now writing to send you the necessary bottles and boxes for the collection of the blood sample.

We hope that the samples can be collected at your GP practice. If your practice has a nurse you should ask for an appointment with her. If not, then please ask your GP for an appointment but make it clear that this is a 'non-urgent' appointment. When you go to the surgery, you should take the bottles and boxes. You will need to show a copy of the consent form you have signed. Please take this second copy of information sheet SS4 to your GP practice.

If this is not convenient for your GP, then please telephone our FREEPHONE number: 0800-783-5281 and my research nurse will contact you to arrange a time when she will collect the sample.

Without your help and that of the other participants, this study would have not been possible.

We are very grateful to you.

Yours sincerely

Freda Alexander

Professor of Epidemiology

Enc. Consent form, SS4, Boxes