Prostate Cancer Risk Factors:
A UK Population based Case-Control Study
centered on
Chronic Diseases, Medications,
Sunlight and Diet

Dr. Fredie Robinson

Thesis submitted to the University of Nottingham
for the degree of
Doctor of Philosophy

March 2012

Abstract

Background: Prostate cancer risk has been associated with several environmental factors but there is little information to indicate the effects of timing and of lifetime exposures that may add to the risk. This thesis aims to investigate the association of six main areas that may contribute to prostate cancer risk (1) body shape & fat distribution, (2) chronic diseases/conditions (diabetes mellitus, hypertension, ischaemic heart diseases and hypercholesterolemia), (3) statin medications (4) painkillers (NSAIDs and paracetamol), (5) skin & sunlight exposure and (6)diet (isoflavones, selenium, vitamin D & lycopene). The exposures will be investigated at different stages of life for subsequent effects on cumulative prostate cancer risk.

Methodology: This study is a part of "The UK Prostate Cancer Study: Gene-Environment Interactions", which is an ongoing large scale case-control study and a collaboration between the University of Nottingham, University of Warwick and the Institute of Cancer Research UK. Data were collected using questionnaires. Subjects were recruited between the years of 1999 to 2009 as cases and controls from hospitals and GPs' referrals in England. Possible risk factors for prostate cancer are investigated through statistical analyses using unconditional logistic regression to obtain odds ratios (OR) and confidence intervals.

Results: The response rate was 85.0% among cases and 74.4% among controls, with a total of 4041 males (1963 cases and 2078 controls) recruited into the study. The mean age among cases and controls was 59.6 and 59.1 years respectively. Multivariate analysis of socio-demographic factors showed education, ethnic group and family history were statistical significantly associated with prostate cancer risk and therefore are treated as confounders. Further, (1) Body fat distribution of 'apple' and 'oval' shapes were found to have protective effect towards prostate cancer when compared with a symmetrical shape with an OR of 0.69 (95% CI: 0.55-0.87) and 0.73 (95% CI 0.53-1.00) respectively, however body shape at age 20's, 30's, 40's and last 5 years showed no statistical difference between cases and controls. (2) The cumulative duration of diabetes mellitus categorised as 5 years or more and 10 years or more when compared to non-diabetic individuals had a

protective effect towards prostate cancer risk at OR 0.45 (95%CI: 0.27-0.75) and 0.44 (95% CI: 0.22-0.86) respectively while hypertension, hypercholesterolemia and ischaemic heart disease did not associate with prostate cancer risk. (3) Use of Statins for less than 5 years compared to non-users, produced an OR 0.61 (95%CI: 0.47-0.82). A dose response relationship for duration of use was also seen. (4) Paracetamol showed a protective effect for prostate cancer risk when used for 20 years to 30 years when compared to none-users, OR 0.54 (95%CI: 0.28-1.00). Similarly paracetamol showed a cumulative risk reduction against prostate cancer for all categories of use of up to 20 years or more. However aspirin and ibuprofen did not show any statistical significant associations with prostate cancer risk. (5) Higher exposure to sunlight received in non-working situations and more frequent use of suntan cream showed protective effects against prostate cancer and also when accounted for exposure at different stages of life age. (6)Dietary isoflavones and tablet supplements of selenium at higher intake quartiles levels showed a protection effect against prostate cancer risk when compared to lowest quartile intake.

New surrogate indicators for body size and sunlight exposure and a proposed model for overall vitamin D levels from sunlight and dietary sources were also introduced.

Conclusions: Body fat distribution of 'apple' and 'oval' body forms, diabetes mellitus, statin usage, higher exposure to sunlight and higher dietary intakes of isoflavones were shown to associate with a decreased risk for prostate cancer. The findings of this case-control study strengthen and support the current understanding of environmental factors associated with prostate cancer risk, whilst at the same time provides further evidence on the effects of exposure at different stages in life and their cumulative effect, as well identifying new surrogate indicators as parameters measurement for such exposures.

Publication & Conferences

One of the topics in this thesis was presented as a poster presentation and published in the proceedings for the AACR (American Association for Cancer Research) Annual Meeting in Chicago, United States 31 March – 4 April 2012.

The title of the paper was:

'Body Fat Distribution and Prostate Cancer Risk: A UK Case Control Study'

Acknowledgements

This thesis was produced with lots of effort, dedication and love, not just from me, but also of many whom I am most grateful for.

I, first and foremost would like to convey my gratitude from the bottom of my heart, to all my PhD supervisors: Professor Dr. Kenneth Muir, Associate Professor Dr. Terrence Parker and Dr. Artitaya Lophatananon, who has always been there for me whether near or far, in good and bad times, and constantly encouraging also guiding me closely in my PhD study and work.

To Professor Kenneth and Dr. Artitaya, your care, dedication and commitment to make sure that I succeed in my PhD work and as a researcher, will always be treasured. Besides sharing your expertise knowledge and experiences, you have also taught me the values of giving others the best without expecting anything in return, the virtue of patience and understanding, as well as what constant encouragement can do to make others do the impossible. Thank you being such good teacher. I will always remember your generosity, kindness and constant friendship.

To Dr. Terry, you've all this while been caring, being vigilant of the status of my PhD study, helping me to get through the milestones in my PhD and at the same time has always been supportive, in making me feel at home in the School of Biomedical Sciences, whether as a supervisor or a friend. I will not forget your kindness and passionate care as a teacher and guardian.

I would not be at this stage of my study if not because of the many people who have been most helpful along the way in providing me with technical and valuable advices, also assistance in my PhD research with open arms. I would like to thank in person: Professor David Walker, AP Dr. Tricia McKeever, Mdm Gail Faulkner, Dr. Aneela Rahman, the subjects/patients, doctors, hospitals & GPs who agreed to take part in this study and provided the data, the members of the UK Research Consortium of Prostate Cancer for Gene-Environment Interaction, the Prostate Cancer Research Foundation & Cancer Research UK for funding this research and Malaysia Ministry of Higher Education & UMS Scholarship for funding my PhD study. Special thanks to Dr. Artitaya & Prof Ken for editing most of my thesis work.

I too, wish to thank my dad Vitus, mom Elsie and sister Irene who have always been there for me when I needed encouragement, prayer and love. Last but not least, I thank the Almighty God for teaching me to put my trust in Him with practice of humility and perseverance in all my work.

May God Bless You All.

Table of Contents

Appendices

Cancer Registry and Report of Prostate Cancer Prevalence & Incidence in Asia and Malaysia

Progress of Gene-Environment Interactions in Prostate Cancer Research (United Kingdom)

Prostate Cancer Research Questionnaire

List of Tables

List of Figures

List of Abbreviations

BMI	Body Mass Index
BPH	Benign Prostatic Hypertrophy
CI	Confidence Interval
CRUK	Cancer Research United Kingdom
DM	Diabetes Mellitus
EPIC	European Prospective Investigation of Cancer
FFQ	Food frequency Questionnaire
GP	General Practitioner
HDL	High-density Lipoprotein
IGF	Insulin-like Growth Factor
IGFBP	Insulin-like Growth Factor Binding Protein
IHD	Ischaemic Heart Disease
LDL	Low-density Lipoprotein
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OR	Odds Ratio
PSA	Prostatic Specific Antigen
s.d.	Standard Deviation
SNP	Single-nucleotide Polymorphism
SPF	Sun-protection Factor
TNM	Tumour Nodes Metastases
UVR	Ultraviolet Radiation
WC	Waist Circumference
WHR	Waist-Hip Ratio

Chapter 1 Introduction

1.1 Introduction

1.1.1 Literature Review

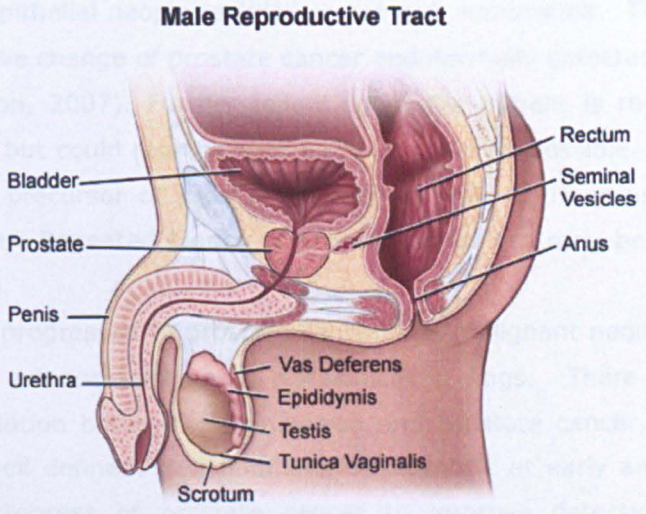


Figure 1-1 Male Reproductive Tract
(Reproduced with permission from www.mainlinehealth.org (Dec 2, 2010))

1.1.2 Anatomy and physiology of Prostate gland

The prostate is a walnut size gland in the male located in the pelvis at the base of the urinary bladder. It grows and develops during infant life by testosterone and growth hormones. During adolescence or puberty, there is a rise in androgen level and a second peak occurrs around age of 50 when there is an increase of estrogen to androgen ratio (Syrigos, 2001)

Prostate growth continues with age and enlargement of the gland can result in urination problems because the urethra passes through the prostate gland and may be obstructed at the neck of bladder. Common prostate problems include Benign Prostatic Hyperthrophy (BPH), Prostatitis, associated with infection or acquired as a

result of sexual activity and Prostate cancer. Development within prostate will produce prostatic specific antigen (PSA), a fluid with an important role in sexual activity by nourishing the sperm for its function in reproduction. The level of PSA present in the bloodstream reflects the activity and health of the prostate gland (Waxman, 2002).

1.1.2.1 Pathophysiology of Prostate cancer

The exact change from normal prostate gland (a secretory gland) to prostatic intraepithelial neoplasia (PIN) is not well established. The PIN is considered as pre-invasive change of prostate cancer and normally detected only through needle biopsy (Ramon, 2007). Further follow up of the patient is required as progression could occur but could regress back to normal is also possible. High grade PIN is the most likely precursor of prostate cancer, therefore PIN is useful as a predictive cancer marker. Repeated biopsy of prostate specimen may be warranted (Montironi *et al*, 2000).

Once progressed to prostate cancer, the malignant neoplasm would most commonly be of adenocarcinoma in histological findings. There is evidence to support the association between inflammation and prostate cancer, but exact mechanisms are not well defined. Molecular markers specific at early and late events are critical to the progress of prostate cancer to improve detection and prognostic strategy (Gonzalgo, 2003).

When Gleason score was introduced as a model for prostate cancer progression, the study of aggressiveness of cancer was made possible (Epstein *et al*, 2005). When cancer is invasive, the nuclear matrix also changes with differentiation, hence there is a progressive loss of the normal prostate gland pattern and increased stromal invasion.

There is increasing evidence that predisposing genetic factors, oxidative damage and dietary or environmental factors play account or role in the steps of neoplastic transformation. These factors will be discussed further in the chapter on associated risk factors of prostate cancer.

1.1.3 Clinical features of Prostate cancer

Prostate cancer is a heterogeneous disease and can remain silent for years before presenting with metastatic diseases features. However, any obstructive or irritation

in urine voiding would present itself early such as in localized prostate cancer. Development of prostate cancer doesn't present typical clinical symptoms that would warrant immediate referral to a urologist (Syrigos, 2001).

Presentation of patients with prostate cancer varies and can be broadly divided into three sets of level namely at local disease, local advanced or invasive and metastatic.

Table 1-1 Clinical presentation/signs or symptoms of Prostate Cancer

Local disease	Local invasive/advanced disease	Metastatic disease
• Asymptomatic • Elevated PSA	• Dysuria • Haematuria • Perineal and suprapubic pain/discomfort • Erectile dysfunction • Bladder incontinence • Renal failure symptoms e.g. loin pain, anuria, uraemia • Rectal symptoms e.g. tenesmus	• Bone pain • Sciatica or paraplegia due to spinal cord or nerve compression • Lymph node enlargement • Weight loss and cachexia • Lethargy due to anaemia or uraemia

Adapted from Kirby, R. S. 2009. *Fast facts: Prostate cancer*. Oxford Health Press (Kirby, 2009)

1.1.4 Investigation & Diagnosis of Prostate cancer

Digital rectal examination (DRE) is the simplest form and cheapest form of detecting prostate cancer provided that the tumour growth is posteriorly located in palpable or sufficiently enlarged prostate. This examination or test can be done while patient lying left lateral position leaning forward. Findings that could indicate prostate cancer include palpable nodule, asymmetry of the prostate gland, reduced mobility due to adhesion to surrounding tissue and palpable seminal vesicles (Kirby,

2009). False positive diagnosis could be due to BPH, prostatic calculi, prostatitis (especially granulomatous type), duct or vesicle abnormality and rectal polyps.

Prostatic specific antigen (PSA) measurement of blood serum specimen is the most important and widely used tumour marker in urological oncology (Syrigos, 2001). It is used in diagnosis, staging and monitoring prostate cancer. However PSA is organ-specific to prostate gland and not cancer specific. A traditional cut-off value of PSA serum 4.0ng/ml is normally used however almost one-fifth of prostate cancer patients have serum PSA below that level. A higher PSA value may also be due to BPH or other prostatic diseases and urinary retention not limited to prostate cancer. PSA sensitivity and specificity can be enhanced through usage of several parameters including PSA density, PSA age-specific, PSA velocity, percentage of free-PSA.

Ultrasound examination including **transrectal ultrasound examination (TRUS)** of the prostate through probe inserted into the rectum of subject. This method gives an idea to the outline and internal structure of the gland, as well the structures surrounding the prostate such as seminal vesicles, and also changes in the prostate capsule which could suggest that the gland has been breached by tumour. However there's no correlation between TRUS appearance and macroscopically pathological findings (Waxman, 2002).

Biopsy or removal of samples of tissue of the prostate gland is performed by inserting small spring loaded needles in the ultrasound probe during TRUS and into prostate through rectum wall. Six core biopsies are normally taken. The specimens collected are then sent for process in pathology lab and examined under microscope by a pathologist who will confirm if there's cancer growth, the degree of infiltration of the prostate by the tumour, type of tumour and staging or grading of the prostate cancer (Waxman, 2002).

1.1.5 Staging/Grading of Prostate cancer

There are a couple of staging systems for prostate cancer including Whitmore Jewett, American Joint Cancer Committee (AJCC), American Urological System and Prout. However the most widely used is the TNM (Tumour, Nodes & Metastatic) classification (Syrigos, 2001).

1.1.5.1 TNM Classification

The International Union Against Cancer (UICC) and American Joint Committee on Cancer (AJCC) started using the TNM (Tumour, Nodes and Metastases) Classification since 1970's but over the years has been united and undergone 1992 Consensus to come out with TNM Classification for prostate cancer (Schroder *et al*, 1992). It serves both clinical and pathological staging.

Clinical staging includes digital rectal examination (DRE) of the prostate and cytological confirmation of prostate cancer. Clinical examination, serum PSA level and imaging investigation such as TRUS are suggested. Pathological staging mostly requires histological examination of resected specimen of prostate, seminal vesicles and pelvic lymph node.

Table 1-2 TNM Classication of Prostate Cancer (Schroder *et al*, 1992)

Tumour (T)	
T Primary Tumour (Incidental prostate cancer)	TX Primary tumour cannot be assessed
	T0 No evidence of primary tumour
	T1 Clinically inapparent tumour, not palpable nor visible by imaging • T1a Tumour incidental, histologic finding in 5% or less tissue resected • T1b Tumour incidental, histologic finding in more than 5% of tissue resected • T1c Tumour identified by needle biopsy (e.g. due to elevated serum PSA level)
T2 Tumour confined within prostate (Palpable or visible carcinoma confined to prostate)	T2a Tumour involves half of a lobe or less
	T2b Tumour involves more than half a lobe but not both lobes
	T2c Tumour involves both lobes
T3 Tumour extends through prostate capsule (Locally extensive prostate cancer)	T3a Unilateral extracapsular extension
	T3b Bilateral extracapsular extension
	T3c Tumour invades seminal vesicle(s)
T4 Tumour is fixed or invades adjacent structures other than seminal vesicles (Locally extensive tumours with fixation or invasion into neighbouring organs)	T4a Tumour invades bladder neck and/or external sphincter and/or rectum
	T4b Tumour invades levator muscles and/or is fixed to pelvic wall

Tumour (T)	
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single regional lymph node, more than 2 cm or less in greatest dimension
N2	Metastasis in a single regional lymph node, more than 2 cm but not more than 5 cm in greatest dimension, or multiple regional lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a regional lymph node more than 5 cm in greatest dimension
Distant Metastases (M)	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis • M1a Non regional lymph nodes(s) • M1b Bone(s) • M1c Other site(s)

In terms of grading systems for prostate cancer, Gleason is the most used. The other grading systems include Mostofi, MD Anderson, Bocking, Gaeta and Broders.

1.1.5.2 Gleason Grade for Prostate Cancer

Table 1-3 Prostate Cancer Grading using Gleason Grading System
(Adapted from *Fast facts: Prostate cancer*. Oxford Health Press)(Kirby, 2009)

Grade	Description
Grade 1	Well differentiated cancer cells consist of small uniform glands with minimal nuclear changes and likely to be of a less aggressive nature as they are slow growing.
Grade 2	Medium sized acini but irregular with stromal separation but closely arranged.
Grade 3	Moderately differentiated cells with marked variation of glandular size and organization with infiltration of stromal and neighboring tissues; at this grade cancerous cells may have invaded surrounded prostate tissue. This is the most common grade of prostate cancer.
Grade 4	Cytological atypia cells of undifferentiated cancer cells with extensive infiltration to the gland.
Grade 5	Sheets of undifferentiated anaplastic cancer cells, which are likely to be fast growing and spreading.

1.1.5.3 Gleason Score

The Gleason score is the sum of the two most prominent grades found on cytology findings of the biopsy specimen of prostate tumour with scores between 2 to 10. This score can predict the likelihood of growth and spread of the cancer cells.

Table 1-4 Gleason Score for Prostate Cancer
(Adapted from *Fast facts: Prostate cancer*. Oxford Health Press)(Kirby, 2009)

Gleason score	Histological Features	10-year likelihood of growth and spread (%)
2-6	Well differentiated cells	25
7	Moderately differentiated cells	50
8-10	Poorly differentiated cells	75

1.1.6 Management and Prognosis of Prostate cancer

(Adapted from *Fast facts: Prostate cancer*. Oxford Health Press)(Kirby, 2009)

Management of prostate cancer cases are best divided into localized, localized advance and high risk group. For the localized prostate cancer group they may further be categorized as low, intermediate and high risk of recurrence, based on Gleason score, PSA level and clinical stage. However it is not possible to say which treatment will produce the optimum result on individuals.

Radical prostatectomy is a procedure whereby the entire prostate, seminal vesicles and adjacent tissues are surgically removed, also helps to excise precisely all confined cancer cells for surety removal of all prostatic tissues. This procedure is normally indicated for histological evidence of prostate cancer with localized disease T1-T2, patient longer life expectancy of more than 10 years with no surgery contraindications.

External-beam radiotherapy is indicated in patients who cannot undergo surgery or has extraprostatic extension of cancer tissue but still regionally localized. The new coming of intensity-modulated radiotherapy (IMRT) has allowed more precise to prostate gland and radiation can be given in higher doses without significant toxicity.

Low-dose seed brachytherapy a procedure putting seeds of iodine-125 or palladium-103 into the prostate through transperineal route and TRUS guidance. It is indicated for low risk group of prostate cancer patients.

High-dose-rate (HDR) brachytherapy using high intensity iridium is indicated for intermediate and high risk cancer group of localized cancer.

Watchful waiting is ideal for men who are at advanced age or those who have shorter life-expectancy and who will unlikely to have shortened life span due to prostate cancer. Those with high risk category also it will be a valid treatment. This management requires patients reviewed regularly with clinical examination and PSA testing. Palliative androgen deprivation treatment is given for those identified with cancer disease progression.

High-intensity focused ultrasound (HIFU) uses a probe transrectally to the prostate to destroy cancer cells. Although new, it is quite promising and also used for cancer recurrence patients even after radiotherapy at low risk group.

Cryoablation is by way of freezing the prostatic tissue under TRUS guidance using cryogenic probes circulating liquid nitrogen inserted via perineum. This treatment is currently used in low risk group or recurrence cases even after radiotherapy.

Hormonal therapy (cytoreduction) for prostate is achievable by using luteinizing hormone-releasing hormone (LHRH) analogs with an anti-androgen to reduce tumour burden. This is done prior to radical prostatectomy. It is normally indicated for advanced cases. Similarly hormonal therapy is used prior to external-beam radiation.

1.2 Epidemiology of Prostate Cancer

1.2.1 Introduction

Prostate Cancer has become of higher importance among the male cancers because of the improved medicine and health care in developed and developing countries and even most parts of the third world which had led to the increase of life expectancy. The Cancer Research UK (2010) age specific incidence rates for prostate cancer in United Kingdom in 2007 show steep increases with age (CRUK, 2010). In response to these pertinent events, the study of the associated risk factors and the preventive predictive factors has been progressing rather rapidly. The study of prostate Cancer preventive and risk factors in the United Kingdom has also progressed and on-going (Dimitropoulou *et al*, 2009; Lophatananon *et al*, 2010; Myles *et al*, 2008; Rahman *et al*, 2010).

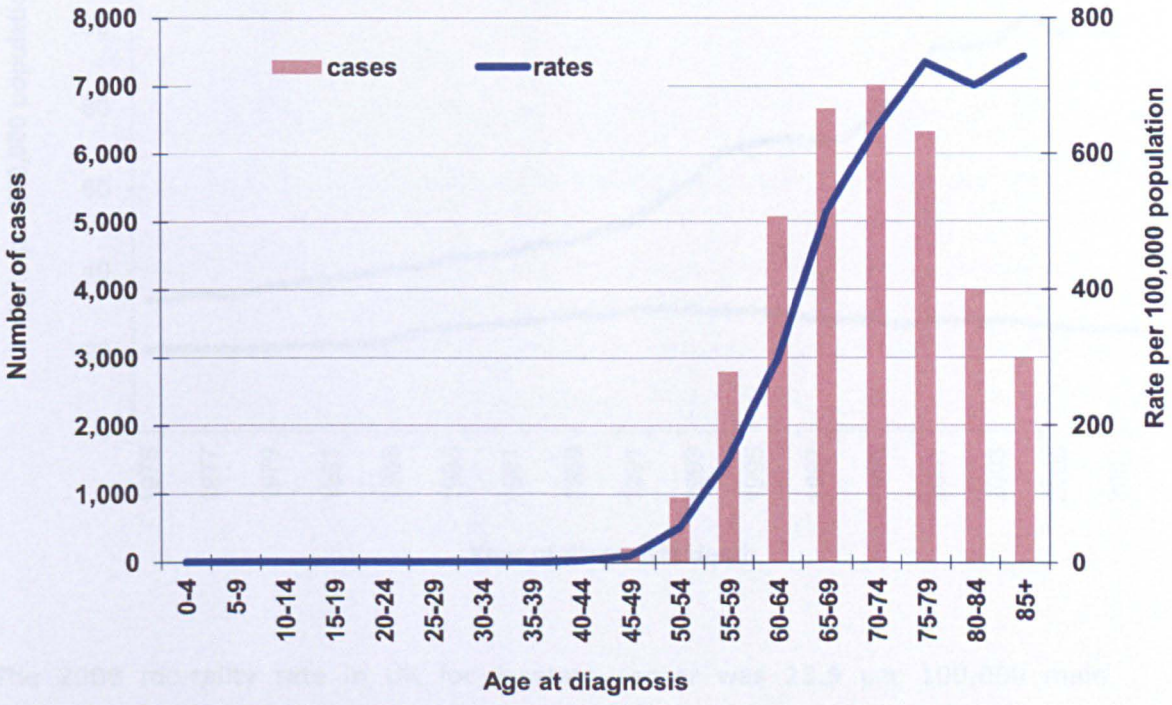
1.2.2 Burden of Disease

Prostate cancer is the second most common cancer diagnosed in men globally about 14% based on estimation of 2008 Cancer burden study (Ferlay *et al*, 2008), but based on 2007 actual incidence in United Kingdom (UK) the percentage is 24%, almost a quarter in terms of proportion. Prostate cancer is the most common cancer diagnosed in men in the UK, followed by lung and colorectal cancer at 15% and 14% respectively (CRUK, 2010).

1.2.3 Incidence

A rise in the prostate cancer incidence over the last 30 years in UK has been due to the increased detection of prostate cancer following procedure transurethral resection of the prostate (TURP) and the use of prostate specific antigen (PSA) testing (CRUK, 2010).

Figure 1-2 Numbers of new cases and age-specific incidence rates of prostate cancer UK 2007

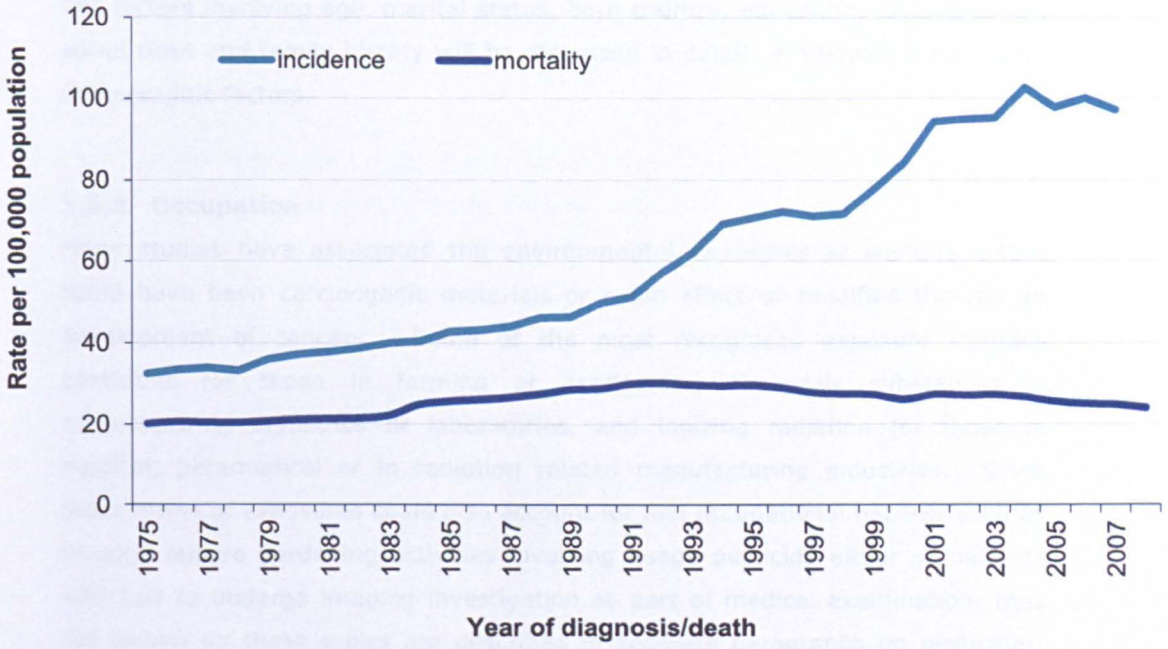


The incidence rate of prostate cancer in 2007 for United Kingdom was 97.5 per 100,000 male population(age standardized European population) (CRUK, 2010).

1.2.4 Mortality

In terms of mortality from cancer in men, worldwide estimate is 4.2 million in 2008, mainly from lung cancer (23%), with prostate cancer in the 6th place at 6%. The UK 2007 cancer mortality data reported prostate cancer deaths of 10,170 people, as the 2nd highest among men at 12%, behind lung cancer of 24%. It is obvious that Prostate cancer is responsible for relatively higher number deaths in the UK than the worldwide (CRUK, 2010).

Figure 1-3 Age-standardized (European) incidence and mortality rates of prostate cancer in males for Great Britain 1975 to 2008



The 2008 mortality rate in UK for Prostate cancer was 23.9 per 100,000 male population.

1.3 Overview Factors Associated with Prostate Cancer

1.3.1 Socio-demographic Factors

The factors involving age, marital status, born country, education, race/ethnicity, social class and family history will be discussed in detail in Chapter 3 on Socio-demographic factors.

1.3.2 Occupation

Many studies have associated the environmental exposures at workplace that could have been carcinogenic materials or could affect or modified the risk to development of cancers. Some of the most recognized exposure includes pesticides for those in farming or applicators, chemicals substances in manufacturing industries or laboratories, and ionizing radiation for those in medical, paramedical or in radiation related manufacturing industries. Since these forms of exposures could also account for non occupational hazards such as through leisure gardening activities involving usage pesticide either or patients who had to undergo imaging investigation as part of medical examination, thus the review on these topics are described in separate paragraphs on pesticides, chemicals and radiation.

1.3.3 Physical features or characteristics

Height and prostate cancer studies have shown inconsistent associations and most probably has a positive interaction with family history, where a combination of the factors of height and family history of prostate cancer would increase relative risk as much as 5.49 (CI: 1.31-22.94) to all types of prostate cancer or 7.41 (CI: 1.68-32.7) for advanced prostate cancer in compared with those of lower height and no family history (Norrish *et al*, 2000b). More recent study of PLCO (Prostate lung colorectal and ovarian cancer) Screening Trial showed the risk of aggressive prostate cancer of Gleason score 7 or more, were greater in taller men with statistical significant trend across height categories, and significant in those diagnosed before age 65 with RR 1.76 (CI: 1.06-2.93) for those with 190cm and above in height versus those less than 170cm, suggestive that the height association to prostate cancer for younger onset aggressive type of prostate cancer (Ahn *et al*, 2009). A cancer risk cohort study on Korean population also revealed height adjusted ratio for age, body mass index, smoking

and alcohol and exercise, to be positively associating with prostate cancer with increased risk 13% for every 5cm increment in height (Sung *et al*, 2009).

1.3.4 Physical activity

There are many inconsistent findings of the relationship between leisure activity of exercise and prostate cancer, some appear statistically protective (Moore et al. 2009), although many appear of non-significant statistically, but suggesting of reduction of risk (Nilsen *et al*, 2000) and others an increase in risk (Platz *et al*, 2003). A recent study in Canada showed that high physical activity which is associated with occupation has a decreased odds ratio of prostate cancer OR 0.54 (CI: 0.31-0.95) while recreational physical activity was found not statistically significant (Parent *et al*, 2010).

1.3.5 Sexual history

Frequency of sexual activity and number of sexual partners also positively associated with increasing risk of prostate cancer (Dennis, 2002a). It was also discovered a statistically significant trend of increase risk to prostate cancer on more frequent amount of sexual intercourse per week, while those having 7 or more times of sexual intercourse per week will double the risk compared to those at 3 times or less (Fernandez *et al*, 2005). Rosenblatt and colleagues reported that having two or more female sexual partners was also found to show statistically significant trend in frequency to non-aggressive prostate cancer (Rosenblatt *et al*, 2001).

In 2002, a meta-analysis on sexual activity included 40 studies between 1966-2000 showed an increased risk of men with history of sexually transmitted diseases (STD) to develop prostate cancer, especially Syphilis infection at relative risk 2.3 (CI: 1.3-3.9). Gonorrhoea infection was found to increase the risk to prostate cancer at OR 1.5 (CI: 1.02-2.18) (Dennis, 2002a). Another study also described history of gonorrhoea and syphilis with increased risk to prostate cancer to 60% and 80% respectively, while threefold increase risk if have history of gonorrhoea three or more times (Hayes *et al*, 2000). Another published data of meta-analysis of 29 case control studies showed significant combined calculated odds ratio for any STD, gonorrhoea and human papillomavirus at 1.48(CI: 1.26-1.73), 1.35(CI: 1.05-1.83) and 1.39(CI: 1.12-2.06) respectively (Taylor et al. 2005). Other STD such as herpes simplex virus type 2 was also associated with increased prostate cancer risk (Dennis *et al*, 2009), while

trichomonas vaginalis infection was associated with extraprostatic cancer and lethal or bony metastases death (Stark *et al*, 2009). History of prostatitis in one meta-analysis study showed increased risk to prostate cancer with pooled relative risk estimates of 1.57 (1.01-2.45) in random effects model (Dennis *et al*, 2002b).

In terms ejaculation count, an Australian study showed that at age 20's, subjects with ejaculation frequency of 5 times or more per week were at reduced risk (OR 0.66, CI: 0.49-0.87) compared to those who reported less frequent (Giles *et al*, 2003b). Another study of all forms of sexual activity showed that frequent sexual activity at younger age i.e. 20's showed higher risk of prostate cancer while at age 50's, frequent sexual activity would provide protective effect. However, the possibility of reverse causation could explain for these results. As the mean age of prostate cancer diagnosis among the cases in the study was 54.7 years, therefore due to prostate problems or diseases, they would experienced reduce sexual activity compared to the control group at their 50's. (Dimitropoulou *et al*, 2009).

1.3.6 Radiation or imaging

Ionizing radiation has been recognized to be carcinogenic to humans including exposure to imaging. A case control study in the United Kingdom by Myles on the effect of diagnostic radiation procedures has revealed statistically significant positive association with risk of prostate cancer. For an exposure to barium enema and hip x-rays at least 5 years prior to diagnosis, the odds ratio were 2.06(CI: 1.01-4.20) and 2.23(CI: 1.42-3.49) respectively. Upon selection among those with family history of cancer, only hip or pelvic x-ray remained having positive association with prostate cancer risk dating 5, 10 and 20 years before diagnosis at adjusted OR=3.55 (95%CI: 1.46-8.58), 5.01 (95%CI: 1.64-15.31) and 14.23 (95%CI: 1.83-110.74) respectively (Myles *et al*, 2008). Rahman did the analyses of the same exposures but based on the larger sample size and the results showed statistically significant increased risk of prostate cancer when exposed at any one time of hip or pelvic x-ray regardless of time of exposure if OR=3.15 (95%CI: 1.81-5.47) (Rahman, 2010).

1.3.7 Hormonal

The study of androgen hormonal level especially testosterone and its association with prostate cancer has used several surrogate markers in males such as presence of baldness, right hand pattern or 2^{nd} to 4^{th} digit length ratio in males,

and acne. In the right hand pattern, it has been explained in previous studies as due to higher levels of androgen such as testosterone prenatally causing men with phenotype of lower 2nd to 4th digit ratio (Manning *et al*, 2002). This could explain why quite a number studies showed those with lower ratio of 2nd to 4th digit, has increased prostate cancer risk. A Korean population study showed statistical significant odds ratio of 3.22 (CI: 1.33-7.78) for those with measurement 2nd to 4th digit ratio of less than 0.95 compared to those with ratio 0.95 and above (Jung *et al*, 2010). Alternatively, Rahman et al with the same data set used in this thesis showed a protective effect of 33% (OR 0.67, CI: 0.57-0.80) of those with higher 2nd to 4th digit ratio compared to those with lower ratio towards prostate cancer risk (Rahman *et al*, 2010).

1.3.8 Genetic mutation

Genetic studies are found to be less susceptible to confounding than observational epidemiology and can suggest associations between phenotype and diseases (Davey Smith & Ebrahim, 2003) to further suggest cause and effect. The existence of genetic variations can alter risk of developing phenotype as in obesity and diseases prostate cancer (Lewis *et al*, 2010). Hereditary prostate cancer cases are able to identify suggestive evidence for genetic linkage and can then be used as markers for absolute risk (Stanford *et al*, 2009; Xu *et al*, 2009). Some studies on genetics have identified prostate cancer susceptible loci i.e. single nucleotide polymorphisms (SNP) with relationship to family history and Gleason score of prostate cancer (Fitzgerald *et al*, 2009).

1.3.9 Pesticides

A case control study in Montreal Canada between 1979 to 1985, revealed leisure exposure to pesticides or garden sprays showed an increase OR of 2.3 (CI: 1.3-4.2) with prostate cancer risk (Sharpe *et al*, 2001). In an Agricultural Health Study(AHS) of 45 common pesticides used in agricultural industries of subjects between 1993 to 1997, only methyl bromide showed a statistically significant association with increase risk to prostate cancer as levels of exposure increased (Alavanja, 2003). A sub-study of Fonofos used by pesticide applicators showed increased rate ratio 1.77 (CI: 1.03-3.05) of those at highest lifetime exposure or intensity compared to those never been exposed as well as a significant dose response trend. However this was found to be true only in the stratified group with family history of prostate cancer showing a significant interaction of RR 1.28 (Mahajan *et al*, 2006). Agent Orange, a type of herbicide exposure used in the

Vietnam war veterans also showed an increased risk of prostate cancer at OR 2.19 (CI: 1.75-2.75) and development of prostate cancer at younger age and higher risk of two fold of developing more aggressive disease (Gleason score 8 – 10) compared to the unexposed (Chamie *et al*, 2008). A review and meta-analysis on the relationship between pesticide exposure in manufacturing workers showed quantitative meta-rate ratio of 1.28 (CI: 1.05-1.58) for risk of prostate cancer (Van Maele-Fabry *et al*, 2006).

1.3.10 Chemicals

Sharpe et al showed that leisure exposure to chemical lubricating oils or greases increased prostate cancer risk, OR 2.2 (CI: 1.2-3.7) (Sharpe *et al*, 2001). Diesel engine emissions exposure during farming in a study was also found to increase the risk of prostate cancer at OR 5.7 (CI: 1.2-26.5) (Parent *et al*, 2009). A significant dose respond trend association was found with the exposure to Trichloroethylene(TLC) and high exposure the risk of prostate cancer, OR 2.1 (CI: 1.2-3.9) (Krishnadasan *et al*, 2007).

1.3.11 Other factors

Vasectomy was found not significantly associated with prostate cancer in two case control studies (Cox *et al*, 2002; Holt *et al*, 2008).

Alcohol has been suggested in many epidemiological studies as causes of several cancers especially those of the digestive tract. However, findings on alcohol intake and prostate cancer risk have been inconsistent. Dennis & Hayes in their review article has suggested that only alcohol at high level intakes is associated with an attribute risk towards prostate cancer (Dennis & Hayes, 2001). A meta-analysis by Bagnardi concerning the association of alcohol and cancers, revealed no statistically significant association with prostate cancer (Bagnardi *et al*, 2001). Similar findings was found in cohort studies of Health Professional Follow up study by Platz (Platz *et al*, 2004) and European Prospective Investigation into Cancer and Nutrition (EPIC) by Rohrmann (Rohrmann *et al*, 2008). However a more recent study on Prostate Cancer Prevention Trial (PCPT) showed heavy consumption of alcohol was associated with double risk of developing high grade prostate cancer (Gong *et al*, 2009).

Smoking is an important risk to many cancers, but shows inconsistent associations with prostate cancer. An Australian study of case control subjects

found no significant association between smoking and prostate cancer (Giles *et al*, 2001). While a cohort study in US showed current smokers had an increased hazard risk for fatal prostate cancer at HR 1.69(CI: 1.25-2.27), but both current and former smokers are at reduced risk for non-advanced prostate cancer at HR 0.82(CI: 0.77-0.88) and 0.89(CI: 0.86-0.93) respectively, while no association with advanced prostate cancer (Watters *et al*, 2009).

Meat or meat related compounds have been associated with quite number of chronic diseases. A cohort study with nine years follow up with baseline diet intake taken, done in US for those age 50-71 years, revealed a statistically significant trend of increased hazard ratio for prostate cancer at higher level intake of red and processed meat. It was also found that both red meat and processed meat increased intake have higher risk for advanced prostate cancer (Sinha *et al*, 2009). However, a recent meta-analysis reported in 2010 on specific red or processed meat intake and dose response analysis to risk of prostate cancer, using random effects model to generate summary relative risk estimates (SRRE) has shown no association between high and low intake to prostate cancer risk (Alexander *et al*, 2010).

1.4 Background Work in Malaysia

This background work has been added to the first chapter in recognition of the substantial amount of work and time spent during the first year of my PhD program. A research project on prostate cancer was proposed under the Malaysia-Nottingham Doctoral Programme (MNDP Split programme) to be carried out in Sabah, Malaysia. However due to unforeseen circumstances and difficulties faced with limited time duration and an unsuccessful application of project funding, a study idea with similar topic, but based here in the UK, was provided as an alternative by my external supervisors.

The UK Prostate Cancer Case Control: Gene-Environment Interaction study a consortium of collaboration work between the University of Nottingham , University of Warwick and the Institute of Cancer Research UK. It began in 1999 and aimed to investigate environmental exposures associated with risk prostate cancer and to explore genetic aspects of prostate cancer aetiology. Since this UK study project is similar to my earlier agreed proposed study in Malaysia, and had already had data collected my supervisors allowed me to the use this data as an

alternative research project to ensure the achievable of PhD completion within 4 years.

Hence, the literature review, methodology, analysis, results and discussion of this thesis report are based on the UK experience.

The proposed Sabah (Malaysia) Prostate Cancer Risk Factors study report is depicted here as below.

WORK DONE WHILE IN MALAYSIA JULY 2008 – AUG 2010

Background Study site & Research Questions

Study site background

The state of Sabah, Malaysia was chosen as I'm from there and based at the University Malaysia Sabah, School of Medicine for the 2nd phase of my PhD study. Since Sabah has only one tertiary hospital situated in Kota Kinabalu, and one state urologist surgeon attached with Queen Elizabeth Hospital, it presented an ideal study site within this hospital; all patients from Sabah will be under the single state urologist. It was intended that district hospitals and health clinics may be involved during the course of the project.

Study Design & Sample size

The proposed study was a case-control study aiming to recruit 400 cases from government health clinics /hospitals within 5 years (allowing 3 years of previous diagnosed cases and 2 years of new incidence cases), and similar number subjects for controls.

Study Aims

To study possible role of diet, pesticide exposure, lifestyle habits and genetic factors on the risk of developing prostate cancer in Sabah, Malaysia

Tools for Research

Preparing the Prostate Cancer Questionnaire

The Questionnaire used in this study is adapted from the ones used in Gene-Environment Interactions in Prostate Cancer copyright of Division of Epidemiology and Public Health, University of Nottingham, Institute of Cancer Research and Royal Marsden Hospital, NHS Trust, United Kingdom.

The Questionnaire has been prepared both in English and Bahasa Malaysia. The Questionnaire was designed to suit both; self completed or by interview completion. Since majority of people in Sabah may prefer interview technique,

due to diversity of ethnic language and dialect, the researcher decided that both methods would be used for information gathering.

The questionnaire for the study would take about 30-45 minutes to complete by interview technique. Participants may decide to complete the questionnaire on their own if they are preferred. However they will be supervisor available in case of inquiry or unanswered sections.

The initial preparation of the Questionnaire was done in English, and then translated to Bahasa Malaysia. Work was carried to retranslate the Bahasa Malaysia version back to English. Corrections were made to in order to get the best suited terms, to obtain the same information with either language. This was done with the help and expertise of several language lecturers/tutors and translators.

To assure content validity of the Questionnaire, experts' help were obtained from local Nutritionist epidemiologists, Surgeons and Public Health epidemiologists. Corrections were made based on consensus and majority recommendation.

Preparing the Research Protocol & Budget

Research Protocol

The research protocol was prepared with the help of review by PhD supervisors.

Budget Requirement

Budget for the study in Malaysia was estimated to be RM211,800 (equivalent to £43,000).

Collaboration work with participating centres

Identifying sources of data

Data sources on prostate cancer incidence were obtained from National Cancer Registry 2002 & 2003 of Clinical Research Centre (Kuala Lumpur General Hospital), Penang & Sarawak State Regional Cancer Registry, Public Health Department of Ministry of Health Malaysia, and Globocan.

Collaboration effort

The research project on prostate cancer in Sabah, Malaysia was proposed through collaboration of the following agencies/centres.

i. School of Medicine, University Malaysia Sabah, Kota Kinabalu, Sabah
ii. Queen Elizabeth Hospital, Kota Kinabalu, Sabah
iii. Sabah State Health Department, Sabah

iv. University of Nottingham, UK

A memorandum of understanding was prepared that bears the signatures the main investigator (myself) representing University Malaysia Sabah, co-investigator (state urologist), the Head of Surgical Department and Director of Queen Elizabeth Hospital, stating clearly the duties and rights of each agency/centre, also the ownership of data, publication authorship, etc.

Ethical Approval & Ministry of Health Malaysia Approval

Medical Ethical Approval

The project received its unconditional approval from the highest level of medical research ethical committee authority in Malaysia, namely MREC, Malaysia Ministry of Health, on 3rd August 2009.

Ministry Approval

The study project received its approval to start work with consent letter from the Queen Elizabeth Hospital Director and also the Sabah State Health Department Deputy Director (Hospital Services) in March 2009.

Grant/Funding Application

Potential Sources of Funding & Application made

Several applications for funding were done during the course of events beginning in UK, with help from my PhD supervisors. I've also personally made several enquiries of funding possibilities while in Malaysia with University Fundamental Research Grant, e-science Ministry of Science & Technology, then Ministry of Health. Since this research project is done by a lecturer on full study leave, the grant application could not be proceed further at that time for university fundamental research grant and e-science Ministry of Science & Technology. Furthermore, I'm doing a split PhD programme between UK and Malaysia, not fully based in Malaysia. The Ministry of Health Malaysia ranked cancer study as 3rd level priority therefore approval was not granted at the 1st round of review board committee without explanation. Other funding possibilities were explored but were unsuccessful as prostate cancer was not major cancer in Malaysia, and the economic climate was not conducive at that time in 2008-2010.

Discussion & Outcome of First/Second Year Work

Results

The disappointment of the failed funding application was further compounded by the recognition of significant risks. Some of the issues that could hinder the prostate cancer risk factors study in Sabah Malaysia were:

i. Logistics & Transportation

The feasibility of conducting the study is quite a challenge which requires availability of transportation to reach patients in their own homes or nearest health clinics either by motor road, on foot if hilly mountains and by boat. Since most of the patients are old and poor, it is a major issue for them to move around even to the closest health centre due to both financial and transportation issues.

The logistics and transportation factors would also be an issue for relaying blood samples for genetic studies after collection because of the requirement for fast freezing at -80 degree celsius within the same day of collection to ensure the samples' viability. For patients living in remote locations away from centres for blood collection, poor accessibility, or unreliable transportation, would possibly preclude the involvement of biological protocol for the study.

ii. Language barrier & Literacy

As population of Sabah is of diverse races and ethnicity, even though Malay is the national language of Malaysia, the people in Sabah are only 10% of Malay origin, while the rest are of native/indigenous group or Chinese. For those aged 50 and above, many would struggle with usage of Malay in their daily conversation so this would affect recruitment.

Even though the reported literacy rate in Sabah as of 2008 was at 87%, the lowest among all the states in Malaysia, the actual literacy rate is lower. It could be expected that there have been unfamiliarity of intermediate to advanced vocabulary; which would further reduce recruitment. Previous attempts at postal questionnaires have been unsuccessful, favouring face to face interviews, but this requires appointment, more personnel/enumerators and most importantly reliable interpreters.

iii. HIV Screening for blood sample

This study involved the collection of 10-20ml of blood from subjects for genetic chromosomal studies. Before it can enter UK for processing either DNA extraction or chromosomal studies, the law requires the identification of HIV status of each sample for biohazard reasons. In Malaysia, HIV testing or screening is not a routine procedure and requires consent and counselling to patients as guidelines were given by Ministry of Health. HIV screening without consent only done to prisoners under special circumstances, otherwise in cases of Tuberculosis or

women 1st pregnancy, it is a routine procedure, but patient can still refuse to undergo such test/screening.

iv. Storage of blood samples

Based on the survey done on the availability of freezer with -80 degree Celsius capability, only University Malaysia provides the facility free of charge but with limited storage. Although I obtained approval to use this special freezer based in the Institute of Tropical Biology and Institute of Biotechnology, the actual volume with blood 10ml test tube would take up lots of space, as the centres only allowed usage of pipette tip tubes 2ml. The fridges, approximately three in total are also of common use of all researchers. The government hospitals in Sabah, do not have these special fridges. The coldest freezers they have are only capable to reach -20 to -30 degree Celsius maximum.

v. Funding

This is the most critical factor to consider. The budget for this study costing approximately £43K is based on estimation of two years with most expenditure spent on salary and honorarium, which account for almost 65%. However considering the need for interpreters of various languages would require additional funding, as the proposed budget only costed 1 person to do interviewing or as enumerator.

Due to the lack of research money in the sector of cancer prevention research, most government doctors and clinicians are referring to academicians for help in getting the grant as well as leading the research work. Funding from Ministry of Health or other grants are only offered for level 1 priority applications. Furthermore, previous epidemiological studies in Malaysia justified grants of no more than £20,000.

Discussion how to move forward

Although it would be a great challenge to start an ambitious yet achievable research project on prostate cancer in Sabah, Malaysia, the preparatory work had identified ground arrangements and sites had been identified, there were major and minor issues that needed to be smoothed out in order to ensure the project could progress which would have led to new scientific discoveries and learning as well as experiences to be used to help other similar in the near future.

Since I've brought up the issues as in the results paragraph, I might as well try to discuss for any possibility of any of these areas within my control of improvement or self solving.

i. Logistics & Transportation

The issues of logistics and transportation became an important obstacle in carrying the prostate cancer study because the crucial tasks of trying to obtain all reported cases of prostate cancer in the state of Sabah, since the incidence rate in Sabah is low approximately of 3.8 per 100,000 male populations or 65 new cases yearly. The issue is to balance between not losing any cases subject while at the same time saving cost for transportation.

The improvement and cost saving methods would be to set up appointments at health centres which are easily accessible by road for the research team, and probably need help with the local town healthcare system's staffs to assist in the issue of patients coming from areas inaccessible by road. The appointment for each individual subject should be minimized, so that within a single appointment all procedures such as consent, questionnaire filling and blood sample be collected, so that subject need not return for a second appointment.

If the blood collection were done on weekdays, it should be stored temporarily in cool box with ice and within 6 hours or less be sent to a proper freezer, or stored immediately to a -80 degree centigrade freezer. However as said earlier, the only free storage of the blood samples in this special freezer is available in University Malaysia Sabah, Kota Kinabalu.

ii. Language barrier & Literacy

In order to best address this problem of multiple languages recruitment local people from each district with fluent grasp of the local language and dialects to be employed as enumerators. They would need to be trained to be able to interpret any specific terms used during the interview. The primary language used would still be Malay or English (as these two versions have been prepared by the principal investigator much earlier).

The advantages of interviewing patients would be to minimise the loss any information and to ensure subjects understood the content of the questionnaire. The only disadvantage would be lack of openness or disclosure of the truth in information by the subject especially when the questions are of intimate or

private such as number of sexual partners or other prohibited habits/behaviour by religion.

iii. HIV Screening for blood sample

HIV screening if required can still be done with proper consent and counselling to subjects by specific trained healthcare staff. However the cost of doing HIV testing would be high as it is normally taken up by private labs, and at the same time would require steps to follow up subjects who are found to be HIV reactive/positive. Arrangement can be done for such subjects by referring them to the system of healthcare available in the district.

iv. Storage of blood samples

This is a worrying issue as the availability of special freezer with capability temperature -80 degree Celsius which provide free storage are scarce, at the same time provide minimal storage volume. The best solution would be to buy such freezer and be placed at the University in Sabah as it would be valuable for any research involving life cells. This would take time and lots of justification as School of Medicine in the University Malaysia Sabah has not geared much into areas of molecular or genetic medicine or research, therefore only time will tell.

Another option would be to try to store the blood sample collected in private fridges but would incur cost over the course of time, but quite safe.

v. Funding

The cost of hiring staff technicians and enumerators as well as travelling claims for patients requires proper budgeting. The inclusion of blood sample collection increased the cost because of the raw materials, containers, ice, transportation etc.

Based on the latest news on funding for genome/chromosomal analysis, a group of funders of the United States provide minimal amount of money, measured by the number of blood test tube collected. This might be able to cover some of the cost of the raw materials and transportation to overseas, but doesn't necessarily cover the whole expenditure of the research project.

Another way would be to seek seed money from small funders such as local medical association/society (RM5000 or £1000) for a pilot project of epidemiological study of the prostate cancer, and producing initial findings and

publishing an article that would hope to get the government's attention on the importance of such research and gain the bigger funders in Malaysia to allow approval for grant in prostate cancer risks study at bigger scale.

Redefining the prostate cancer risks study to the approach of prevention and contributing to world statistics information on genetic or hereditary predisposition in Malaysia is still new, as most of such studies are initiated by foreign countries collaborators. Malaysia Genome Institute (GENOMalaysia) is a network-based not-for-profit research organization engaging in discovery research on tropical bio-resources through projects on genome sequencing, comparative and functional genomics, and structural biology. There could be a potential approach to collaborate with this institute in the near future.

Conclusions

In order to assure the success of the above according to the created standards equivalent to similar studies done in more developed countries such as in the Europe, there will be a need to iron out all the above issues as well as scrutinize the finer details before the research ever commence.

The uptake of the prostate cancer risks study would be a good collaboration work between the consortiums of Prostate Cancer Study in UK, and would benefit towards the building of information on the associated risks of prostate cancer whether in South East Asian countries or Europe. The short term goal of this project would be to explore common risks factors in different population, while associating the genetic interaction with environmental factors. The middle term goal would be to find specific risks factors which are unique for Sabah (Malaysia) population, smoothing the project with a view to expand to wider areas and building larger database as to create for more study strength. The long term goal would be the look at the cause and effect of prostate cancer, as well as setting up public health guidelines on preventive measures.

Chapter 2 Rationale, Hypothesis & Objectives

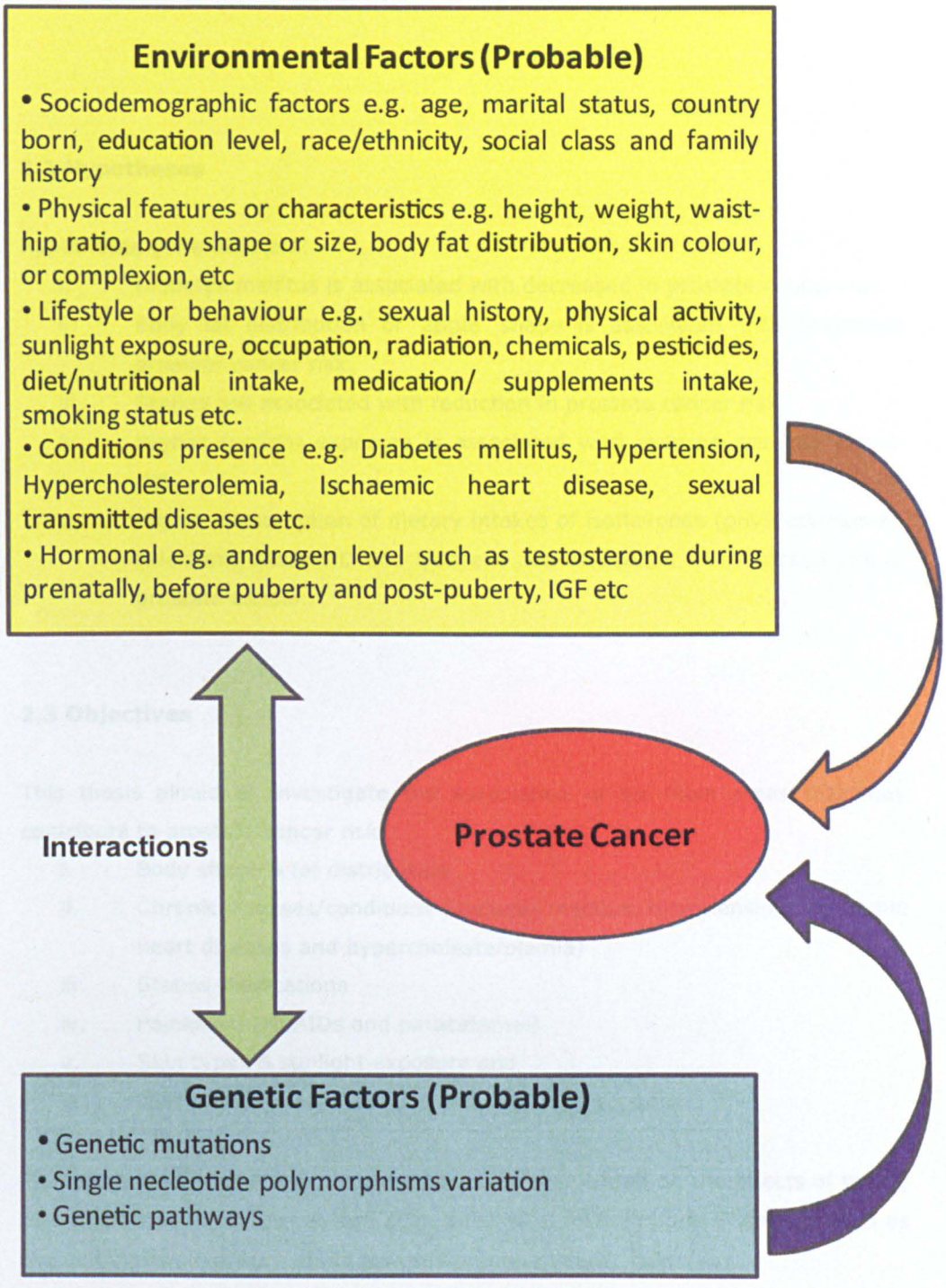
2.1 Rationale

Prostate cancer is the most common male cancer in Europe and the United Kingdom. Due to the higher number of men diagnosed with prostate cancer, knowledge on factors associated with risk towards this cancer is important. Prostate cancer risk has been associated with several environmental factors, although genetic factors are also suggested to be involved. Literature review suggests some of these environmental exposures (both modifiable and non-modifiable) including physical features/characteristics, lifestyle behavior, diet or medication intake as well as presence of medical conditions which could be associated with prostate cancer risk.

The current knowledge on the environmental factors that could be associated with prostate cancer remain poorly understood when compared to other common cancers such as breast or lung cancers. Furthermore, the exploration of dose response aspects based on the effects of timing and of lifetime exposures that may add to the risk are lacking and therefore explored further in this study.

Our hypotheses focused on certain environmental exposures which may increase or reduce the risk of prostate cancer are largely based on previous publication in prominent journals during the last decade. Hypotheses are generated based on the biological plausibility of current understanding.

Figure 2-1.Possible Factors Associated with Prostate Cancer Risk



2.2 Hypotheses

Hypotheses generated are:

i. Diabetes mellitus is associated with decreased in prostate cancer risk.

ii. Body fat distribution of 'apple' shape is associated with decreased prostate cancer risk.

iii. Statins are associated with reduction in prostate cancer risk.

iv. Higher sunlight exposure is associated with reduced prostate cancer risk.

v. Higher consumption of dietary intakes of isoflavones (phytoestrogens), selenium, vitamin D and lycopene are associated with reduced risk of prostate cancer.

2.3 Objectives

This thesis aimed to investigate the association of six main areas that may contribute to prostate cancer risk:

i. Body shape & fat distribution

ii. Chronic diseases/conditions (diabetes mellitus, hypertension, ischaemic heart diseases and hypercholesterolemia)

iii. Statins medications

iv. Painkillers (NSAIDs and paracetamol)

v. Skin types & sunlight exposure and

vi. Diet (isoflavones, selenium, vitamin D & lycopene)

This study also aimed to explore the dose response based on the effects of timing and of lifetime exposures at age 20's, 30's, 40's, 50's and last 5 years as well as the cumulative exposure effect towards prostate cancer risk.

Chapter 3 Methodology

3.1 Sabah Malaysia Prostate Cancer Study Protocol

The early work and initial proposed PhD study protocol was based on a Prostate Cancer Case-Control in Sabah, Malaysia and is briefly presented here.

Title of project

Possible role of diet, pesticide exposure, lifestyle habits and genetic factors to risk of developing prostate cancer in Sabah, Malaysia.

Aims

i. To assess the association between prostate cancer and diet.

ii. To explore the potential risk of prostate cancer due to pesticide and environmental factors.

iii. To determine the relationship of lifestyle habits such as exercise, smoking, etc to prostate cancer.

iv. To determine genetic role in prostate cancer.

Project Background & Rationale

In the Malaysia Cancer Registry 2002 and 2003, prostate cancer is recorded the 6th highest incidence and rate of cancers among men after lung, nasopharynx, colon, leukemia and rectum. We proposed a three year project on the basis that the study will inform Malaysia, UK and the world generally about the risk factors that associate with prostate cancer in Sabah, Malaysia. Given that this study would probably be the biggest study on cancer on this population and in particular prostate cancer risk factors, it would provide useful information on different ethnic groups of Asia in particular state of Sabah in Malaysia about the potential risk and interaction of endocrine disrupters towards prostate cancer. The study would be on successful collaboration work between the University of Nottingham, UK, University Malaysia Sabah and Ministry of Health, Malaysia. Furthermore, the study would further look at genetic factors that could post a risk of prostate in the Malaysian population.

Study Design

Matched case-control study of 1:2 ratio

Study Duration

Three years beginning January 2009.

Sample Size, Power & Statistical analysis

A sample size of 383 cases and 766 controls is required to detect odds ratios greater than 2.0 or less than 0.6 with a power of 80%. The calculation is based on the following assumption: matched ratio 1:2, exposure rate 15% in control group, type-I error 5% and a correlation coefficient of 0.6 for exposure between matched cases and controls.

According to Malaysian National Cancer Registry in 2002 the total cancer incidence in Sabah population is about 59.3 per 100,000 male populations. If 6.4% of all male cancers are prostate cancer, based on Peninsular Malaysia figure, therefore the incidence rate of prostate cancer in Sabah is 3.8 per 100,000 male populations. Population in Sabah is about 3.3 million in 2007 based on projection population census 2000 with 4.0% growth annually.

Therefore with population of males around 1.7 million in Sabah and prostate cancer incidence rate of 3.8 per 100,000 male populations, the no. of prostate cancer cases would be approximately 65 cases per year. In order to obtain 400 cases for the study, the subjects enrolled would need to accumulate 5 years of prostate cancer cases (2004-2008) from registered lists of cancer patients from Sabah state Cancer Registry and hospitals which diagnosed and manages prostate cancer patients, then another two years after the study began, considering some patients would have died subsequent years after diagnosis. Only incident and primary cases will be included. In case of shortfall in the number of cases, the researcher would include neighbouring state of Sarawak, or Kuala Lumpur, Malaysia.

Selection of Cases and Controls

i. Source and identification of cases:

Case is defined as pathologically confirmed prostate cancer newly diagnosed in Sabah during the study period for data and specimen collection which would be 1.5 years duration as well as confirmed cases reported earlier within five years since the study began. This is done to ensure the number of subjects would be adequate.

The subjects enrolled would accumulate 5 years of prostate cancer cases from registered lists of cancer patients from Sabah state Cancer Registry and hospitals which diagnosed and manages prostate cancer patients, if alive 2004-2008 then another two years after the study began sometime in 2009, considering some patients would have died subsequent years after diagnosis. Only incident and primary cases will be included.

ii. Source and identification of control:

Controls and cases will be matched on age (within 5 years), residence area (in the same district area) and major ethnic group. They will be randomly selected from the outpatient list in the same hospital where the index cases diagnosed however differ in diagnosis which is not related with prostate cancer. Subjects will be excluded if they had any previous history of cancer.

Eligibility of Cases and Control

Inclusion criteria are:

Men newly diagnosed with primary prostate cancer confirmed histology during the research period; or

Prostate cancer patients who were diagnosed with confirmed histology as primary cases between 2004-2008 and still alive

Cases who have given informed oral or signature consent.

All age group as long as they're able to understand and response to the interview.

Control eligibility:

Five years age matched men from same hospital or district registry of cases in the outpatient list who has never been diagnosed of any cancer except skin cancer

Controls who have given informed oral or signature consent.

All age groups as long as they're able to understand and response to the interview.

For those above 60 years old, only normal PSA test result would be invited to become controls.

Case and control ineligibility:

Inability to understand and respond to the interview.

Those who have not given their consent either orally or signature.

Recruitment

Case Recruitment:

This study obtained its permission to conduct the research from the Malaysia Ministry of Health and Ethic committee. This study would seek further approval from respective hospitals and Sabah state health department to view cancer registry list, hospital records of diagnoses, as well as persons, subjects or patients' medical records.

The cancer registry list at the state health office of Sabah will provide the prostate cancer patients, however since these may not be an up to date and complete list of all reported cases, further scrutiny for unlisted cases will be done at hospitals which diagnose or manage prostate cancer patients through their discharge diagnosis record or medical records of the hospital. The hospitals that would be covered in Sabah would be hospitals with prostate cancer patients care namely Queen Elizabeth Hospital. After prostate cancer patients have been identified, they will be recorded in a new list of prostate cancer patients in Sabah or in the individual hospital. Main variables of interest would be to identify the time of the diagnosis which would be year 2003 onwards, as well as identifying their date of birth and current addresses in order to match them with control group selection.

All subjects would be contacted by phone call or letter to invite them to participate in the study. An appointment would be set up in the nearest hospital or health centre to meet up with them and explain to them about the study before requesting their consent to participate. To all who agree to participate, interviews using the questionnaire would be carried out, as well as venous blood samples extraction.

Control recruitment:

Control subjects will be matched on age (within 5 years) and residence area (in the same province). They will be randomly selected from the outpatient list in the same hospital where the index cases were diagnosed and differ in that they had a diagnosis which is not related with prostate cancer. Subjects will be excluded if they had any previous cancer history apart from skin cancer.

All subjects would be contacted by phone call or letter to invite them to participate in the study. An appointment would be set up in the nearest hospital or health centre to meet up with them and explain to them about the study before requesting their consent to participate. To all who agree to participate, interview through questionnaire would be carried out, as well as venous blood samples extraction.

The Questionnaire

The questionnaire used in this study is adapted from the ones used in Gene-Environment Interactions in Prostate Cancer copyright of Division of Epidemiology and Public Health, University of Nottingham, Institute of Cancer Research and Royal Marsden Hospital NHS Trust, United Kingdom.

The questionnaire has been prepared both in English and Bahasa Malaysia. The questionnaire was designed to suit both; self completed or interview. Since the majority of people in Sabah may prefer an interview due to diversity of ethnic language and dialect, the researcher decided to use both methods for information gathering.

The questionnaire for the study would take about 45 minutes to one half hour to complete through interview. Participants may decide to fill up the questionnaire on their own if they are more comfortable to do so. However they will be supervised closely in case of inquiry and unanswered sections.

The initial preparation of the questionnaire was done in English, and then translated to Bahasa Malaysia. Work was carried to retranslate the Bahasa Malaysia version to English to check for consistency. Corrections were made in order to get the best suited terms and to obtain the same information required. This was done with the help and expertise of several language lecturers/tutors and translators.

To assure content validity on the questionnaire, help was obtained from local Nutritionist epidemiologists, Surgeons and Public Health epidemiologists. Corrections are made based on consensus and majority recommendation.

The questionnaire used in the research would be tested on people of the common population in Sabah, similar to the case subjects and covers main ethnic groups in Sabah. Corrections were made after pre-testing. Finally it would be pretested on actual 30 cases and control subjects and tested for reliability through Cronbach alpha test. These pretested groups will not be included in the final analysis of the result of this study.

The structured questionnaire will consist of the following sections:
Clinical Data (completed separately by researcher)
Personal details and socio-economic background
Job history and chemical substance exposure
Physical features
Social history
Physical activity
Diet history
History of medical illness & family history of prostate cancer

Biological Samples

Written consent would be sought prospectively from all cases and controls who agree to participate including questionnaire and blood samples taken in this study.

The main biological sample obtained in this study is 10mls of venous blood collected from both cases and controls through phlebotomy/venupuncture done by a medical officer, nurse or lab technologist. Samples collected will be labeled with codes and dates, preserved in 400 micro-units of heparin and stored in a tube box temporarily before transferred to the laboratory. The blood specimens will then be centrifuged and separated into three components, red blood cells or blood clot, buffy coat and serum. Each component for the blood samples from individuals was then contained in a 1.5 ml micro-tube with its cover and stored in the freezer at temperature of -80 celcius. in two different freezers in Universiti Malaysia Sabah, Kota Kinabalu until the end period of data collection before being sent to the principal investigator in United Kingdom for genome scan analysis and DNA extraction.

The genetic analyses done on the blood samples are to find the prostate cancer predisposition genes, however the results will not be conveyed to the cases and controls research subjects.

Study Outcome

Due to unforeseen circumstances namely inability in obtaining grants to fund the Prostate Cancer study in Sabah, as well as limited time to complete my PhD, this study was halted until a further suitable time. As a continuation of the much initial groundwork planning done in Sabah, my supervisors has offered an alternative similar study by providing the data from the UK Prostate Cancer Case-Control Study. Data is in its' raw form for data entering, cleaning, analysis, interpretation and write-up. The focus of the analysis was centred on chronic diseases, medications, sunlight and diet.

The UK Prostate Cancer Study Background

All data analysed and presented in this thesis were from the Prostate Cancer Study on Gene-Environment Interactions. The study is an ongoing and a large scale case-control study. The study is in collaboration between the University of Nottingham , the University of Warwick and the Institute of Cancer Research UK. It began in 1999 and is aim to investigate environmental exposures associated with risk prostate cancer and to also collect biological samples/markers for further genotyping aspect of prostate cancer aetiology.

The data collection was divided into two phases, the first phase collection being focussed on young onset cases (≤60 years), began in March 1999 through to December 2004, data set was frozen for the purpose of interim analyses, critical reviewed/modified questionnaire, simplified/improved data collection process. The second phase collection was started in December 2007 through to September 2009. This was done to assess any new leads of both genetics and environmental exposures. The second phase extended the cover subjects at all ages.

Aims

This Prostate Cancer Case-Control study design aims to study the epidemiological association between environmental factors and risk to prostate cancer. The study also aimed to examine the aspects of time of exposure at different age period and cummulative effect as to prostate cancer risk.

Specific Objectives

Part of the extensive dataset was analysed by previous PhD student, Dr Aneela A Rahman (Rahman, 2010). In this present thesis, a further six main areas were analysed thus the study objectives are as follows;
To study the association of the following variables of interest on prostate cancer risk:

- Chronic diseases: Diabetes Mellitus, Hypertension, Ischaemic Heart Diseases and Hypercholesterolemia
- Body shape and Body Fat distribution
- Statins medication
- Painkiller NSAIDs Aspirin & Ibuprofen and Paracetamol
- Skin colour, sun effects and Sunlight exposure
- Diet nutrition of Isoflavones (Phytoestrogens), Selenium, Vitamin D and Lycopene

Literature review

Searches for articles of scientific, relevant and most up to date materials were carried out through the search engines in Medline and Pubmed. However relevant publication such as theses and textbooks were also searched through Unloc search engine of medical school university library. Only scientifically sound published articles of journals, textbooks, scientific documents including theses and reports, as well as online documents from nationally or internationally well regarded and recognized websites of good reputability were used for information resources in this PhD thesis.

Study Design

The Prostate Cancer Gene-Environment Interaction is a case-control study design.

Power and Sampling technique

Sample size and power was calculated using power and sample size programme (PS) version 3.0.43. The total number of cases and controls in the study are 1963 and 2078 respectively. This setting will have 80% power to detect odds ratios of 1.502, 1.363, 1.314 or the same power is also able to detect risk reduction with odds ratios of 0.643, 0.723 and 0.756 when the exposure rates in controls are at 10%, 20% and 30% respectively when Alpha level was set at 0.05, correlation coefficient at 0.5 for the calculations (Refer Figure 3-1 page 3-39, Figure 3-2 page 3-39 and Figure 3-3 page 3-39).

Figure 3-1 Detectable odds ratio at prevalence of exposure in controls at 10%

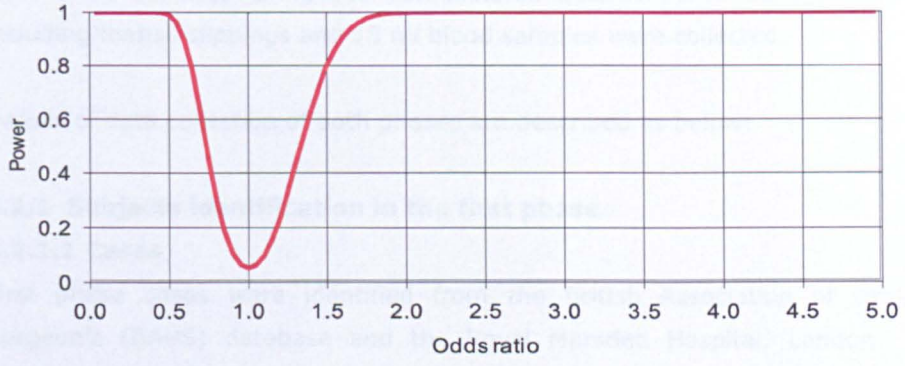


Figure 3-2 Detectable odds ratio at prevalence of exposure in controls at 20%

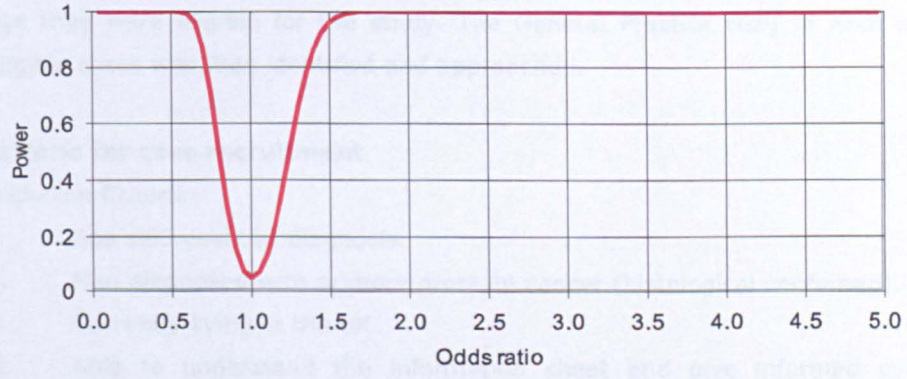
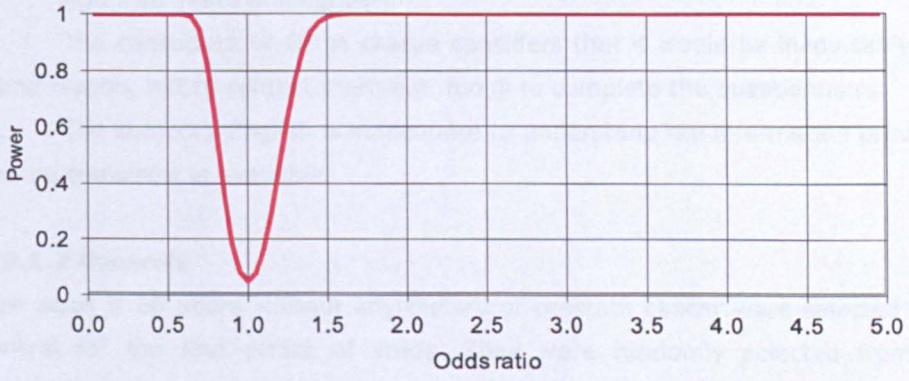


Figure 3-3 Detectable odds ratio at prevalence of exposure in controls at 30%



3.2 Data collection

Data were collected using self administered questionnaire. Biological samples including toenail clippings and 18 ml blood samples were collected.

Details of data collection of both phases are described as below:

3.2.1 Subjects identification in the first phase

3.2.1.1 Cases

First phase cases were identified from the British Association of Urological Surgeon's (BAUS) database and the Royal Marsden Hospital, London. These patients are registered with the UK Genetic Prostate Cancer Study (UKGPCS). The BAUS database is a nationwide cancer registry for urologists who have notified urological cancers to the BAUS organisation. If cases had been diagnosed with prostate cancer from January 1997 to September 2004 and were ≤60 years of age they were eligible for the study. The General Practice (GP) of each of the eligible cases was then identified and approached.

Criteria for case recruitment

Inclusion Criteria:

i. Age ≤60 years at diagnosis.

ii. Men diagnosed with primary prostate cancer (histological confirmed).

iii. Currently living in the UK.

iv. Able to understand the information sheet and give informed consent directly or via an interpreter.

Exclusion criteria:

i. Age >60 years at diagnosis.

ii. The consultant or GP in charge considers that it would be inadvisable, for some reason, not to contact them e.g. too ill to complete the questionnaire.

iii. The subject's English is inadequate to understand the information provided and no translator is available.

3.2.1.2 Controls

Men aged ≤ 60 years without any history of prostate cancer were selected as a control for the first phase of study. They were randomly selected from GP practices where cases were registered. Controls were matched by age and geography. Controls were only excluded by their GPs if they are too ill or unwilling to participate.

3.2.2 Subject identification in the second phase

3.2.2.1 Case

Second phase cases were identified from The Royal Marsden Hospital, London. These patients registered with the UK Genetic Prostate Cancer Study (UKGPCS). The list of cases had been received through series of case downloads from the Royal Marsden Hospital, London. These cases are either referral cases or had been notified by their consultant to the study team at the Royal Marsden Hospital.

Inclusion criteria:

i. Men diagnosed with primary prostate cancer at any age.
ii. Histological confirmed diagnosis.
iii. Currently living in the UK.
iv. Able to understand the information sheet and give informed consent.

Exclusion criteria:

i. The consultant or GP in charge considers that it would be inadvisable for some reason, not to contact them e.g. too ill to complete the questionnaire.
ii. The subject's English is inadequate to understand the information provided and no translator is available.

3.2.2.2 Control

Age-frequency-matched men were randomly selected from the GP practices without any history of prostate cancer. All participants have to be able to understand the information sheet and give informed consent. Exclusion criteria for controls were identical as for cases. In addition, those who were ineligible or were unwilling to participate were recorded and further removed from the working database.

3.2.3 Recruitment Procedure

3.2.3.1 Case recruitment for the first phase

The initial approach to GPs was made to explain the study and seek their co-operation. Those GPs willing to take part in the study, the study group would arrange patient information sheets and consent forms to be dispatched to practices. The invitation letter was signed by the GP and printed on practice headed paper. All documents including invitation letter, patient information sheet,

consent form and one reminder letter were sent out via GP practices until the consent was given or if no reply received within 4 weeks, no further follow-up would be made. Patient consent forms were returned to the centre; and personal information including study ID, NHS number, name, date of birth, and contact details was then be recorded onto database. Once patients consented to fill the questionnaire and provide biological samples including blood, toe nail clippings, the questionnaires would be sent to participants and blood kit and plastic vial was sent to the practice and with the arranged phlebotomist of the practice, the blood sample was taken and sent back to the research team at the Royal Marsden Hospital. Toenail samples were sent back to the epicentre.

3.2.3.2 Case recruitment for the second phase

The Royal Marsden hospital were in charge of identifying and getting consent from eligible cases, taking blood samples and notifying epicentre if the patients gave consent to provide questionnaire data. Data was sent to epicentre through secure FTP server. Personal information including study ID, NHS number, name, date of birth, date of blood collection and contact details was recorded on the epicentre database.

As the UKGPCS consent form only covers blood sample collection and permission to participate in epidemiological study, a separate invitation letter together with the patient information sheet and consent form was sent out from epicentre. One reminder was sent via epicentre, if no reply was received within 4 weeks, no further follow-up was made. Consent form includes:

i. Completing the study questionnaire
ii. Giving a toenail clipping sample (optional)
iii. Providing the blood sample (optional)
iv. Giving the permission for the study group to access their medical records (optional).

Once the consent form was received, a written instruction to explain the procedure, a copy of the questionnaire and/or a plastic vial/bag for toenail sample collection together with a self-addressed envelope for returning questionnaire and toenail clipping sample were sent to the subject home address.

A telephone helpline was provided at the back of the questionnaire to help clarify any further queries regarding the study (see the appendix). If questionnaire/

toenails were not received within four weeks, one reminder was sent without further follow-up.

Blood collection for cases was carried out by Research team at the Royal Marsden Hospital, London.

3.2.3.3 Control recruitment procedure

For both phases of data collection, there were similar approaches only the second phase controls were sought locally within the Nottingham area as well as nationally. Initially, the study was designed to use individual-matched controls (matched on age within five years and GP surgery). However, due to low response rate of GP practices, an alternative approach was introduced later on by selecting GPs from ten representative areas (one GP per one area) in the country to help identify age-frequency matched controls. Practices were asked to randomly select 50 healthy controls with no prostate cancer history from their patient list. Initial approach was made by GP and participants were invited to fill out the study questionnaire, to give 2 x 9 ml of blood sample (optional) or give toenail clipping samples (optional) for further analysis. All blood samples were taken at GP practice then posted to the Royal Marsden Hospital (first phase) or the epicentre (second phase) on the same day or the next working day. All samples were logged and kept at -70 degree Celsius secured deep freezer.

It is noted that the study had offered to cover administrative costs for each practice. As mentioned above, controls selection was expanded to cover local area in Nottinghamshire. The reason is that the study applied a newly developed computer program aiming to help saving GP time/workloads and as it was done locally, any technical problems could be sorted out in person very quickly to make sure the program functioned well.

3.2.3.4 The Nottingham Centre

Controls from city of Nottingham had been selected from GP electronic records using series of Medical "Read" codes. The Read Codes cover a wide range of clinical terms from signs and symptoms, diagnostic tests, drug appliances, treatment and therapies received to diagnosis. A list of codes was set up to identify both prostate cancer patients and healthy control based on Read Codes versions 2 and 3. A computerised programme compatible with the GP practices working system EMIS and System One had been designed to generate a list of potential control subjects. The list was then passed onto the GP for further

checking/confirmation of their well-being. After GP validation, any subjects that were not suitable were removed from the database. Invitation letters were generated automatically from the list at the practice using installed letter template that accompanied with the program. All documents were then packed and sent out from the practice to each individual. Once subject sent their consent form back to the researcher; the next steps followed the same procedures as described above.

3.2.3.5 Blood Collection for local controls (Nottinghamshire)

After receiving questionnaire, the letter was sent to the participant (along with a blood sample collection pack together with an instruction letter to practice nurse/phlebotomist) to book an appointment for blood collection with their GP practice.

To facilitate the phlebotomist at different GP practices in Nottingham and to help other prostate study running simultaneously by the study group such as Benign Prostatic Hyperplasia study, the research team had taken phlebotomy course at King's Mill hospital, Mansfield for seven days; this was carried out to comply with the UK regulations. A separate honorary contract was obtained to work as phlebotomist.

Blood samples were sent back to study base in Nottingham, from there, samples were sent back to the Royal Marsden Hospital for DNA extraction and further genetic analysis.

3.2.4 The Study questionnaire

The questionnaire was design in 1999 and comprised sub-sections of formerly validated questionnaires or sections have been used before in other large scale previous studies. The usage of pictogram and pictures was also validated and has been described elsewhere (Must et al. 1993). Paper published using the current questionnaire are as described in the Appendix section on *Progress of Gene-Environment Interactions in Prostate Cancer Research (United Kingdom).*

The questionnaire was designed to investigate the potential factors attributed to the prostate cancer including lifestyle and diet. The design of the questions was inspired by questionnaires from reputable national studies. The permission from the leader of each individual study was obtained prior to question inclusion. The following studies were used for questions:

- The UK Aplastic Anemia study
- The UK Testicular Cancer study
- The UK Knee Pain study
- The UK Osteo-arthritis study
- The Trent Lifestyle survey
- European prospective investigation of cancer (EPIC)

The questionnaire covers a wide range of topics and took approximately 45 minutes on average to complete. It was well received by the target population and no complaint was raised during the study period. Information under the following broad headings from cases and controls using a structured questionnaire designed for this study were collected.

The first phase and the second phase of questionnaire used have some slight differences. With updated knowledge on the prostate cancer, possible new risk factors based on literature review search were added. The main content construction of questionnaire used in 1st and 2nd phase of study is displayed in Table 3-1 page 3-46.

The second phase questionnaire was modified by inclusion of skin type & sunlight exposure, chronic diseases, medication statin, painkiller NSAIDs & paracetamol, and body fat distribution.

Table 3-1 Main Difference in Contents of Phase I and Phase II Questionnaires used in this study

No.	Section/Topic	Subtopic Difference	Phase I	Phase II	Total no. Subjects (N=4041)
1	Socio-demographic	Nil	√	√	4041
2	Employment/Occupation	Nil	√	√	4041
3	Hormone markers	Nil	√	√	4041
4	Smoking habits	Nil	√	√	4041
5	Sexual behaviour	Additional information on problem related to sexual activity in Phase II	√	√	4041
6	Skin and sun exposure		X	√	2209
7	Family history	Nil	√	√	4041
8	Physical activity	Nil	√	√	4041
9	Pesticide	Pesticide topic was removed in Phase II	√	X	1832
10	General health and medication	Medical diagnostic procedures such as X-ray information taken more detail in Phase II	√	√	4041
		Chronic Diseases	X	√	2209
		Statin	X	√	2209
		Painkiller NSAIDs & Paracetamol	X	√	2209
11	Further details	Other contents	√	√	4041
		Information on Waist/trouser size and hip size	X	√	2209

No.	Section/Topic	Subtopic Difference	Phase I	Phase II	Total no. Subjects (N=4041)
		Information Body Fat Distribution	X	√	2209
12	Food Frequency	Additional items included in Main Food Table are soy milk and spices, while in Vitamins & Supplements Table include saw palmetto, garlic, pomegranate, soy-based drink and tomato juice in Phase II questionnaire	X	√	4041

3.3 Data management

Data from the first phase was already entered and cleaned. For the second phase data entry database was created in Microsoft Access. Data was then entered in Microsoft access database and then transferred to Microsoft Excel. Data was checked thoroughly using filters in Excel. As data were entered by different people, data input was re-checked for quality control purpose. Data was checked to exclude any error using Microsoft Excel by re-entering randomly 10% selected questionnaires and compare them with the actual data. Upon findings of inconsistencies, the original questionnaires where data were obtained from were referred, corrections were made. These processes were repeated until there was less than 0.5% error. After that data of first and second phase was merged taking in account the difference in questionnaires of both phases.

Social class coding was manually cross checked by an expert. Data cleaning was done prior to recoding with intention to salvage any raw data especially subjective answers of loose words or misspelled data for purpose of classification later. Recoding of variables was also done based on category of ordinal or nominal as the next important step to make the analyses easier and flawless.

3.4 Analysis

For statistical analysis, SPSS (Statistical Package for the Social Sciences) version 17 was used. To compare the demographic characteristics of cases and controls, such as age, ethnicity, social class, education and marital status, univariate logistic regression were performed. All statistically significant univariate analysis of socio-demographic variables were re-entered into multivariate logistic regression method to obtain the remaining statistically significant variable for association to prostate cancer risk. The next nearest to statistically significant variable was retested and re-entered for backward logistic regression into the logistic regression model.

The statistically significant remaining variables in multivariate regression model (residual variance confounders) was put up as the middle model and was used to fit in all other environmental factors/variables of interest in subsequent analysis. Unconditional logistic regression was used to generate odds ratios and 95% confidence intervals (CI). To assess for a trend in prostate cancer risk across, the categories test for linear p trend was also performed.

The following variables were analysed for the purpose of the PhD thesis:

i. Demographic features
ii. Skin type
iii. Sunlight exposure
iv. Chronic diseases of diabetes, hypertension, cardiovascular disease, etc
v. Pain killer medication-NSAIDS and Paracetamol
vi. Statin medication
vii. Diet of lycopene, phytoestrogens and selenium

3.5 Possible confounders

Possible confounders were identified using methods of multivariate analysis as described above. These confounders could derive from demographic factors as well as other studied variables. Adjusted and best fitting models were done to reduce the potential influences of these confounders and seek the factors' association in prostate cancer risk.

3.6 Ethical approval

The study has been ethically approved by the Trent Multi Research Ethics Committee MREC/99/4/013(Mar) and 07/MRE04/29.

3.7 Funding

There were main funding streams to support all epidemiological data collection and control biological sample collections including the Prostate Action Charity formerly known as the Prostate Cancer Research Foundation (PCRF), the Cancer Research UK (CR UK). For the genetic part of the study, the study partner, the ICR UK was responsible for case blood collections and further genetic analysis. The genetic work was funded by the Cancer Research UK grant C5047/A335.

Chapter 4 Sociodemographic Factors

4.1 Literature Review

4.1.1 Age

Age is a significant factor strongly associated with the risk of prostate cancer (Pourmand *et al*, 2007; Tseng, 2011). As men grow older, the probability of developing prostate cancer increases. The Cancer Research UK (2010) age specific incidence rates for prostate cancer in United Kingdom in 2007 showed rate of steeply increases with age. Men aged 55-59 had incidence rate of 155 per 100,000 men, then at age 65-69, had triple incidence rate to 510 per 100, 000 and at age 75-78, the rate was further up to 751 per 100,000 men (CRUK, 2010). The Surveillance Epidemiology and End Results (SEER) data based in USA, showed between 2002 to 2007, the mean age of diagnosis of prostate cancer in men is 67 years old (Altekruse *et al*, 2010)

4.1.2 Marital status

Married adults were generally found to be healthier than other marital status categories according to a study by Schoenborn (Schoenborn, 2004). However being married is also associated with negative health indicators, for example being more prone for being overweight or obese. Married adults, particularly men, had higher rates of overweight or obesity relative to adults of other marital status. Never married adults were among the least likely to be overweight or obese.

Marital status could also be associated with socioeconomic stability, lifestyle behaviour such sexual activities and habits and personal health care. Some studies used indicators such as being single but married late or number of marital partners, and showed associations of these sexual and lifestyle factors. The positive associations were evident in studies, such as being married more than once (La Vecchia *et al*, 1993), or having higher number of sexual partners and frequency of sexual activity, based on a meta-analysis study (Dennis, 2002a).

4.1.3 Country born

Country of origin could indicate the prevalence or incidence of prostate cancer and study whether there is any change to the likelihood of contracting cancer if migrated to other countries outside of origin.

A study by Wild et al, on the cancer mortality in England and Wales by their country of birth has shown lower combined cancer deaths including prostate cancer deaths among those born in Bangladesh, India, Pakistan, China or Hong Kong and higher prostate cancer mortality among men born in West Africa or the West Indies, when using those born in England and Wales as reference (Wild *et al*, 2006). These findings could provide further study on the aspect of migration to prostate cancer risk in the population.

4.1.4 Always lived in United Kingdom (UK)

Being in UK all one's lifetime could only mean similar environmental exposures in many ways for the subjects especially exposure to food, healthcare, air and water supply, lifestyle, type of house and entertainment, etc. For someone who had been abroad either for studying, working or migrating for good could mean a whole new or different lifestyle, environmental exposures, education and healthcare offered altogether.

4.1.5 Education

The American Cancer Society (2011) has published an article on the cancer death rates by educational attainment of United States population for year 2007 based on data obtained from National Center for Health Statistics. The report indicated that prostate cancer deaths relative risk among those lowest level of education compared to those with highest level was 1.66 (95%CI: 1.44-1.93) constitute of all races.

However in the study of prostate cancer incidence and education level, some studies have concluded that higher education level has higher risk of prostate cancer (Lund Nilsen *et al*, 2000; Mouw *et al*, 2008; Vidarsdottir *et al*, 2008).

4.1.6 Ethnic Group

The study of racial differences and prostate cancer has been done in USA and recent study has shown that black non-hispanic are of greater risk compared to white non-hispanic and their incidence rate are higher (Wells *et al*, 2010).

With regard to larger comparison between populations in world regions, and the age adjusted incidence rate of prostate cancer, based on Cancer Incidence in Five Continents Vol. IX, on average North America countries top the rate followed by Europe, South America and Oceania, then Africa with Asia showing the lowest rate (Curado. M. P. *et al*, 2007). Although these are true reported cases, and could really be associated with true risk of prostate cancer, but bear in mind there's still high possibility of undiagnosed and unreported cases particularly in less developed countries due to poor reporting systems.

4.1.7 Social class

It was found that the better social economic status encompassing education, income and occupation, will have higher risk of developing prostate cancer as it is linked with lifestyle behaviour and environmental risk, as well as ability to access better healthcare facilities for medical screening and diagnosis (Harvei & Kravdal, 1997; Liu *et al*, 2001).

A study by Cheng revealed a statistically significant trend of higher relative risk to have prostate cancer of 1.28 (CI: 1.25-1.30) when compared between the highest to the lowest socioeconomic status (Cheng *et al*, 2009). Another study on Norwegian population also found an increase of 30% risk to prostate cancer among higher socioeconomic status group. Higher education level also increase 56% risk of prostate cancer (Nilsen *et al*, 2000).

4.1.8 Family History

Prostate cancer has been found in many studies to be associated with first degree relatives with cancer. The possibility of strong genetic link could be the explanation. A meta-analysis done for all epidemiological studies on looking at relationship between the 1st degree family i.e. father or brother with prostate cancer with patients of prostate cancer up to year 2002 has revealed increased risk of two to three fold with father and male siblings at 2 times and 3 - 4 times respectively (Zeegers *et al*, 2003).

Prostate cancer was found in one study to have statistically significant odds ratio of 2.60 of adjusted family standardized incidence ratio (AFSIR) which meant increased risk due to family history (Kerber & O'Brien, 2005). In the same study, prostate was the only cancer that had strikingly the highest familial factors population attributable risk estimates at 57% compared to other types of cancers with breast cancer as second.

A case control study in Japan has found a statistically significant increased risk of 5.6 times of getting prostate cancer patients who have family history of similar cancer (Suzuki *et al*, 2007). A study on Sweden population of 205,638 cancer cases showed prostate cancer as having the highest proportion of familial association at 20.15% followed by breast cancer at 13.58% (Hemminki *et al*, 2008).

In terms of association with first degree relative with prostate cancer by age of diagnosis, young cancer patients of less than 60 years old have higher relative risk compared to those diagnosed at 60 years or above at 2.16 and 1.95 respectively, meaning those with first degree relatives with prostate cancer will have higher chances of early onset of prostate cancer (Chen *et al*, 2008).

4.2 Methodology

4.2.1 Demographic Factors Definition

4.2.1.1 Age

Age in case subjects refers to age at the date of diagnosis obtained from GPs or hospitals records while for control subjects refers to age on the date when the questionnaire was returned to the researcher and recorded.

4.2.1.2 Marital status

Married and common law partnership were merged as one group, while widowed, divorced or separated as another group. Single is a group by itself.

4.2.1.3 Country born

Country born ask on whether born in United Kingdom or other countries. If other, country is named.

4.2.1.4 Always live in UK

Unless significant time out of UK, then subject would record the number of year's concrete in UK, otherwise always live in UK is same as age in years.

4.2.1.5 Education

Levels of education are recorded based on recognized qualification hierarchy in UK of four categories namely no education, GCSE/O level or equivalent, A level or equivalent and lastly Higher or professional qualification.

4.2.1.6 Ethnic

Using tick box selection ethnic list was done. Due to the smaller numbers of some of the ethnic group and for appropriate use of statistically test, they are collapsed into White, Black (Black-Carribean, Black-African & Black-Other), Indian or Pakistan, and lastly Others (Jewish, Sephardic, Askenazi, Chinese, etc)

4.2.1.7 Social class

Social class classification was based on *Standard Occupational Classification 2000* (ONS, 2000) categorize into the following:

Class I	Professional
Class II	Managerial and Technical occupations
Class IIIN	Skilled Non-Manual
Class IIIM	Skilled Manual
Class IV	Partly Skilled occupation
Class V	Unskillled occupation

4.2.1.8 Family History

Only subject's first degree relatives of biological origin i.e. parents, siblings and children are recorded as having family history.

The analysis was done to look at family history of any cancer and specific family history of prostate cancer.

4.3 Analysis

All analysis were performed using statistical software SPSS version 17.0

Central tendency measures of mean and median as well as dispersion standard deviation and inter-quartile range calculation were computed for age variable data to compare characteristics between cases and control group. The age data has also been categorized to assess p-value for trend and to identify age group with significant association with prostate cancer risk.

All socio-demographic variables were tested for Chi-square test to study the differences in the proportion or characteristics between cases and control group. Level of significance was at α (alpha) =0.05, and 95% confidence interval (95%CI). For variables with statistically significant Chi-square test results, further analyses of univariate and age-adjusted logistic regression models were carried out to study their association towards prostate cancer risk.

Multivariate analyses were completed among socio-demographic factors which have shown in univariately statistically significant regression modelling and with age-adjusted models, in order to identify potential confounders. The backward regression modelling method was employed. The best fitting model were identified by any factors which remained statistically significant. However a priori variable 'age' would be used in all regression analysis models on prostate cancer risk.

4.4 Results

4.4.1 Overall Response Rate

Response rates presented in Table 4-1 are the response rates after subjects' initial consent to participate the study. The true recruitment rates are unknown due to confidentiality issue as guided by ethics. Only subjects who consented were disclosed to study team (by GPs if they are controls and by the study partner ICR UK if they are cases). Letters and further consent forms to provide biological samples were sent. To obtain response rates, subjects who consented to complete the questionnaire and to provide biological samples were used as denominator. Subjects who sent back their questionnaire were used as nominator.

Table 4-1 Response rate among case-control group

Study Phase	Case %	Control %
Phase 1	78.9	61.8
Phase 2	91.0	87.0
Overall Total	85.0	74.4

Number of subjects with questionnaire data:

Cases	1963
Controls	2078
Total	**4041**

4.4.2 Age

Total: 4041 (4039 valid & 2 missing)
Age was normally distributed (scatter plot- not shown)

Table 4-2 The mean and median age of case-control groups

Group	No.	Range	Mean	SD	Median	Interquartile range
Case	1962	36-85	59.58	6.005	60	6
Control	2077	36-76	59.13	6.551	59	7

Independent t-test, **p=0.020**, which was statistically significant to show mean age is higher in cases group.

Univariate logistic regression for age as continuous variable showed **p=0.025** with **OR=1.011 (95%CI: 1.001-1.021).**

Table 4-3 Cross-tabulation of age group among case-control group

Age Category	Group		Total
	Control	Case	
	(%)	(%)	(%)
49 and below	118	79	197
	5.7%	4.0%	4.9%
50-59	1094	875	1969
	52.7%	44.6%	48.7%
60-69	668	872	1540
	32.2%	44.4%	38.1%
70 and above	197	136	333
	9.5%	6.9%	8.2%
Total	2077	1962	4039
	100.0%	100.0%	100.0%

Majority of subjects (almost 87%) are in the category of 50-59 and 60-69 years old. Between cases and control, there appear to have higher proportion of age group 50-59 among the control compared to cases, while at the same time, higher proportion of 60-69 age group among cases compared to control.

Chi-square test, $p<0.001$ (statistically significant) confirmed the difference in the age group distribution.

Table 4-4 Odds Ratio and Confidence Interval for Prostate Cancer Risk for Age Category

Age Group	Group		OR (95% CI)	P value
	Control (%)	Case (%)		
49 and below	118 (5.7%)	79 (4.0%)	-Ref-	<0.001
50-59	1094 (52.7%)	875 (44.6%)	1.195 (0.886-1.610)	0.243
60-69	668 (32.2%)	872 (44.4%)	**1.950 (1.441-2.638)**	**<0.001**
70 and above	197 (9.5%)	136 (6.9%)	1.031 (0.720-1.477)	0.867

P for trend <0.001

The above showed that age category 60-69 alone showed statistically significant increased in prostate cancer risk when compared to the youngest age group, at OR=1.950 (95%CI: 1.441-2.638) or almost double the risk. P for trend, $p<0.001$, showed statistically significant trend increase in prostate cancer risk with increased in age.

4.4.3 Marital status

Table 4-5 Cross-tabulation of age group among case-control group

Marriage Category	Group		Total
	Control	Case	
	(%)	(%)	(%)
Married or partnership	1725	1611	3336
	83.9%	83.3%	83.7%
Divorced, separated or widowed	260	232	492
	12.7%	12.0%	12.3%
Single	70	90	160
	3.4%	4.7%	4.0%
Total	2055	1933	3988
	100.0%	100.0%	100.0%

Chi-square p=0.119, was not statistically significant to show differences in the marital status and prostate cancer status, although univariate logistic regression showed 'single' status in comparison with 'married or partnership' status has statistical significance increase at p=0.05 of prostate cancer risk, OR=1.377 (95%CI: 1.000-1.895).

Upon adjustment for age, the marital status variable was not statistically significant towards prostate cancer risk, however 'single' status remained statistically significant with increase prostate cancer risk of approximately 40% compared to the status of 'married or partnership).

Table 4-6 Odds Ratio and Confidence Interval for Prostate Cancer Risk for Marriage Category

Marriage Category	Control n	Case n	OR[a] (95% C.I)	P value[a]	OR[b] (95% C.I)	P value[b]
Married or partnership	1725	1611	-Ref	0.121	-Ref-	0.102
Divorced, separated or widowed	260	232	0.955 (0.790-1.155)	0.638	0.955 (0.790-1.155)	0.637
Single	70	90	**1.377 (1.000-1.895)**	**0.050**	**1.396 (1.014-1.923)**	**0.041**

[a]Unadjusted regression models

[b]Adjusted for age, regression models

4.4.4 Country born

Table 4-7 Cross-tabulation of Country born among case-control group

Country Born	Group		Total
	Control	Case	
	(%)	(%)	(%)
UK	1959	1806	3765
	95.0%	93.3%	94.2%
Other	103	129	232
	5.0%	6.7%	5.8%
Total	2062	1935	3997
	100.0%	100.0%	100.0%

Chi-square test, **p=0.024** (statistically significant), with **OR = 1.359 (95%CI: 1.040-1.774)** or increased risk of 36% of those born in UK to develop prostate cancer compared to those born in countries other than the UK.

Logistic regression adjusted for age showed that the odds ratio for country born in UK group, prostate cancer risk remains significant at **p value 0.027** and **OR 1.351 (95%CI: 1.035-1.764)** or approximately 35% increased risk compared to those born outside UK.

4.4.5 Always live in UK

Table 4-8 Cross-tabulation of Always in UK among case-control group

Always in UK	Group		Total
	Control	Case	
	(%)	(%)	(%)
No	231	246	477
	11.4%	12.9%	12.1%
Yes	1797	1666	3463
	88.6%	87.1%	87.9%
Total	2028	1912	3940
	100.0%	100.0%	100.0%

Chi-square test with p value of 0.156, suggesting no statistically significant association between status of always been in UK and staying in other countries to prostate cancer risk.

4.4.6 Education

Table 4-9 Cross-tabulation of Education category among case-control group

Education Category	Group		Total
	Control	Case	
	(%)	(%)	(%)
None	570	439	1009
	27.8%	22.8%	25.4%
GCSE, O levels or equivalent	343	362	705
	16.7%	18.8%	17.7%
A levels, higher or equivalent	151	136	287
	7.4%	7.1%	7.2%
Higher or professional qualification e.g. degree, HND	973	968	1941
	47.4%	50.4%	48.8%
Other	15	17	32
	0.7%	0.9%	0.8%
Total	2052	1922	3974
	100.0%	100.0%	100.0%

Chi-square test with **p value of 0.007** showed statistical significant differences in the proportion of prostate cancer cases between different levels of education.

Table 4-10 page 4-64 showed estimated risk of education and prostate cancer. P for trend, p=0.008 showed a statistically significant trend across all education levels is associated with higher prostate cancer risk.

Using group of those with 'No education' as reference, the risk of prostate cancer is suggestive of higher in all other categories (of OR>1) but found to be statistically significant only with groups GCSE/O levels education and Higher/professional qualification at **OR = 1.370 (95%CI: 1.130-1.662) and 1.292 (95%CI: 1.108-1.505)** respectively.

After age adjustment, using 'No education' as reference, the risk of prostate cancer remains higher in all other categories (of OR>1) but only with groups GCSE/O levels education and Higher/professional qualification showed statistically significant **at OR = 1.376 (95%CI: 1.134-1.657) and 1.296 (95%CI: 1.112-1.511)** respectively.

Table 4-10 Odds Ratio and Confidence Interval for Prostate Cancer Risk for Education Category in Unadjusted and Age-adjusted regression models

Education Category	Control n	Case n	OR[a] (95% C.I)	p value[a]	OR[b] (95% C.I)	p value[b]
No Education	570	439	Ref	0.007	Ref	0.006
GCSE, O levels or equivalent	343	362	**1.370 (1.130-1.662)**	**0.001**	**1.376 (1.134-1.657)**	**0.001**
A levels, higher or equivalent	151	136	1.169 (0.899-1.521)	0.243	1.170 (0.899-1.523)	0.244
Higher or professional qualification e.g. degree, HND	973	968	**1.292 (1.108-1.505)**	**0.001**	**1.296 (1.112-1.511)**	**0.001**
Other	15	17	1.472 (0.727-2.979)	0.283	1.473 (0.727-2.985)	0.282

P for trend **=0.008**

[a]Unadjusted regression models
[b]Adjusted for age, regression models

4.4.7 Ethnic Group

Table 4-11 Cross-tabulation of Ethnic category among case-control group

Ethnic Category	Group		Total
	Control	Case	
	(%)	(%)	(%)
White	2029	1862	3891
	98.6%	96.4%	97.5%
Black	5	31	36
	0.2%	1.6%	0.9%
Indian-Pakistan	9	13	22
	0.4%	0.7%	0.6%
Others such as Chinese Jewish etc	14	26	40
	0.7%	1.3%	1.0%
Total	2057	1932	3989
	100.0%	100.0%	100.0%

White constitutes the majority of the study subjects at 97.5%. The proportion of White is higher in control groups, while the other ethnic categories are higher among the cases. Chi-square test, **$p<0.001$**, showed statistically significant difference in the proportion of ethnic types between case and control groups.

Referring to Table 4-12, using White ethnic category as reference, there is statistically significant increased risk of prostate cancer in the Black and Others ethnic categories at **OR = 6.756 (95%CI: 2.622-17.411) and 2.024 (95%CI: 1.054-3.887)** respectively.

The p value remains significant even after adjusted for age, at **$p<0.001$** with still statistically significant increased risk of prostate cancer in the Black and Others ethnic categories at **OR = 6.942 (95%CI: 2.692-17.899) and 2.036 (95%CI: 1.059-3.912)** respectively when compared to white ethnic group.

Table 4-12 Odds Ratio and Confidence Interval for Prostate Cancer Risk for Ethnic Category in Unadjusted and Age-adjusted regression models

Ethnic Category	Control n	Case n	OR[a] (95% C.I)	P value[a]	OR[b] (95% C.I)	P value[b]
White	2029	1862	-Ref-	<0.001	-Ref-	<0.001
Black	5	31	6.756 (2.622-17.411)	<0.001	6.942 (2.692-17.899)	<0.001
Indian-Pakistan	9	13	1.574 (0.671-3.691)	0.297	1.558 (0.664-3.655)	0.308
Others such as Chinese Jewish etc	14	26	2.024 (1.054-3.887)	0.034	2.036 (1.059-3.912)	0.033

[a]Unadjusted regression models
[b]Adjusted for age, regression models

4.4.8 Social Class

Table 4-13 Cross-tabulation of Social Class among case-control group

Social Class	Group		Total
	Control	Case	
	(%)	(%)	(%)
I	228	238	466
	11.5%	12.6%	12.1%
II	858	813	1671
	43.3%	43.2%	43.2%
IIIN	210	195	405
	10.6%	10.4%	10.5%
IIIM	540	509	1049
	27.3%	27.0%	27.1%
IV	113	111	224
	5.7%	5.9%	5.8%
V	31	18	49
	1.6%	1.0%	1.3%
Total	1980	1884	3864
	100.0%	100.0%	100.0%

The spread of social class category did not appear to show remarkable difference characteristics among cases and control group although slightly higher proportion of cases with social class I, whereas among control subjects higher social class V. Chi-square test, p=0.552 showed non-statistical significant association between social class and prostate cancer risk.

Test for trend (p value 0.334) showed no association with ranking in social class with prostate cancer risk.

Logistic regression analysis results are shown Table 4-14. The results showed no statistical association between highest social class (Class I as reference) to other classes in prostate cancer risk, although it was observed that social class V showed most protective risk at 0.556 (95%CI: 0.303-1.022).

After adjustment for age, there were still no statistically significant findings.

Table 4-14 Odds Ratio and Confidence Interval for Prostate Cancer Risk for Social Class in Unadjusted and Age-adjusted regression models

Social Class	Control n	Case n	OR[a] (95% C.I)	p value[a]	OR[b] (95% C.I)	p value[b]
I	228	238	-Ref-	0.560	-Ref-	0.574
II	858	813	0.908 (0.739-1.115)	0.356	0.908 (0.739-1.115)	0.357
IIIN	210	195	0.890 (0.682-1.161)	0.389	0.889 (0.681-1.160)	0.387
IIIM	540	509	0.903 (0.726-1.123)	0.360	0.912 (0.733-1.135)	0.408
IV	113	111	0.941 (0.684-1.294)	0.709	0.951 (0.691-1.309)	0.760
V	31	18	0.556 (0.303-1.022)	0.059	0.951 (0.691-1.309)	0.063

[a]Unadjusted regression models
[b]Adjusted for age, regression model

4.4.9 Family History

4.4.9.1 Family History of any cancer in 1st degree relatives

Table 4-15 Cross-tabulation of Family history of cancer among case-control group

Family history cancer	Group		Total
	Control	Case	
	(%)	(%)	(%)
No	1092	662	1754
	54.0%	35.0%	44.8%
Yes	929	1230	2159
	46.0%	65.0%	55.2%
Total	2021	1892	3913
	100.0%	100.0%	100.0%

Chi-square test **p<0.001**, with statistically odds ratio of **2.184 (95%CI: 1.920-2.484)**. There is twice the risk of prostate cancer among those with first degree family history of cancer compared with those who have no history.

Upon adjustment by age, the logistic regression model remained statistically significant at **p<0.001** and **OR=2.173 (95%CI: 1.910-2.472).**

4.4.9.2 Family History of prostate cancer in 1st degree relatives

Table 4-16 Cross-tabulation of Family history of prostate cancer among case-control group

History of Prostate Cancer	Group		Total
	Control	Case	
	(%)	(%)	(%)
No	1911	1337	3248
	95.0%	71.2%	83.5%
Yes	100	540	640
	5.0%	28.8%	16.5%
Total	2011	1877	3888
	100.0%	100.0%	100.0%

Chi-square test **p<0.001**, with statistically odds ratio of **7.718 (95%CI: 6.166-9.661).** The risk of having prostate cancer among those with first degree family history of prostate is 7.7 times fold compared to those without such history.

Even after age adjustment, the prostate cancer risk for those with family history of Prostate cancer remains significant at **p<0.001** and **OR=7.690 (95%CI: 6.142-9.629).**

4.5 Discussion

4.5.1 Response Rate

In this study, efforts have been made to increase the response rate of both the cases and control subjects towards the filling up and returning of questionnaire booklet, as well as samples of toe-nail clippings through mail. A telephone helpline was provided at the back of the questionnaire for clarification of any queries or fulfilling any extra information required by subjects in order to fill in the answers to the best of their understanding. A reminder letter was sent out to those subjects whose questionnaire/toenails samples were not received after 4 weeks duration of sending the questionnaire, vacant container for nails clippings and stamped return envelope.

According to systematic review by Edwards, showed that personalized questionnaires and letters, usage of return stamped envelope as well as follow up contact were shown to have increased response rate to studies using questionnaires (Edwards *et al*, 2002).

The response rate for first phase and second phase were 78.9% & 91.0% among cases and 61.8% & 87.0% among controls, while overall response rate in total was 85.0% and 74.4% for cases and control respectively. This finding is better than a pooled analysis study of population based case-control study done in Germany (Stang *et al*, 1999) which had response proportion of 80% among cases and 68% among controls. Another survey on case-control studies done in articles published in 2003 Science Edition of Journal Citation Reports of Thompson Corporation, Philadelphia, Pennsylvania by Morton (Morton *et al*, 2006) showed median response rate of 84% among cases and 74% among controls which is very similar with our study. Therefore overall on average, it is considered good and adequate response rate because of cost and time saving benefit obtained through this method applied well in case-control study design.

Cases seem to be more receptive towards responding to this study probably could be explained due to their interests of what the outcome of the study would benefit prostate cancer patients like themselves and towards the prevention of this ailment among their loved ones or of the population on the whole, as well as contributing to science of knowledge in this area. However controls are selected by general practitioner (GP) and numbers of respondents would depend a lot on

persuasion manner used by GP and different GPs have different approaches. However, ultimately, potential control subjects may more likely refuse to participate in a study if they don't get any follow up with their GP by phone call, compared to cases who would be constantly under regular medical follow up by hospital or GP.

4.5.2 Age

The mean age for both cases and control subjects in this study were 59.58 and 59.13 respectively. Even though age was frequency matched, the independent t-test revealed statistical significant increase of mean age among cases. Univariate logistic regression for age as continuous variable showed p=0.025 with OR=1.011 (95%CI: 1.001-1.021). The prostate cancer risk increase estimated at 1.1% with each year increase in age.

Similar analysis done in the median calculation although approximate value is close to mean, the median age for cases was 60 while for control was lower at 59. It was both bell-shaped distributions.

A case-control study of prostate cancer by Key was conducted in Oxfordshire, West Berkshire and Leeds, they reported older mean ages of cases and controls identical at 68.1 years, of which controls are matched with cases within 1 year of age in either way, with criteria of eligibility all cases diagnosed before 75 years old (Key *et al*, 1997). The marked difference in the mean age between our study and the other studies is because our study in Phase 1 was focused on prostate cancer patients of less than 60 years old, but in Phase 2 age was extended to cover all ages.

By stratifying age into categories of 10 years interval, the analysis finding showed statistically significant p for trend, with the average 19% increase of prostate cancer risk or between the ranges of 9% to 30% for each ascending in age group category. (Refer Table 4-4 page 4-58)

By using age 49 and below as reference group, the only statistically significant increase in prostate cancer risk are the age group '60-69 years old' of almost double the risk.

The Cancer Research UK (2010) age specific incidence rates for prostate cancer in United Kingdom in 2007 showed the rates steeply increase with age (CRUK, 2010). Study in Iran has established as age increases, so does the risk of getting prostate cancer (Pourmand *et al*, 2007). The Surveillance Epidemiology and End Results (SEER) data based in USA, showed between 2002 to 2007, the mean age of diagnosis of prostate cancer in men is 67 years old (Altekruse *et al*, 2010).

4.5.3 Marital status

Based on the results of this study, the majority (approximately 84%) of the subjects are either still married or in common law partnership with a smaller proportion of singles or not in relationship because of separation, divorce or death of partner.

Initial cross-tabulation analysis did not show any statistically significant difference in the proportion of prostate cancer by marital status. However, upon comparison between marriage category by using 'married and partnership' as reference, it was observed that the 'single' was of borderline statistically significant at p=0.050 with odds ratio (OR) =**1.377** or 37.7% higher risk. The prostate cancer risk became more statistically significant with age adjustment to the model (OR at **1.396, 95%CI: 1.014-1.923).**

The author could not locate prostate cancer studies in United Kingdom for comparison however study by La Vecchia on the population of case control study in Italy between 1985 to 1990 showed prostate cancer risk was protective in 'never married' compared to married men at risk ratio (RR)=0.6 but not statistically significant (La Vecchia *et al*, 1993). Only those who married twice or more showed a statistically significant increased risk of prostate cancer in comparison with never married man, at RR=3.2 (95%CI: 1.2-8.9). Similar findings for the study by Harvei & Kravdal that showed significant excess incidence of about 20% in 'ever-married' compared to 'never married' men (Harvei & Kravdal, 1997).

Another study by Nilsen suggested a higher risk of prostate cancer among men who divorced or separate compared to married man but was not statistically significant (Lund Nilsen *et al*, 2000).

In this current study, there is possibility that 'single' status could mean having multiple partners instead of no partner and that could be associated with other probable factors such as sexual activity involving multiple partners with a higher possibility of sexual transmitted diseases which has been documented in some studies to increase risk to prostate cancer.

4.5.4 Country born

The majority of the subjects both cases and controls, were born in the United Kingdom (UK) at 94%. The prostate cancer risk was found to be higher in those born in UK at OR=**1.359**, and after adjustment for age remain statistically significant at **1.351** or 35% increase in risk compared with those born outside of UK.

Global Cancer registries such as 'Cancer Incidence in Five Continents' and data from 'Globocan' have shown higher reported incidence rates of prostate cancer among developed countries such as USA, Canada, Australia and most European countries and lower in Asian continent countries such as Japan, China and developing world regions (Curado. M. P. *et al*, 2007; Ferlay *et al*, 2008; Parkin *et al*, 2002). The possible explanation could be due to environmental factors of exposure or habits of the population.

It is also possible to say 'westernization' in the low-risk population of Asians has led to increase of incidence rate over the years when moving to the western country. A study on the international trends and patterns of prostate cancer incidence by Hsing concluded the possibility that this was due to a combination of genetic and environmental factors (Hsing *et al*, 2000b).

4.5.5 Always live in UK

There was no difference in the proportion of prostate between those who always stay in UK and those who did not.

4.5.6 Education

Almost 50% of the subjects both of cases and control have a higher or professional qualification. There was a statistical significant difference in the proportion of prostate cancer between the levels of education. There was also an increased trend to develop prostate cancer as the level of education is higher (Refer Table 4-9 page 4-62).

When using those 'no education' as reference, only those who had education of 'GCSE, O levels or equivalent' and also those with 'higher or professional qualification' shown a statistically significant increase risk of developing prostate cancer at 37% and 29% respectively. Even after adjustment for age, the prostate cancer risk remains statistically significant at OR 1.376 and 1.296 for 'GCSE, O levels or equivalent' and 'higher or professional qualification' respectively (Table 4-10 page 4-64).

A study by Nilsen on Norwegian men confirmed similar findings when the prostate cancer risk was elevated among men with high education compared to the least educated (RR = 1.56; 95% CI 1.11–2.19) (Lund Nilsen *et al*, 2000).

A cohort study among Icelanders population also showed elevated standardized incidence ratio of prostate cancer of 1.17 (95%CI: 1.05-1.30) for higher level of education (Vidarsdottir *et al*, 2008), while a cohort study in the USA population by Mouw using postgraduate education level as reference, showed a statistically significant trend of reduced risk of prostate cancer as the level education was lower (Mouw *et al*, 2008).

It is possible that higher educated people would seek healthcare providers and treatment earlier compared to less educated level, couple with better socioeconomic status and level of affordability in seeking earlier prostate screening could explain this finding or differences in diet and lifestyle may also be part of the explanation.

4.5.7 Ethnic Group

97.5% in this study listed themselves as 'White' ethnic group (refer Table 4-11 page 4-65). The cross-tabulation analysis showed a statistically significant difference in proportion of different ethnic groups between cases and control. Further analysis using 'White' as reference ethnic group, showed that 'Black' and 'Other ethnics' have increase prostate cancer risk. Upon adjustment of age in the logistic regression, the odds ratio remained statistically significant at 6.942 (95%CI: 2.692-17.899) and 2.036 (95%CI: 1.059-3.912) for 'Black' and 'Other ethnic' respectively (refer Table 4-12 page 4-66).

Based on data from Cancer Incidence in Five Continents Vol. IX to a look at larger comparison between populations in world regions, and with age adjusted incidence rate of prostate cancer, on average, North America countries top the rates followed by Europe, South America and Oceania, then Africa with Asia showing the lowest rate (Curado. M. P. *et al*, 2007). Although these are true reported cases, and could really be associated with true risk of prostate cancer, but bear in mind there is still a high possibility of advanced and wider screening methods done in developed countries resulting in more diagnosis of prostate cancer in such region, whereas there are more undiagnosed and unreported cases particularly in less developed countries due to poor reporting systems.

4.5.8 Social class

Analyses of social class classification were completed using both methods. Firstly the original classification of I, II, IIIN, IIIM, IV & V was used and secondly, social class was collapsed into three categories. None of the results showed any significant association with prostate cancer risk. Similarly, there was no trend across social class categories.

The distribution of education and social class were not of normal distribution (refer Table 4-13 page 4-67). By looking further at the cross-tabulation data between education and social class, results did not reveal any trend of higher education resulting in social class level. This could be due to certain occupations being classified as Social Class II such as managerial job. Furthermore, the 'Higher or professional qualification' which consist both of degree (Bachelor & postgraduate) and certification (C&G, HNC, HND) qualifications could dilute the effect of actual higher level of education and therefore resulting in some doing manual job in Social Class IIIM.

All the above reasons could have resulted social class level not show any association with prostate cancer risk.

4.5.9 Family History

4.5.9.1 Family History of any cancer

The findings in this study are consistent with previous literature review on family history of cancer or within 1st degree relatives (Hemminki & Chen, 2005). There

is approximate 2.2 times increased risk to prostate cancer risk even after adjustment for age.

4.5.9.2 Family History of prostate cancer

The prostate cancer risk was 7.7 fold higher risk when there is history of prostate cancer in 1st degree relatives. A pooled relative risk of 13 case-control and cohort studies in a meta-analysis done by Johns and Houlston (2003) showed RR of 2.5 (95%CI: 2.2-2.8) in first degree relatives. If two affected relatives of prostate cancer history, the RR would increase to 3.5 (95%CI: 2.6-4.8) (Johns & Houlston, 2003).

Both findings above were of strong statistically significance at $p<0.001$. These findings are consistent with many studies of prostate cancer association for 1st degree relatives with cancer. An increased risk of prostate cancer of early onset in particular, is strongly affected by family history (Bratt, 2002). On average, hereditary prostate cancer is diagnosed 6 to 7 years earlier than sporadic prostate cancer.

The possibility explanation could be due to a strong genetic link. Thomas et al. (2008) in their genome-wide association study (GWAS) identified multiple loci with moderate effects associated with susceptibility to prostate cancer (Thomas *et al*, 2008). Another GWAS study by Eeles, who is the leading members of the genetic part of this study project, had used some of the data from earlier phase of prostate cancer gene-environment interaction study. The results confirmed previous reports of common loci associated to prostate cancer at 8q24 and 17q, as well as identified new possible susceptibility genes for prostate cancer namely MSMB, LMTK2 and KLK3 (Eeles *et al*, 2008).

The explanation for the unusually strong association of family history and prostate cancer seen in this study could possibly be due to case definition in the first phase in particular. The study first phase aims were to identify high penetrance genes and factors that contributing to the disease. Cases were recruited based on either their early onset of prostate cancer (age less than 60) or referral of any of their siblings who were also diagnosed with prostate cancer. This case series is indicative of genetic predisposition enrichment thus could contribute to a higher risk.

As compared to other demographic factors in this study, family history has the highest strength in terms of contributory risk factor for prostate cancer based on multivariate analysis and -2 likelihood ratio test.

Identification of confounding factors using Multivariate Analysis

Table 4-17 Multivariate Analysis among statistically significant univariate analysis demographic factors.

Sociodemographic Factors		p value	OR	95% Confidence Interval	
				Lower	Upper
Age		0.164	1.007	0.997	1.018
Marriage Category	Married or partnership	0.148	Ref	-	-
	Divorced, separated or widowed	0.964	1.005	0.823	1.226
	Single	0.051	1.402	0.999	1.967
Born Country UK		0.343	0.852	0.612	1.186
Education	None	**0.02**	Ref	-	-
	GCSE, O levels or equivalent	0.002	1.377	1.126	1.684
	A levels, higher or equivalent	0.248	1.176	0.893	1.548
	Higher or professional qualification e.g. degree, HND	0.007	1.249	1.064	1.467
	Other	0.276	1.523	0.715	3.246
Ethnic	White	**<0.001**	Ref	-	-
	Black	<0.001	14.74	4.243	51.206
	Indian-Pakistan	0.044	2.689	1.026	7.047
	Others such as Chinese Jewish etc	0.002	3.199	1.525	6.711
Family history of cancer		**<0.001**	2.227	1.951	2.542

The multivariate analysis result showed only education category, ethnic category and family history of cancer variables remained statistically significant associated with prostate cancer risk at p value 0.020, $p<0.001$ and $p<0.001$ respectively (refer Table 4-17 page 4-79).

The above table also showed that prostate cancer risk is highest among those with a family history of cancer at **OR=2.227 (95%CI: 1.951-2.542)**, followed by ethnic category and education.

Table 4-18 Final Logistic Regression Model of Demographic Factors to Prostate Cancer Risk

Sociodemographic Factors		p value	OR	95% Confidence Interval	
				Lower	Upper
Education	None	**0.026**	Ref	-	-
	GCSE, O levels or equivalent	0.002	1.364	1.116	1.667
	A levels, higher or equivalent	0.206	1.193	0.908	1.568
	Higher or professional qualification e.g. degree, HND	0.007	1.244	1.06	1.459
	Other	0.318	1.469	0.691	3.123
Ethnic	White	**<0.001**	Ref	-	-
	Black	<0.001	12.965	3.893	43.176
	Indian-Pakistan	0.103	2.076	0.863	4.995
	Others such as Chinese Jewish etc	0.012	2.386	1.206	4.719
Family history cancer		**<0.001**	2.234	1.958	2.548

Backward logistic regression modelling, by including each one of the other non-significant variables into the model of significant variables showed no new statistically significant variable.

The final best fitting model which included significant statistically sociodemographic variables were for education category, ethnic category and family history of cancer.

However in adjusting the regression model for all other variables of interest in this study, age would be included as a-priori confounder.

Chapter 5 Body Size and Shape

5.1 Literature Review

Body shape or more commonly body size is often used to describe the characteristics of human body for purpose of health. Similarly some parameters such as weight, height, skin folds thickness have been developed into various health indices to allow comparison such as weight with height (calculation of body mass index or BMI), size of waist and hip (calculation of waist to hip ratio or WHR), and body fat mass calculated from bioelectric impedance analysis, while some have used lean body mass as an index (Liu *et al*, 2005) or even dual x-ray absorptiometry (DXA) and total body water (TBW) (Funkhouser *et al*, 2000).

Bianchini described in an article in the Lancet, the evidence that excess body weight is directly associated with risk of cancer of colon, breast (postmenopausal women), endometrium, oesophagus and kidney (Bianchini *et al*, 2002).

Many of the studies association between obesity and prostate cancer has produced mixed findings. The types of measurement or manner of describing body shape or size also differs in studies from using for example direct measurements of height, weight, waist size or hip size (Hernandez *et al*, 2009; Hsing *et al*, 2000a), to some based on body mass index (BMI)(Jackson *et al*, 2010; Robinson *et al*, 2005), while others have used pictorial illustrations to describe relative body size (Giovannucci *et al*, 1997).

5.1.1 Body mass index (BMI) findings

The World Health Organization (WHO) has recommended the use of Body Mass Index (BMI) to differentiate the levels obesity for health and clinical management purposes. BMI is calculated by weight in kilogram is divided by the squares of height in metres. WHO defined BMI of 25 and above as overweight and 30 and above as obese. Some studies that used BMI as comparison for body size have shown some association with prostate cancer (Dal Maso *et al*, 2004; Dimitropoulou *et al*, 2011; Freedland *et al*, 2008; Littman *et al*, 2007; MacInnis *et*

al, 2003; Rodriguez *et al*, 2007; Stocks *et al*, 2010; Wright *et al*, 2007). Among these, the majority showed obesity was associated with an increased risk for high grade cancer or fatal cancer (Dal Maso *et al*, 2004; Littman *et al*, 2007; MacInnis *et al*, 2003; Rodriguez *et al*, 2007; Stocks *et al*, 2010; Wright *et al*, 2007), however, some showed a reduction in risk for low grade prostate cancer (Dimitropoulou *et al*, 2011; Littman *et al*, 2007; Rodriguez *et al*, 2007). There were also studies which did not indicate any association with prostate cancer (Hsing *et al*, 2000a; Jackson *et al*, 2010).

5.1.2 Waist and Hip circumference

The use of waist and hip circumference measurement and the waist to hip ratio as a proxy for obesity has been used to study its association with prostate cancer and the results has also been mixed. MacInnis *et al*. found that increased circumference for waist and hip was associated with increased risk of aggressive (high grade, Gleason score $\geq$8) prostate cancer (MacInnis *et al*, 2003). However, another study showed hip circumference of more than 97.4cm has lower risk of prostate cancer at OR=0.46 (95%CI: 0.29-0.74) at p trend 0.0001 compared to lowest quartile of <76cm (Hsing *et al*, 2000a).

In terms of waist to hip ratio (WHR), the calculation is made by dividing the waist circumference by the hip circumference measurements. In males, the recommended WHR by World Health Organization (WHO) as a cut-off point for risk of metabolic complications is 0.90 or more while female is 0.85 or more, however there maybe some slight differences between regions and ethnic groups to reach optimal sensitivity and specificity (WHO Geneva. 2008). WHR is also good is describing the type of obesity. Abdominal adiposity has been described also as 'Apple' shape or 'android' obesity with higher WHR values due to wider waist circumference; also found more commonly in males. . 'Pear' shape obesity on the other hand, has wider hip circumference compared to waist circumference is found more commonly in females than males.

Higher waist to hip ratio (WHR) >0.92 has been reported to be associated with increased risk in prostate cancer up to three-fold by Hsing at OR=2.71 (95%CI: 1.66-4.41) when compared to men with lowest quartile of WHR <0.86 (Hsing *et al*, 2000a) . In other studies, higher WHR was found to be statistically significantly associated with increased risk for high grade prostate cancer

(Jackson *et al*, 2010; Pischon *et al*, 2008), while others showed no significant association (Dimitropoulou *et al*, 2011).

5.1.3 Body Fat Distribution

Determinants of body fat distribution could include environmental factors such as age, level of energy balance, composition of diet and physical activity. However heritability, genetic, gonadal or adrenal steroids could also influence truncal fat disposition (Bouchard *et al*, 1990).

The study of fat distribution or adiposity in males and females is important as it has been found to predict the metabolic complications of obesity. Abdominal adiposity or 'Apple' body shape has been associated with cardiovascular risk in general (Field *et al*, 2001), but more importantly abdominal obesity which resulted in wider waist circumference and higher waist-hip ratio is also associated with the male hormones of free or total testosterone, dehydroepiandrosterone sulphate (DHEAS) and sex hormone-binding globulin (SHBG). Obesity predicts greater decline in testosterone and SHBG levels with age, while central obesity is an important predictor of decline in DHEAS (Derby *et al*, 2006).

Lower testosterone levels in obesity may impact on reduced prostate cancer development and progression due to its dependency on this hormone for growth, however at the same time also affecting differentiation of prostate cells, resulting in tumour cells poorly differentiated in histopathology. Some studies showed reduced non-aggressive prostate cancer risk while at the same time increased risk for aggressive or high grade prostate cancer (Littman *et al*, 2007; Rodriguez *et al*, 2007; Wright *et al*, 2007). Hack *et al*. however found adiposity was not associated with aggressive prostate cancer (Hack *et al*, 2010).

5.1.4 Weight gain and weight changes

There are few studies that specifically look at weight changes and prostate cancer. However in the literature, weight changes are sometimes analysed in addition to body mass index. Wright *et al*. found that adult weight gain (from age 18 years and above) was associated with increased of fatal prostate cancer at $p=0.009$ but not with incident cases (Wright *et al*, 2007). Rapp, however found that high weight gain of 0.50 kg/m2 per year or more, was inversely associated

with prostate cancer at hazard ratio of 0.43 (95%CI: 0.24-0.76) (Rapp *et al*, 2008), while Rodriguez found that a weight loss of 11 lb or more in compared with those who lost 5 pounds or less, had reduced prostate cancer risk of non-metastatic high grade at rate ratio (RR) = 0.58 (95%CI: 0.42-0.79) (Rodriguez *et al*, 2007).

Hernandez who conducted a study stratified by ethnic group and discovered that increased weight gain in whites increased the risk for advanced and high-grade prostate cancer, and in African American man increased the risk for localized prostate cancer. However among Japanese men, increase weight reduced the risk for localized prostate cancer (Hernandez *et al*, 2009).

5.2 Aims

This Chapter aims to investigate an association of the following aspects to prostate cancer risk:

a. Body shape size at age 20's, 30's. 40's and last 5 years
b. Trend of change in body shape
c. Body fat distribution or types of adiposity

5.3 Methods

This study used the method of gathering data through the questionnaires for both cases and control subjects with self-reported recalled information on body shape size in their 20's, 30's, 40's and last 5 years through pictorial illustration of body shape from thin to obese (scale of 1 to 9) with 1 representing thinnest body shape to 9 representing severe obese. The changes in the pictorial diagrams are made in such a way that can describe the amount muscle and fat proportion as reduced in thin, moderate in medium and increased in obese. Although the illustrations may be proportionally drawn based on the ordinal arrangement, the actual increases of body mass index or waist to hip ratio proportion are not known.

Somatotype drawings from 1 to 9 answers were used on the surviving 181 elderly in 1988 and compared with their measurements taken during the Harvard Growth Study 1922-1935. Must et al. has shown in their study on long-term recall of individuals' height, weight and body build by elderly subjects were of moderate correlations, sensitivities and high specificities in obesity classification including pictogram conveying valid information (Must *et al.* 1993).

Body fat distribution in 4 different forms including Apple, Pear, Oval and Symmetrical were described in words in the questionnaire of their characteristics, and subjects were asked to select the best fit body fat distribution that described their body appearance adhered to most of their lives.

Body fat distribution or type of adiposity has been described in words as follows:

a. Apple shape: where your body fat is distributed mainly around your tummy area.
b. Pear shape: where your body fat is distributed mainly on your hip and thigh.

c. Oval shape: where your body fat is distributed around your neck, your chest, your tummy area and also your thigh.
d. Symmetric shape: where you are lean with no fat distribution around your body.

5.3.1 Analysis

5.3.1.1 Body shape and body shape changes from 20s to 40s

The analysis included 1934 cases and 2050 controls. Data of ordinal score for body shape at age 20's, 30's, 40's and last 5 years collected were then cross tabulated for descriptive analysis and chi-square test. P for trend was also obtained for each decade of age. Data were then recoded into categories having and not having changes in body shape size. If there were changes, they are then recoded further in increasing or decreasing trend from age 20's to 40's. Last 5 years' data were excluded in the trend of changes because of the vast differences in the age to describe last 5 years from age 40's to 70's. Trend of body shape changes were further analyzed into logistic regression modelling and adjusted for age and multivariate potential confounders.

5.3.1.2 Body fat distribution

The analysis was carried out in a smaller sample size. Only data collected from 2007 onwards were included with 1343 cases and 817 controls. Body fat distribution data were analyzed descriptively. Chi-square test was performed to test the null hypothesis (no difference in distribution between case and control group). Further analysis of logistic regression modelling with age-adjusted and full multivariate potential confounders was carried out.

5.4 Results

5.4.1 Body shape at 20's, 30's, 40's and last 5 years

Table 5-1 Distribution of Body Shape at 20's for Case-Control Group

Shape 20's	Group		Total
	Control	Case	
	%	%	%
1	51	44	95
	2.5%	2.3%	2.4%
2	202	193	395
	9.9%	10.0%	9.9%
3	485	454	939
	23.7%	23.5%	23.6%
4	563	530	1093
	27.5%	27.4%	27.4%
5	502	479	981
	24.5%	24.8%	24.6%
6	148	155	303
	7.2%	8.0%	7.6%
7	72	72	144
	3.5%	3.7%	3.6%
8	23	5	28
	1.1%	0.3%	0.7%
9	4	2	6
	0.2%	0.1%	0.2%
Total	2050	1934	3984
	100.0%	100.0%	100.0%

Three-quarters of case and control group subjects reported their size of body shape that lies between 3 (thin) to 5 (medium). Chi-square p value of 0.14 did not reveal any statistically significant difference in body shape size distribution between case and control. Proportion of overweight and obese (body shape scale 7 to 9) was approximately at 5%.

Table 5-2 Distribution of Body Shape at 30's for Case-Control Group

Shape 30's	Group		Total
	Control	Case	
	%	%	%
1	8	5	13
	0.4%	0.3%	0.3%
2	42	36	78
	2.1%	1.9%	2.0%
3	224	214	438
	10.9%	11.1%	11.0%
4	494	496	990
	24.1%	25.6%	24.9%
5	689	638	1327
	33.7%	33.0%	33.3%
6	392	367	759
	19.1%	19.0%	19.1%
7	153	156	309
	7.5%	8.1%	7.8%
8	41	22	63
	2.0%	1.1%	1.6%
9	4	0	4
	0.2%	0.0%	0.1%
Total	2047	1934	3981
	100.0%	100.0%	100.0%

Three-quarters of case and control subjects reported their size of body shape that lies between 4 to 6 (medium range). At p=0.217, chi-square test did not reveal any statistically significant difference in body shape size distribution between case and control. Proportion of overweight and obese (body shape scale 7 to 9) was also increased to approximately 9%.

Table 5-3 Distribution of Body Shape at 40's for Case-Control Group

Shape 40's	Group		Total
	Control	Case	
	%	%	%
1	2	1	3
	0.1%	0.1%	0.1%
2	10	11	21
	0.5%	0.6%	0.5%
3	79	58	137
	3.9%	3.0%	3.4%
4	209	208	417
	10.2%	10.8%	10.5%
5	499	510	1009
	24.4%	26.4%	25.4%
6	605	576	1181
	29.6%	29.9%	29.7%
7	470	434	904
	23.0%	22.5%	22.7%
8	150	112	262
	7.3%	5.8%	6.6%
9	22	19	41
	1.1%	1.0%	1.0%
Total	2046	1929	3975
	100.0%	100.0%	100.0%

Almost four-fifths of case and control subjects reported the size of body shape that lies between 5 (medium) to 7 (slight obese). The non significant Chi-square test of 0.418 suggested no difference in the body shape distribution at 40's among cases and control group. Proportion of overweight and obese (body shape scale 7 to 9) has increased further to approximately 30%.

Table 5-4 Distribution of Body Shape at last 5 years for Case-Control Group

Shape during the last 5 years	Group		Total
	Control	Case	
	%	%	%
1	1	0	1
	0.1%	0.0%	0.0%
2	7	5	12
	0.8%	0.4%	0.6%
3	22	26	48
	2.7%	1.9%	2.2%
4	50	74	124
	6.1%	5.5%	5.7%
5	108	165	273
	13.1%	12.2%	12.6%
6	182	357	539
	22.1%	26.5%	24.8%
7	271	443	714
	32.9%	32.8%	32.9%
8	144	233	377
	17.5%	17.3%	17.3%
9	39	46	85
	4.7%	3.4%	3.9%
Total	824	1349	2173
	100.0%	100.0%	100.0%

Approximately 75% of case and control group subjects reported their size of body shape that lies between 6 (medium) to 8 (obese). Chi-square test showed p value of 0.155 which was not statistically significant. There was no difference in the body shape distribution at last 5 years among cases and controls. The proportion of overweight and obese (body shape scale 7 to 9) during the last 5 years was already slightly more than 50%.

5.4.2 Body shape changes between age 20's to 40's

Table 5-5 Body Shape Changes among Case-Control Group

Types of changes	Group		Total
	Control	Case	
	(%)	(%)	(%)
No Change	239	224	463
	11.7%	11.6%	11.7%
Decrease	39	24	63
	1.9%	1.2%	1.6%
Increase	1764	1677	3441
	86.4%	87.1%	86.7%
Total	2042	1925	3967
	100.0%	100.0%	100.0%

About 87% of subject had had their body shape size increase from their 20s through to 40s. The result of Chi-square test (p=0.246) suggested no differences in the proportion of body shape changes between case and control group.

Table 5-6 presents odds ratios of body shape changes and prostate cancer risk. No change of body shape was used as reference category. The point estimated risk in the fully adjusted model for decrease in body shape size from 20s to 40s is 0.71 with 95% CI 0.40-1.26 indicative of no association between decrease body shape size and prostate cancer risk. For increase in body shape size, point estimated risk is closed to 1 and confident interval also included 1 suggesting also no association between increase body shape size and prostate cancer risk.

Table 5-6 Logistic Regression Modelling for Body Shape changes and Prostate cancer Risk

Body Shape changes	Control	Case	Odds ratio[a] (95%CI)	P value[a]	Odds ratio[b] (95%CI)	P value[b]	Odds ratio[c] (95%CI)	P value[c]
No Change	239 (11.7%)	224 (11.6%)	-Ref-	-	-Ref-	-	-Ref-	-
Decrease	39 (1.9%)	24 (1.2%)	0.657 (0.383-1.127)	0.127	0.672 (0.391-1.155)	0.150	0.706 (0.396-1.262)	0.240
Increase	1764 (86.4%)	1677 (87.1%)	1.014 (0.835-1.232)	0.886	1.030 (0.848-1.251)	0.768	1.076 (0.875-1.321)	0.488

[a]Unadjusted regression model
[b]Age-adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic and family history of cancer

5.4.3 Body Fat Distribution

Table 5-7 Types of Body Fat Distribution among Cases-Control Group

Body fat distribution	Group		Total
	Control	Case	
	(%)	(%)	(%)
Symmetric	175	354	529
	21.4%	26.4%	24.5%
Apple	507	740	1247
	62.1%	55.1%	57.7%
Pear	17	52	69
	2.1%	3.9%	3.2%
Oval	118	197	315
	14.4%	14.7%	14.6%
Total	817	1343	2160
	100.0%	100.0%	100.0%

A quarter of subjects reported having a symmetrical body shape. Controls reported a higher percentage of apple shape as compared to cases (62.1% and 55.1% respectively). The result of Chi-square test (**p=0.002**) shows a statistically significant difference in the distribution of body fat distribution between case and control groups.

Table 5-8 presents estimated risks of different body shape and prostate cancer risk. A symmetrical body shape was used as reference category. Subjects with an 'apple' shape were at 30% risk reduction (OR in the fully adjusted model = 0.689 with 95% CI 0.546-0.870). 'Pear' shape did not show any association with prostate cancer risk (OR = 1.382, 95% CI 0.749-2.549). Subjects with 'oval' shape also showed 27% risk reduction as compared to symmetrical body shape (OR = 0.731, 95% CI 0.534-1.000) although at borderline of p=0.050.

Table 5-8 Regression Models of Body Fat Distribution on Prostate Cancer Risk

Body fat distribution	Control	Case	OR[a] (95%CI)	P value[a]	OR[b] (95%CI)	P value[b]	OR[c] (95%CI)	P value[c]
Symmetric	175 (21.4%)	354 (26.4%)	-Ref-	-	-Ref-	-	-Ref-	-
Apple	507 (62.1%)	740 (55.1%)	**0.722 (0.583-0.893)**	**0.003**	**0.669 (0.537-0.833)**	**<0.001**	**0.689 (0.546-0.870)**	**0.002**
Pear	17 (2.1%)	52 (3.9%)	1.512 (0.849-2.692)	0.160	1.599 (0.884-2.889)	0.120	1.382 (0.749-2.549)	0.300
Oval	118 (14.4%)	197 (14.7%)	0.825 (0.617-1.104)	0.196	0.77 (0.571-1.039)	0.087	**0.731 (0.534-1.000)**	**0.050**

[a]Unadjusted regression model
[b]Age-adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic and family history of cancer

5.5 Discussion

5.5.1 Body shape at 20's 30's 40's and last 5 years

Overall the age progression from 20's to 40's showed that men's body shape size increased from thin medium to medium obese (results are shown in Table 5-1 page 5-87, Table 5-2 page 5-88, Table 5-3 page 5-89 and Table 5-4 page 5-90). The possible explanation for increase in body size is because of decreased metabolic rate with aging and accumulation over the years of unburned calorie intakes. Environmental factors such as eating high-fat foods or lack of exercise, as well as Sedentary Lifestyle Syndrome (SeDS) is to be blamed too (Wellman & Friedberg, 2002).

We compared our results with the data obtained from Health Survey for England (2009), by taking into account the mean age of the study subjects of 59 years old. Comparison was made by looking back at prevalence data of overweight and obesity of relevant year. For example subjects reported data of body shape at age 40's (median age of 59 subtract by 45 =14 years backward) were compare with UK health survey data in 1995.. The obesity (body shape 7 to 9) prevalence at age 40's is approximately 30% in our study (refer Table 5-3 page 5-89), but England data of overweight and obese in 1995 for age 35-44 and 45-54 were 62.8% and 68.7% respectively (ONS, 2009). Similarly when last 5 years data is picked (refer Table 5-4 page 5-90), the data in our study showed obesity (body shape 7 to 9) prevalence at approximately 54%, but England data of 2005 to 2009 for age 55 to 64 showed total obesity and obese prevalence between 76 to 81%. Our data seems to suggest a lower prevalence of overweight and obese compared to national survey data.

The findings in this study showed that body shape size did not differ at age 20's, 30's, 40's and last 5 years between cases and control. This finding agrees with some earlier studies on body size and prostate cancer risk. A multiracial cohort study of 2079 men of Kaiser Permanente Medical care programme in California USA by Habel, used body size measurement of height, weight, body mass index (BMI) found no association of body weight and BMI with prostate cancer risk and did not vary by decade of life Furthermore, other anthropometric measurements including sub scapular skin fold, posterior-anterior chest and abdomen diameters, transverse diameters of chest, bi-trochanteric and bi-iliac size and shoulder height did not reveal any association (Habel *et al*, 2000).

Another cohort study by Lee *et al.* on 8922 men of Harvard Alumni Health Society using body mass index and waist girth as measurement for body size, also did not show any association with prostate cancer with obesity during middle age or older. When analyses were done examining BMI at college entry (age 18 most) to the association of prostate cancer development later in life also did not show any statistical significant findings (Lee *et al*, 2001).

An Australian case-control study by Giles *et al.* which investigated body mass index (BMI) and lean body mass at age 21, also found no statistically significant association with prostate cancer risk (Giles *et al*, 2003a). Hack *et al.* in studying the association of BMI with aggressiveness of prostate cancer defined by Gleason score also did not show any significant statistical findings (Hack *et al*, 2010).

The fact that data was obtained by self report, recall bias should be taken into account when interpreted the results. The tendency is control subjects under-reported levels of overweight or obesity and case subjects recalled more accurately or over re-ported. The application of pictorial illustration was to indicate change in body shape size throughout lifetime and not to absolute conversion to actual BMI or waist size in the measure of degree of obesity. It has been used before in some studies in studying the relationship of body size and prostate cancer (Giovannucci *et al*, 1997).

However, the use of pictorial illustrations in this study is better for recalling the body size at earlier age because subjects do not normally or consistently weigh themselves or measure their waist and hip circumference, and even remember the figures later, but they will recall better in comparatively body shape size at different decades of life.

5.5.2 Change of body shape

The finding showed that almost 90% of both case and control subjects had history of changes in body shape. Our analysis also showed that the magnitude of changes of body shape from age 20's to 40's varies between individuals (result not shown here). Approximately 87% of those body shape changes were an increase in body size. The increase in body size is mostly due to environmental factors of diet and lifestyles behaviour, as well as reduced metabolic rate when aging. Leptin hormone may also play some roles. High levels of leptin are found

in obese persons. Leptin is released by white adipose tissues and its effect is an uninhibited hunger making obese people maintain their weight by keep eating (Mantzoros, 1999).

The findings on estimated risk did not demonstrate any association between changes of body size and prostate cancer risk (Table 5-6 on page 5-93). These finding are in disagreement with most published studies that showed some relationship with prostate cancer (Hernandez *et al*, 2009; Rapp *et al*, 2008; Rodriguez *et al*, 2007; Wright *et al*, 2007). A possible explanation could be because the other studies used markers of measurements such as actual weight, BMI or waist circumference to indicate the change in body size, while our study use body shapes change. Furthermore, the other studies used multiple parameters to measure body size when trying to look at relationship with prostate cancer, therefore higher possibility of obtaining statistical significant findings in at least one of the measurement parameters.

Secondly, there are many other factors that could confound the relationship of body shape changes and prostate cancer risk such as hormone. Leptin, a hormone produced by adipocytes in proportion to fat cell volume in the body, has been found to have correlation with body weight (Chang *et al*, 2001) and those with higher leptin have increased risk of high volume (tumour size) prostate cancer at OR = 2.41 (1.16-5.01).

The limitation of only looking at pictorial illustration is the inability of making the actual measurement of changes in body size in compared with usage of parameters such as weight, waist or hip circumferences as well as BMI or body fat mass. The body shape although only shows the relativity of body size changes over the decades of life, are of more dependable based on recalling body shape in case-control studies, as numbers or figures if given may be more subjected to recall bias. Personal perception of body shape of each individual could introduce bias such as intention and classification bias.

Cohort study is often used to obtain more valid data by measuring and recording body weight, waist/hip circumference, body fat mass, etc periodically. This procedure was not possible to implement in this case-control study. Furthermore, some potential confounders need to be taken account or exclusion criteria need to be introduced to subjects with certain conditions of endocrinal disease such hypo or hyperthyroidism and pituitary tumours.

5.5.3 Body fat distribution

The cross-tabulation result showed that there were higher proportion of 'apple' type of body fat distribution among both cases and control (Table 5-7 on page 5-94). This has been expected because 'apple' also known as 'android' type of fat disposition is most common in males where fat is concentrated over the abdomen or waist and chest area. It was also found in our study that 'apple' shape is more prevalent among control subjects at 62.1% in proportion compared to cases at 55.1%. The chi-squared test confirms the difference in the proportion between cases and control group.

The author is not aware of any research done to see the prevalence of different types of body fat distribution in the population, however waist and chest circumference measurement in males are closest to describe whether one is 'apple' shape or proxy of central adiposity (Wells *et al*, 2007). Male shape seems to remain highly stable throughout adult life, therefore assumption can be made to suggest that characteristic of body fat distribution remains the same too.

The results shown in the Table 5-8 page 5-95, suggested that subject with 'apple' shape where body fat is distributed mainly around tummy area, would have a reduction risk to prostate cancer at unadjusted OR = 0.722 (95%CI: 0.583-0.893) when compared to those with 'symmetrical' shape. The Odds ratio for prostate cancer risk remained statistically significant even after adjusted for age, education, ethnic and family history of cancer at reduction risk of almost 30% (OR 0.689, 95%CI: 0.546-0.870). However, the 'pear' and 'oval' body shape did not show any statistically significant findings, although in the fully adjusted regression models showed that 'oval' shape had a borderline significance of reduced prostate cancer risk with odds ratio of 0.731 (95%CI: 0.534-1.000) when compared with those with 'symmetrical' shape.

'Apple' body shape which corresponds with waist measures of abdominal fat, whereas hip circumference measures of subcutaneous fat or 'pear' shape. Measurement of waist circumference or hip circumference alone has been used before when trying to classify types of body fat distribution. 'Apple' body shape in true measurement would predict wider waist circumference (WC) or higher waist to hip ratio (WHR), which has been shown in studies using true measurement to increase risk in advanced or high grade prostate cancer (Jackson *et al*, 2010; MacInnis *et al*, 2003; Pischon *et al*, 2008).

Our findings are unique in that none of the studies in the literature have used body shape as proxy measure of body fat distribution to describe its association with prostate cancer. The findings suggested that abdominal obesity maybe protective of prostate cancer.

In this study, word descriptions in the questionnaire was used to capture the types of body fat distribution which is potentially less accurate than using a 3-dimensional body shape scan as used in UK National Sizing survey (Wells *et al*, 2007), it is much cheaper than a costlier body scan. The accuracy of 3D body shape scan is higher, and the survey conducted in 2001 to 2002 in UK of cross-sectional study over 9617 adults found that male body shape remained highly stable throughout adulthood.

5.6 Conclusions and Recommendations

An 'apple' body shape was associated with a reduced prostate cancer risk when compared to symmetrical shape. There is no difference in body size distribution at age 20's, 30's, 40's, and last 5 years between cases and controls. There is no association between body shape changes from 20s to 40s either increases or decrease of body size and prostate cancer risk.

In future studies, it is recommended that records of endocrinal conditions should be included wherever possible in order to strengthen the exclusion criteria. Biomarkers indicative of any hormones related to obesity would also strengthen the findings.

Chapter 6 Chronic Diseases

6.1 Literature Review

6.1.1 Diabetes Mellitus and Prostate Cancer

Diabetes Mellitus is a condition characterized by a group of heterogenous disorders with common elements of hyperglycemias and glucose intolerance due to insulin resistance or deficiency (IDF, 2006). A growing number of studies have identified a reduction or decreased risk of prostate cancer in men with diabetes mellitus.

In particular, several studies have identified diabetes mellitus as protective against the risk of prostate cancer in men through the approach of case control study (Baradaran *et al*, 2009; Coker *et al*, 2004; Gong *et al*, 2006; Pourmand *et al*, 2007; Zhu *et al*, 2004) and cohort studies (Calton *et al*, 2007; Darbinian *et al*, 2008; Kasper *et al*, 2009; Leitzmann *et al*, 2008; Rodriguez *et al*, 2005; Waters *et al*, 2009; Weiderpass *et al*, 2002). Meta-analysis by Kasper & Giovanucci and Bonovas also showed an overall protective risk to prostatic cancer for men with diabetes (Bonovas *et al*, 2004; Kasper & Giovannucci, 2006).

A case-control study by Coker obtained adjusted odds ratio of 0.64 (95%CI: 0.45-0.91) and reported higher protection for those with diabetes and complications with adjusted OR of 0.61 (95%CI: 0.42-0.90), also African-american men at adjusted OR of 0.36 (95%CI: 0.21-0.62) (Coker *et al*, 2004). Gong study focused the different grades of prostate cancer and showed diabetics had 47% reduction risk to low grade prostate cancer (Gleason score ≤ 7) and 28% reduced risk for high grade prostate cancer (Gleason score ≥ 8) (Gong *et al*, 2006).

However, there were some published studies which showed no significant association between prostate cancer and diabetes mellitus (Chan *et al*, 2005b; Gallus *et al*, 2007; Li *et al*, 2010; Pierce *et al*, 2008; Tavani *et al*, 2005b; Wallstrom *et al*, 2009; Will *et al*, 1999).

Despite inconsistent evidence, some researchers have attempted to look at the possibility of anti-diabetic medication as the reason for the decreased risk of prostate cancer among diabetics. Gonzalez-Perez and G. Rodriguez found that only treated diabetes showed significant reduction in prostate cancer risk and possibly due to insulin or sulphonylureas (Rodriguez *et al*, 2005). A specific study on the association of metformin usage in diabetics to the risk of prostate cancer reported a borderline significant decreased risk (Wright & Stanford, 2009).

In another study, significant decreased odds ratio of prostate cancer risk were observed even when different types of anti-diabetic medications were taken, suggesting that diabetic status is the reason behind the protective event, not certain diabetic medication (Murtola *et al*, 2008).

Some biological mechanisms have been proposed suggesting that diabetic men have lower androgen and growth factors such as insulin, Insulin-like Growth Factor 1 (IGF-1), Insulin-like Growth Factor binding protein 3 (IGFBP-3), leptin, etc., therefore resulting in lower risk to prostate cancer (Giovannucci & Michaud, 2007; Hsing *et al*, 2001; Kasper *et al*, 2008; Stattin *et al*, 2000; Tavani *et al*, 2002).

Since diabetes mellitus seem to cause systemic microvascular abnormalities causing complications such as retinal blindness, there are hypotheses that this dysfunction can result in prostate ischaemia which in turn prevent the development of prostate cancer at the initiation phase through inhibition of angiogenesis, a similar mechanism to 5-Alpha-reductase inhibitors such as Finasteride suggesting local ischaemia may prevent prostate cancer initiation (Pareek *et al*, 2003; Thompson *et al*, 2009; Zhang & Hu, 2010).

6.1.2 Hypertension and Prostate Cancer

Hypertension commonly known as high blood pressure is a condition when the systolic or diastolic blood pressure reading is above of normal values. In adult the normal average blood pressure is 120/80 millimetre mercury (mmHg). A systolic and diastolic blood pressure reading of above 140 and 90 respectively would be considered as high blood pressure or hypertensive. In 1977, the First Joint National Committee (JNC) on Detection, Evaluation, and Treatment of High Blood Pressure established guidelines for management, introduced the stepped-care approach to hypertension treatment. In the latest development in the year

2003, the 7th JNC meeting has recommended the classification of pre-hypertension if systolic and diastolic blood pressure of 120-139 and 80-89 Hg respectively. Stage I Hypertension, systolic and diastolic blood pressure are 140-159 and 90-99 respectively and Stage II Hypertension as equal or more than 160 and 100 mmHg for systolic and diastolic blood pressure respectively (Moser). The Health Survey for England data from Department of Health, in 2001 showed the prevalence of 16 years old and above males with high blood pressure was 8% (treated). The rate could rise to 29% if untreated individuals are included (ONS, 2001).

Evidence on hypertension being associated with prostate cancer has been inconsistent. Data from Cardiovascular Health Studies in US followed those age 65 and above showed hypertension is not associated with prostate cancer, however the usage of anti-hypertensive medication was associated with reduced hazard ratio to 0.7 (CI: 0.5-0.9) (Fitzpatrick *et al*, 2001). A case control study by Weinmann also found no association between hypertension and prostate cancer (Weinmann *et al*, 2010).

A Norwegian cohort study called CONOR showed a statistically significant trend of increase hazard ratio for prostate cancer with the increase systolic and diastolic blood pressure (Martin *et al*, 2010). Increasing systolic pressure also showed a significant trend for increase hazard ratio towards advanced prostate cancer.

In another study using Swedish construction workers cohort, showed hypertension associated with reduced relative risk for prostate cancer. A significant trend was observed for higher systolic blood pressure associated with reduced incident of prostate cancer (Stocks *et al*, 2010).

Although the actual mechanism of how hypertension is related to prostate cancer is not fully known, several hypotheses have been described. Gann hypothesized that if high blood pressure is due to increased central sympathetic tone, which also causes increased in adrenergic activity in human body, subsequently neurotrophins in the prostate, leading to androgen-mediated stimulation involving Nerve growth-like factor (NGF) peptide, Epidermal growth factor (EGF) and Insulin growth-like factor 1 (IGF-1), to cause prostate cancer growth (Gann *et al*, 1995). McCarty suggested that increase in blood pressure would down regulate IGF Binding protein-1 (IGFBP1), which caused higher IGF-I activity and in turn prostate cancer growth (McCarty, 1997), as previous studies meta-analysis by

Rowlands had shown that circulating IGF-I is positively associated with prostate cancer risk (Rowlands *et al*, 2009).

However, detection bias is a concern and cannot be ruled out as all chronic diseases patients are under regular follow up by their general practitioner (GP), therefore are more likely to get screened for other diseases such prostate-specific antigen (PSA) testing (Martin *et al*, 2010) compared to those without treatment for hypertension as such.

6.1.3 Hypercholesterolemia and Prostate Cancer

Hypercholesterolemia refers to increased or elevated levels of cholesterol. The usual test is to do fasting blood lipid profile and normally also measure biochemistry three cholesterol levels namely low density lipoprotein (LDL), high density lipoprotein (HDL) and total cholesterol. For the purpose of clinical management of patients, all three readings would be taken into account, however the normal diagnosis of high cholesterol or hypercholesterolaemia is based on the total cholesterol reading. Some of the known causes of hypercholesterolemia include familial hypercholesterolemia or genetic causes, abnormality in cholesterol metabolism, diet high intake of saturated fatty acids, and secondary causes such as hypothyroidism (Grundy & Vega, 1990).

A normal or desirable total cholesterol level is defined as less than 200 mg of cholesterol per deciliter of blood (mg/dL) or 5.1 millimoles cholesterol per litre blood (mmol/l). Blood cholesterol is considered to be borderline high if in the range of 200 to 239 mg/dL (or 5.1 to 6.1 mmol/l). A total cholesterol level of 240 mg/dL (6.2 mmol/l) or above is considered elevated or high.

The National Institute for Health and Clinical Excellence (NICE) and Department of Health, UK, cholesterol guidelines uses normal total cholesterol as less than 5.0mmol/l and LDL cholesterol as less than 3.0mmol/l. Whereas the Joint British Societies (a group of the main UK expert societies involved in cardiovascular disease) recommend different cholesterol limits for people who have, or are at risk of, coronary heart disease of normal total cholesterol of less than 4.0mmol/l and LDL cholesterol less than 2.0mmol/l.

No data is available for prevalence of hypercholesterolemia in the UK, but the Centers for Disease Control and Prevention with US National Centre for Health

Statistics (2010) estimated that between the year 2005 to 2008, an average 14.9% (13.4% and 16.0% for men and women respectively) of USA adult population has high total cholesterol or have total cholesterol level of 240mg/dl and above (CDC, 2010).

Hypercholesterolemia study alone on its association with prostate cancer in case-control study of 312 hospital cases and 319 primary care controls showed increased risk at adjusted odds ratio 1.58(CI: 1.11-2.24) (Magura *et al*, 2008). Magura also revealed low HDL and high LDL increased the risk to prostate cancer at OR 1.57 (CI: 1.04-2.36) and 1.60 (CI: 1.09-2.34) respectively.

Another hospital case-control study looking at possibility of differential effects of age, found OR=1.51 (95%CI: 1.23-1.85) especially stronger in older age $\geq$ 65 years at OR1.80 (95%CI: 1.34-2.40)(Bravi *et al*, 2006).

A study by Colli & Amling using data 1992 to 2000 from National Vital statistics system of Centers for Disease Control and Prevention in USA showed high cholesterol levels were associated with lower prostate cancer mortality rates when statin use was high. With low statin use, there is no effect (Colli & Amling, 2009).

A different aspect in looking at grades of prostate cancer using Gleason score in a cohort study, the Prostate Cancer Prevention Trial between 1993 to 1996, showed those with lower blood serum cholesterol level or normal at $\leq$200mg/dl have reduced risk for high grade prostate cancer (Gleason score 8-10) at OR=0.41 (95%CI: 0.22-0.77), compared to those with elevated blood cholesterol. No clear association was seen in overall prostate cancer or in other lower grades, in relation to cholesterol level (Platz *et al*, 2009).

The mechanism underlying the association between hypercholesterolemia and prostate cancer is still unknown but possibility the association is only true for high grade or late diagnosed prostate cancer.

6.1.4 Ischaemic Heart Diseases and Prostate Cancer

Ischaemic Heart Diseases can be defined as any of a group of acute or chronic cardiac conditions resulting from insufficient supply of oxygenated blood to the heart. It is most synonymous with coronary artery disease and would be

diagnosed by clinicians through signs & symptoms, physical examination but confirmed through test of electrocardiogram (ECG), echocardiogram, stress test and other extra investigations such as computerized tomography (CT) scan. The prevalence of treated coronary heart disease for Wales & England 1998 among men was 37.2 per 1000 males which has been on a rising trend (ONS, 1998c).

There are not many studies investigating the relationship between coronary artery disease and prostate cancer possibly because there was no immediate biologically plausible reason. However smoking has a high association with coronary heart disease and could be a confounder when studying the relationship between coronary heart disease and prostate cancer risk.

A hospital based case-control study with Benign Prostatic Hypertrophy (BPH) as controls by Neugut showed adjusted prostate cancer odds ratio of OR=2.00 (95%CI: 1.18-3.39) associated to coronary artery disease, however when further stratified to age group of 69 below and 70 or above was not statistically significant (Neugut *et al*, 1998).

A study by Stamatiou on coronary artery disease and histological prostate cancer autopsy in a case-control design, showed a statistically significant relationship of severity of coronary artery disease and prostate cancer risk (Stamatiou *et al*, 2007). The more severe types (IV-VI) of coronary artery disease had higher prostate cancer risk. However a nested case-control study by Driver provided a reverse result and showed that coronary artery disease provided a protective risk to prostate cancer at OR 0.72 (CI: 0.62-0.84) (Driver *et al*, 2010).

6.2 Aims

The aim of this chapter is to look at the common chronic diseases in man and their association with prostate cancer risk.

The specific aims are to look at prostate cancer risk in:

i. Diabetes Mellitus
ii. Hypertension or high blood pressure
iii. Hypercholesterolemia or elevated blood cholesterol
iv. Ischaemic heart disease or coronary artery disease

6.3 Methods

Data was obtained through questionnaire. The questionnaire enquired: "Have you ever been told by doctor that you have/had any of the following conditions? Please state Yes/No and age at diagnosis of the conditions.

; Diabetes
; Heart Disease
; Hypercholesterolaemia (high blood cholesterol)
; High blood pressure
; Other please specify.....

The respondents would be considered as having the condition(s) of the listed chronic diseases or other as stated 'yes' in the questionnaire based on their knowledge of being told by the doctor(s) who has seen them. The age of when they were first told to have such condition(s) is the age at diagnosis.

No other record was used.

6.4 Analysis

In order to obtain the valid temporal relationship between the chronic disease condition and prostate cancer, we ensured among the respondents who answered 'Yes' in having the condition in the questionnaire, by only qualifying those who had the condition prior to prostate cancer diagnosis were considered as valid 'yes'. This was rectified by comparing the year of diagnosis of the prostate cancer (cytology confirmation) provided by hospital registry to the self reported date/year of being diagnosed with diabetes, hypertension, ischaemic heart disease or hypercholesterolemia. In essence, year of onset chronic disease(s) must be prior to year of prostate cancer diagnosis in cases or in receiving questionnaire in controls.

After this verification process, each subject was then put into different categories according to duration. Three aspects of categorizing the disease status (yes/no answer) were based on having or not having the condition, having the disease for 5 years or more (before prostate cancer diagnosis) and lastly 10 years or more.

Only subjects from Phase II filled in the data on chronic diseases. Data from questionnaire have been entered into the Microsoft Access then the data on chronic diseases were extracted into Microsoft Excel for data cleaning and further classification before entered to SPSS vs 17.0 for statistical analysis using Chi-square test, univariate binomial logistic regression, followed by age-adjusted modelling of binomial logistic regression and further model adjustment using statistically significant demographic factors in the multivariate analysis and a priori confounders to obtain odds ratios (OR) and 95% confidence interval (95% CI).

6.5 Results

6.5.1 Diabetes Mellitus (DM)

Table 6-1 Cross-tabulation Diabetes Mellitus and Case-Control Groups

Status	DM		DM 5 Years or more		DM 10 Years or more	
	Case	Control	Case	Control	Case	Control
	(%)	(%)	(%)	(%)	(%)	(%)
Yes	68	66	31	46	17	27
	5.7%	9.4%	2.6%	6.6%	1.4%	3.9%
No	1124	633	1161	653	1175	672
	94.3%	90.6%	97.4%	93.4%	98.6%	96.1%
Total	1192	699	1192	699	1192	699
	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

There were statistically significant differences in the diabetes mellitus proportions between cases and control at p=0.002, with controls reporting more diabetes mellitus (9.4% as opposed to 5.7%).

Table 6-2 (page 6-110) showed self reported DM status. The result showed that after adjustment for age, the relationship remained significant at p value 0.010 with the reduced prostate cancer risk of 38% among diabetics. However upon further adjustment of education, ethnic and family history of cancer, the association became not statistically significant at borderline p value level (p=0.056).

Subjects who reported having had diabetes mellitus for a period of 5 years or more before prostate cancer diagnosis for cases or before control subjects enrolled this study showed a statistically significant risk reduction towards prostate cancer among them at OR=0.379 (95%CI: 0.238-0.604), 0.435 (95%CI: 0.270-0.700) and 0.452 (95%CI: 0.272-0.753) of unadjusted, age-adjusted and fully adjusted models respectively.

Similar findings showed that for those who had been diabetic for 10 years or more, had statistically significant protective risk towards prostate cancer compared to those who are non-diabetic or had diabetes mellitus less than 10 years duration (refer Table 6-2 page 6-110).

Table 6-2 Odds Ratio (OR) and Confidence Interval for Univariate/Unadjusted and Adjusted Regression models for Diabetes Mellitus and Prostate Cancer Risk

Types of Analysis Classification n=1891	Control n=699		Case n=1192		Odds ratio, OR[a] (95%CI)	P value [a]	Adjusted OR[b] (95%CI)	p value[b]	Adjusted OR[c] (95%CI)	p value[c]
	No	Yes	No	Yes						
Diabetes Mellitus status	633	66	1124	68	**0.580 (0.408-0.825)**	**0.002**	**0.620 (0.432-0.890)**	**0.010**	0.687 (0.468-1.010)	0.056
Diabetes M 5Y or more	653	46	1161	31	**0.379 (0.238-0.604)**	**<0.001**	**0.435 (0.270-0.700)**	**0.001**	**0.452 (0.272-0.753)**	**0.002**
Diabetes M 10Y or more	672	27	1175	17	**0.360 (0.195-0.666)**	**0.001**	**0.440 (0.235-0.826)**	**0.011**	**0.442 (0.225-0.869)**	**0.018**

[a]Unadjusted Regression Models
[b]Adjusted Regression Models for age
[c]Multivariate Adjusted Regression Models for age, education, ethnic and family history of cancer

6.5.2 Hypertension (HPT)

Table 6-3 Cross-tabulation Hypertension and Case-Control Groups

Status	HPT		HPT 5 Years or more		HPT 10 Years or more	
	Case	Control	Case	Control	Case	Control
	(%)	(%)	(%)	(%)	(%)	(%)
Yes	416	298	285	207	153	130
	33.5%	40.1%	22.9%	27.9%	12.3%	17.5%
No	827	445	958	536	1090	613
	66.5%	59.9%	77.1%	72.1%	87.7%	82.5%
Total	1243	743	1243	743	1243	743
	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

The distribution of hypertension showed that there was a higher proportion of hypertension among controls (40.1%) as compared to cases (33.5%). Chi-square test showed statistically significant at p=0.003 (refer Table 6-3 page 6-111)

Hypertension appeared to reduce risk for prostate cancer at odd ratios of 0.751 (95%CI: 0.622-0.907), 0.770 (95%CI: 0.626-0.948) and 0.662 (95%CI: 0.513-0.853) in unadjusted models of hypertensive status, hypertensive for 5 years or more, and hypertensive for 10 years or more respectively (refer Table 6-4 page 6-112). In age adjusted and fully adjusted models, prostate cancer risks are no longer statistically significant with all confidence intervals include 1.

Table 6-4 Odds Ratio (OR) and Confidence Interval for Univariate/Unadjusted and Adjusted Regression models for Hypertension and Prostate Cancer Risk

Types of Analysis Classification n=1986	Control n=743		Case n=1243		Odds ratio, OR[a] (95%CI)	P value[a]	Adjusted OR[b] (95%CI)	p value[b]	Adjusted OR[c] (95%CI)	p value[c]
	No	Yes	No	Yes						
Hypertension status	445	298	827	416	**0.751 (0.622-0.907)**	**0.003**	0.841 (0.693-1.021)	0.080	0.854 (0.696-1.047)	0.129
Hypertension 5Y or more	536	207	958	285	**0.770 (0.626-0.948)**	**0.014**	0.874 (0.705-1.083)	0.219	0.900 (0.719-1.127)	0.359
Hypertension 10Y or more	613	130	1090	153	**0.662 (0.513-0.853)**	**0.001**	0.797 (0.613-1.037)	0.091	0.804 (0.610-1.059)	0.120

[a]Unadjusted Regression Models
[b]Adjusted Regression Models for age
[c]Multivariate Adjusted Regression Models for age, education, ethnic and family history of cancer

6.5.3 Hypercholesterolemia (HCL)

Table 6-5 Cross-tabulation Hypercholesterolemia (HCL) and Case-Control Groups

Status	HCL		HCL 5 Years or more		HCL 10 Years or more	
	Case	Control	Case	Control	Case	Control
	(%)	(%)	(%)	(%)	(%)	(%)
Yes	315	232	183	150	88	75
	26.3%	32.4%	15.3%	21.0%	7.3%	10.5%
No	884	483	1016	565	1111	640
	73.7%	67.6%	84.7%	79.0%	92.7%	89.5%
Total	1199	715	1199	715	1199	715
	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

There was a higher proportion of hypercholesterolemia among the controls (32.4%) as compared to cases (26.3%) (Refer Table 6-5 page 6-113). Chi-square test of p=0.004 showed a statistically significant difference.

Univariate analysis revealed a significant statistical association between prostate cancer and hypercholesterolemia, with a reduced risk of cancer among those with the hypercholesterolemia (OR=0.742, 95%C.I: 0.606-0.908). These findings of prostate cancer risks were similar when analyses were conducted on those having hypercholesterolemia of 5 years or more and 10 years or more, of approximately 33% reduction in risks (refer Table 6-6 page 6-114). The age adjusted regression models were only statistical significant for overall hypercholesterolemia and those of 5 years and 10 years or more group at OR=0.800 (95%CI: 0.649-0.984) and 0.766 (95%CI: 0.599-0.979) respectively. However the multivariate adjusted models showed non-statistically significant OR for hypercholesterolemia condition at 5 years and 10 years or more.

Table 6-6 Odds Ratio (OR) and Confidence Interval for Univariate/Unadjusted and Adjusted Regression models for Hypercholesterolemia (HCL) and Prostate Cancer Risk

Types of Analysis Classification n=1914	Control n=715		Case n=1199		Odds ratio, OR[a] (95%CI)	P value[a]	Adjusted OR[b] (95%CI)	p value[b]	Adjusted OR[c] (95%CI)	p value[c]
	No	Yes	No	Yes						
HCL status	483	232	884	315	**0.742 (0.606-0.908)**	**0.004**	**0.800 (0.649-0.984)**	**0.035**	0.979 (0.745-1.286)	0.877
HCL 5Y or more	565	150	1016	183	**0.678 (0.534-0.862)**	**0.001**	**0.766 (0.599-0.979)**	**0.033**	0.879 (0.660-1.170)	0.377
HCL 10Y or more	640	75	1111	88	**0.676 (0.489-0.934)**	**0.017**	0.780 (0.560-1.086)	0.141	0.900 (0.628-1.292)	0.569

[a]Unadjusted Regression Models
[b]Adjusted Regression Models for age
[c]Multivariate Adjusted Regression Models for age, education, ethnic, family history of cancer and statin status

6.5.4 Ischaemic Heart Diseases (IHD)

Table 6-7 Cross-tabulation Ischaemic Heart Diseases and Case-Control Groups

Status	IHD		IHD 5 Years or more		IHD 10 Years or more	
	Case	Control	Case	Control	Case	Control
	(%)	(%)	(%)	(%)	(%)	(%)
Yes	95	76	70	60	40	38
	8.1%	11.0%	6.0%	8.7%	3.4%	5.5%
No	1081	615	1106	631	1136	653
	91.9%	89.0%	94.0%	91.3%	96.6%	94.5%
Total	1176	691	1176	691	1176	691
	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Ischaemic heart disease was higher among controls as compared to cases (11.0% among controls and 8.1% among cases). Chi-square test showed statistical significant difference at p=0.035

Univariate analysis showed a statistically significant prostate cancer risk reduction among those with ischaemic heart disease of 5 years or more, and also 10 years or more, at OR=0.711 (95%CI: 0.518-0.977), 0.666 (95%CI: 0.465-0.953), and 0.605 (95%CI: 0.384-0.953) respectively (refer Table 6-8 page 6-116). Upon adjustment of regression models using age alone and then with fully multivariate adjusted potential confounders variables (including smoking status), the relationship between prostate cancer risk and ischaemic heart disease became non-statistical significant.

Table 6-8 Odds Ratio (OR) and Confidence Interval for Univariate/ Unadjusted and Adjusted Regression models for Ischaemic Heart Diseases (IHD) and Prostate Cancer Risk

Types of Analysis Classification n=1867	Control n=691		Case n=1176		Odds ratio, OR[a] (95%CI)	P value[a]	Adjusted OR[b] (95%CI)	p value[b]	Adjusted OR[c] (95%CI)	p value[c]
	No	Yes	No	Yes						
IHD status	615	76	1081	95	**0.711 (0.518-0.977)**	**0.035**	0.848 (0.611-1.176)	0.323	0.906 (0.638-1.288)	0.584
IHD 5Y or more	631	60	1106	70	**0.666 (0.465-0.953)**	**0.025**	0.814 (0.563-1.179)	0.276	0.843 (0.566-1.255)	0.399
IHD 10Y or more	653	38	1136	40	**0.605 (0.384-0.953)**	**0.029**	0.796 (0.498-1.273)	0.341	0.770 (0.465-1.273)	0.308

[a]Unadjusted Regression Models
[b]Adjusted Regression Models for age
[c]Multivariate Adjusted Regression Models for age, education, ethnic, family history of cancer and smoking status

6.6 Discussion

6.6.1 Diabetes Mellitus (DM)

To obtain the temporal relationship of chronic diseases such as diabetes mellitus and the risk developing prostate cancer, the self reported data were used and were censored to ensure only diabetes that existed before prostate cancer diagnosis were included in the analyses.

The proportion of diabetes mellitus is higher among controls (9.4%) as compared to cases (5.7%) (Refer Table 6-1, page 6-109). This pattern remains for those with a history of diabetes of 5 years or more and also diabetes of 10 years or more. When compared to data from England and Wales 1994-1998, on average, males age standardized was 9.9 per 1000 population (or 0.99%) which is much lower compared to the study figure, even if looking at specific age group age 55-64 and 65-74, the England & Wales average was 28.7 and 42.3 per 1000 males or equivalent to 2.87% and 4.23% respectively (ONS, 1998a), these figures are still lower than study figures when mean age of phase II subjects' was used (mean age 62.42 with standard deviation of 6.26 years).

The findings in univariate logistic regression and adjusted models for age showed statistically significant reduced odds ratio. On the fully adjusted models, the regression analysis result showed borderline statistically significant of having diabetes to reduce prostate cancer risk at p=0.056 of OR=0.687 (95%CI: 0.468-1.010) (refer Table 6-2 page 6-110). However if subjects reported having had diabetes for a duration of 5 years or more, and 10 years or more, the risk for prostate cancer were reduced by 45.2% and 44.2% respectively. The protective risk in this present study appears to be higher than most cohort and case-control studies.

These findings may suggest that chronic diabetes may act via a mechanism of lower androgen and growth factor levels such as insulin, IGF-1, IGFBP-3 thus could have protective effect against prostate cancer.

The finding of borderline significant risk reduction when timing of being diabetic was not taking into account could be partly due to possibility of lack of consistency in temporal relationship. Some prostate cancer may exist before

diabetes status, therefore it is possible the new diabetics (of only few years) could have cause a non-significant protective relationship towards prostate cancer and diluted the overall effect of diabetes status when analyzed subjects with or without diabetes. To be able to confirm diabetes mellitus offers a protection against prostate cancer, the former would have to exist before the latter.

Similarly may be said of diabetes mellitus, which were not diagnosed earlier because, no routine medical screening or health check-up. The condition could have existed many years before the onset of carcinogenesis of prostate cancer, resulting loss years of documentation prior to prostate cancer diagnosis.

The findings of diabetes of 5 years or longer duration were of similar to most studies. These studies suggested that diabetes mellitus condition has a protective action against prostate cancer. Diabetes was also associated with prostate cancer reduction of late stage tumours (Gong *et al*, 2006; Zhu *et al*, 2004).

At the molecular level, evidence was established through the link between genes in diabetes and prostate cancer. The study on HFF1B genes revealed SNPs rs11649743, rs4430796 and rs7501939 were association with reduced risk to prostate cancer but increased risk to diabetes mellitus. The JAZF1 SNPs rs6968704 and rs10486567 were associated with reduced risk in prostate cancer, but relationship with diabetes was not established (Stevens *et al*, 2010).

One limitation in this study is the likelihood of under-diagnosed of diabetes mellitus or prostate cancer among the control subjects. Diabetes can be of two types therefore could mean Diabetes mellitus type I or type II. No differentiation was made in this study. Although type I diabetes is hereditary and possibly triggered by infection, there is also an influence of lifestyle behaviour. Similarly type II diabetes could have familial or genetic relationship, but lifestyle is still the most common associated risk for developing full blown diabetes mellitus.

6.6.2 Hypertension

The results displayed in Table 6-3 page 6-111 on hypertension status showed a higher proportion of hypertension among the control subjects as compared to cases at 40.1% and 33.5% respectively. When compared with England Wales 1998 Data, our hypertensive prevalence is much higher as theirs average age-

standardized in 1998 was 2.83%, for specific age group 55-64, 65-74, 75-84 was 7.34%, 11.5% and 13.1% respectively (ONS, 1998b). Subsequent Chi-square test detected a statistically significant difference in the proportion of hypertension between case and control group.

Regression modelling analysis showed reduction in prostate cancer risk among those who have history of overall hypertension, of 5 years or more, and in 10 years or more (refer Table 6-4 page 6-112). Both regression models adjusted for age and fully adjusted for age, education, ethnic and family history of cancer showed non-statistically significant protective risk against prostate cancer among those who were of hypertensive status, hypertensive for 5 years or more, and hypertensive for 10 years or more.

Previous studies investigating the association of hypertension and prostate cancer have also shown non-statistically significant findings such as in Fitzpatrick and Weinmann (Fitzpatrick *et al*, 2001; Weinmann *et al*, 2010).

Among the limitations of this study is the lack of medical record to confirm hypertensive diagnosis. Since true hypertension can only be diagnosed through several follow up readings by health professionals over weeks or months, any reading of hypertensive or high blood pressure based on one reading cannot rule out or rule in as hypertensive. Furthermore, measurement of blood pressure was not conducted in this study. Detection bias is also a possibility.

Some studies have looked at the type of hypertension either of systolic hypertension which is more commonly diagnosed among elderly subjects or at both high systolic & diastolic blood pressure readings. Due to this study not taking any blood pressure readings or information on hypertensive medication, such stratified analysis could not be carried out.

6.6.3 Hypercholesterolemia

From the cross-tabulation display for hypercholesterolemia of overall, 5 years or more and 10 years or more, the controls appeared to show higher proportion of history of hypercholesterolemia compared to cases (refer Table 6-5 page 6-113).

The univariate logistic regression modelling analysis showed that having hypercholesterolemia (regardless of duration), having it for 5 years or more and

10 years or more were protective against prostate cancer at approximately 25.6%, 32.8% and 33.4% respectively with all confidence intervals include 1 (Refer Table 6-6 page 6-114). Upon adjustment for age, only those who have hypercholesterolemia overall and of 5 years or more had statistically significant protective risk against prostate cancer at approximately 20.0% and 23.4% respectively. Whereas upon fully adjusted regression model (controlled for age, education, ethnic, family history of cancer and statin use), none of the hypercholesterolemia categories were statistically significant.

The study findings indicate that chronic hypercholesterolemia does not associate with prostate cancer risk.

The usage of cholesterol reducing drugs or treatments among those who reported having had hypercholesterolemia could interfere with the actual level of cholesterol in the blood, but this cannot be validated as we do not have any record of blood/serum cholesterol level at any time of the study subjects. One previous study by Colli & Amling appeared to show similar protective risk that high cholesterol levels were associated with lower prostate cancer mortality rates when statin use was high but not in low dose (Colli & Amling, 2009). This clearly indicates there might not be a clear protective risk of having hypercholesterolemia towards prostate cancer. Instead statin may be reducing prostate cancer mortality rates.

One of the previous studies by Magura showed the association of hypercholesterolemia as hazardous risk to prostate cancer with adjusted OR=1.58 (95%CI: 1.11-2.24) (Magura *et al*, 2008). The results of further stratified for low HDL and high LDL posted increased risk for prostate cancer at OR 1.57 (95%CI: 1.04-2.36) and 1.60 (95%CI: 1.09-2.34).

Some limitations found in this study is the possible influence of statin over the association between hypercholesterolemia and prostate cancer. Secondly there was no documentation of the actual measuring level of cholesterol of the subjects over the years, it was presumed that when a subject was informed by the healthcare personnel that he has high cholesterol level, the status maintain for the person to keep having raised cholesterol level even if lowering cholesterol medication were to control the level.

Thirdly, it would most useful if measurement were recorded in patients' records if available at different period of time for further stratification to look at whether different levels of total cholesterol levels for the p-trend, and types of cholesterol of good and bad such as HDL and LDL have any association towards prostate cancer risks.

6.6.4 Ischaemic Heart Disease (IHD)

The ischaemic heart disease rate was higher among control subjects compared to prostate cancer cases at 8.1% and 11.0% respectively (refer Table 6-7 page 6-115). This prevalence figures are comparable with data from England & Wales 1998 both on average and specific age group. The 1998 England & Wales at age group of 55-64, 65-74 and 75-84 had prevalence of males coronary artery disease of 9.5%, 18.4% and 23.1% respectively (ONS, 1998c). Chi-square analysis revealed statistically significant difference.

Univariate logistic regression modelling demonstrated lower prostate cancer risk of OR=0.711 (95%CI: 0.518-0.977), 0.666 (95%CI: 0.465-0.953), and 0.605 (95%CI: 0.384-0.953) for IHD (regardless duration, IHD of 5 years or more, and IHD of 10 years or more respectively (refer Table 6-8 page 6-116). Although the logistic regression models of age-adjusted and further adjustment for education, ethnic group, family history of cancer and smoking status showed odds ratio of less than 1.0 or of protective risk against prostate cancer, the statistical test revealed a non-significant association between hypercholesterolemia and prostate cancer.

The analysis of further adjustment for smoking status has been carried out due to its strong association with ischaemic heart disease. Chi-square test indicated difference in proportion of smoking as statistically significant between cases and control (result not presented here). However upon multivariate analysis, smoking status became non-statistically significant, but due to its strong potential confounder effect on ischaemic heart diseases (IHD), it is appropriate to include smoking in fully adjusted multivariate regression models as a priori variable.

Studies focused on the association of smoking and prostate cancer, the findings were inconsistent with mostly concluded to have found lack or weak association of smoking in increasing prostate cancer risk (Adami *et al*, 1996; Rohrmann *et al*, 2007) and risk is stronger related to younger age group (Rodnguez *et al*, 1997).

The findings from British doctors who participated in a 50 years observation on cancer deaths related to smoking suggested prostate cancer to be unrelated (Doll *et al*, 2005).

Few studies were conducted to look at direct association between IHD and prostate cancer. An earlier study by Neugut indicated increase prostate cancer risk due to IHD (Neugut *et al*, 1998), while a recent article by Driver suggested coronary artery disease protect against prostate cancer (Driver *et al*, 2010).

There is a potential limitation in terms of respondents understanding of heart disease in the questionnaire which was meant to indicate ischaemic heart disease and not other types of heart disease unrelated to lack of oxygen supply. Since the column only provide yes or no for answer, is it presumptive to say that if respondents were unsure, they may named their heart disease condition in a separate space of other disease to avoid bias.

Since the biological plausibility explanation of how IHD might be associated with prostate cancer, there might be a place to look medication as a confounder because aspirin (act as a blood thinning agent) is normally given as common drug treatment for any case of IHD in order to reduce the episode of thrombosis or platelet aggregation. Another previous study has found aspirin to be associated with reduced cancer risk and also have a protective effect to prostate cancer. This will be discussed in more detail in relevant chapters.

6.7 Conclusions and Recommendations

Chronic diabetes of five years or more may be protective against prostate cancer. For other chronic disease such as hypertension, hypercholesterolemia and ischaemic heart diseases, none showed protective effect towards prostate cancer.

Further study should be carried out to strengthen the findings such as controlling for potential confounders of these relationships by obtaining proper medical record of diabetes diagnosis and types, anti-diabetic medication, past records readings of blood pressure of hypertension, levels of blood cholesterol and other types at different age period and coronary heart disease medication usage and types, severity of conditions of chronic diseases and proper body mass index at different intervals and severity of prostate cancer.

Chapter 7 Statins

7.1 Literature Review

There are several types of statins which are normally prescribed by doctors to treat mainly the problem of patients with hypercholesterolemia (elevated blood cholesterol) and some for the presence of diseases such as ischaemic heart disease. Some of the commonly prescribed statin drugs include rosuvastatin (Crestor), atorvastatin (Lipitor), Simvastatin (Zocor), Pravastatin (Pravacol/Pravigard), Fluvastatin (Lescol) and Lovastatin (Mecavor).

Since hypercholesterolemia has been associated with cardiovascular diseases, therefore by controlling blood cholesterol, statin may also act as a secondary prevention measure for ischaemic heart disease (IHD) death. A meta-analysis in 2007 study of 61 prospective studies demonstrated that 1mmol/l of lower total cholesterol was associated with approximately 56%, 33% and 17% lower IHD mortality in both sexes at ages 40-49, 50-69 and 70-89 years age group respectively in most developed countries (PSC, 2007).

A study on the prevalence usage of statin among European countries by Walley showed for UK during 1997-2002, the use per day was 23.86 per 1000 population (Walley *et al*, 2004). Actual data on prevalence usage of statins is not known however but they are prescribed mostly for those with cardiovascular risk. The most commonly used statins used are Simvastatin and Atorvastatin. Nowadays statins are mostly given through doctors' prescription, however low dose statins are available at pharmacy over the counter.

Statin act to decrease cholesterol production by inhibiting 3-hydroxy-3-methylglutaryl CoA reductase which normally produce mevalonate (a precursor of cholesterol) and tumorgenic molecules (Solomon & Freeman, 2008). However, findings on the effects of statin on cancer is not convincing as the results from a number of studies are mixed.

Kritchevsky & Kritchevsky who did an epidemiologic review on serum cholesterol level and cancer risk examined two questions; is low cholesterol associated with increased risk of cancer and does reducing serum cholesterol increase cancer occurrence (Kritchevsky & Kritchevsky, 1992). Of the studies examined, showed

a median 30% increased risk of cancer among males with low serum cholesterol, mainly consistent in colon and lung cancers.

A meta-analysis study by Davey Smith & Pekkanen of mortality during trials of primary prevention of coronary heart disease (of between late 1960's to early 1990's) through lowering of cholesterol concentration by drug intervention showed a pooled odds ratio of 1.33 (95% CI: 0.93-1.89) of cancer deaths and other non-coronary deaths 1.69 (95%CI: 1.11-2.57), concluded uncertainty surrounding the benefits and risks of cholesterol lowering drugs for general use, although earlier in 1970's, more common cholesterol lowering drug was clofibrate while statins came later in 1980's (Davey Smith & Pekkanen, 1992).

In 1990's, a population based study using drug prescription study was done on Denmark population from 1991 to 1994 and followed up for cancer occurrence found standardized incidence rations (SIR) of 1.0 (95%CI: 0.7-1.3) for all types of lipid lowering drugs and upon stratification showed among statin users and fibrates users of SIR 0.8 (95%CI: 0.5-1.3) and 1.2 (95%CI: 0.6-2.0) respectively, which was non-statistically significant (Olsen *et al*, 1999).

In contrast to concerns of statins carcinogenicity, there is growing literature to suggest statins may in fact have a chemopreventive potential against cancer (Boudreau *et al*, 2010; Chan *et al*, 2003).

Statins or HMG-CoA inhibitors mechanism of action is by inhibiting HMG-CoA reductase and prevent conversion of HMG-CoA to mevalonate, thereby reduce mevalonate levels products or pathways for critical cellular functions such as membrane integrity, cell signalling, protein synthesis and cell cycle progression. By disrupting these processes, statins result in control of tumour initiation, growth and metastasis (Chan *et al*, 2003), resulting also to apoptotic cell death (Dimitroulakos *et al*, 1999). Laboratory study has demonstrated statins induced apoptosis (programme cell death) in cells lines including prostate stromal cells (Padayatty *et al*, 1997).

Studies that have shown that statin use was not associated with risk of overall prostate cancer (Boudreau *et al*, 2008; Coogan *et al*, 2002; Kaye & Jick, 2004). The meta-analyses papers by Jacobs, Kuoppala and Bonovas did not find significant association (Bonovas *et al*, 2008; Jacobs *et al*, 2007a; Kuoppala *et al*, 2008).

However some studies found statins to be associated with reduction in prostate cancer risk in certain categories of cancer namely advanced cases (Jacobs *et al*, 2007a; Murtola *et al*, 2007; Platz *et al*, 2006; Shannon *et al*, 2005), or low grade cancer (Murtola *et al*, 2010).

7.2 Aim

This study aims to investigate prostate cancer risk association with duration intake of common cholesterol lowering drugs of Statins family.

7.3 Method

Data was collected through questionnaire. Study subjects were asked to record the individual type of drugs above, duration used and reason for taking the medication. Data were entered through a Microsoft access database, before being extracted into excel document.

7.4 Analysis

Data on statin medication were only available in the second phase of the study only as this factor was added into the later questionnaire used in phase II with total of 2209 subjects (1371 cases and 838 controls).

Data from Microsoft Access was extracted into excel document and was transferred to SPSS database. Statin use is defined as consuming Statins regularly within the last 10 years prior to prostate cancer diagnosis for case subjects, or anytime within last 10 years for control. Due to various types of statins reported in the questionnaires, during classification, the types of statins which have smaller number of users were classified as 'others'. Since the numbers of respondents who reported two or more types of main statins used were also small, they have also been classified in a group with 'others' category.

Those who were Statins user were then selected for further coding of their duration using statins. Data on duration was then classified into coding of 5 years interval block as following called Statin Duration Block:

'0' – None

'1' – use statins less than 5 years

'2' – use statins for 5 years or more but less than 10 years

'3' – use statins for 10 years or more but less than 15 years

'4' – use statins for 15 years or more

Based on the above data classification, p for trend analysis was done.

The possibility of cumulative use of statins determining prostate cancer risk as a whole is studied by classifying the users into category of cumulative years use of statin of up to 5, 10, 15 and 20 years.

Statistical software SPSS version 17.0 was used to analyze the data for descriptive cross-tabulation and analytical Chi-square, logistic regression and subsequent adjusted logistic regression modelling in looking at statins on prostate cancer risk to obtain odds ratios and confidence intervals.

7.5 Results & Discussion

7.5.1 Types of Statin

Table 7-1 Types of Statin use among case-control groups

Type of Statin	Group		Total
	Control	Case	
	(%)	(%)	(%)
Atorvastatin	55	77	132
	19.5%	25.1%	22.4%
Pravastatin	11	8	19
	3.9%	2.6%	3.2%
Rosuvastatin	8	9	17
	2.8%	2.9%	2.9%
Simvastatin	185	191	376
	65.6%	62.2%	63.8%
Others and in combination	23	22	45
	8.2%	7.2%	7.6%
Total	282	307	589
	100.0%	100.0%	100.0%

Almost two-thirds of subjects reported using statin in this study used Simvastatin, followed by Atorvastatin approximately a quarter of all subjects. While some over the period of time of usage consumed of more than 1 type of statin or less common type (refer Table 7-1 page 7-127).

7.5.2 Reason for taking Statin

Table 7-2 Reason for taking Statin

Reason use Statin	Group		Total
	Control	Case	
Cholesterol	212	242	454
	73.4%	77.8%	75.7%
GP advice	17	8	25
	5.9%	2.6%	4.2%
Hypertension	11	18	29
	3.8%	5.8%	4.8%
IHD	26	28	54
	9.0%	9.0%	9.0%
Other	23	15	38
	8.0%	4.8%	6.3%
Total	289	311	600
	100.0%	100.0%	100.0%

The above Table 7-2, page 7-127, showed that high blood cholesterol was the main reason for taking statin at average three quarters of all subjects. Chi-square test showed p value of 0.096 suggesting there is no statistical significant difference in the reasons for taking statin between case and control group.

7.5.3 Statin Ever use

Table 7-3 Cross-tabulation of Statin use among case-control group

Statins Used	Group		Total
	Control	Case	
	(%)	(%)	(%)
No	530	1030	1560
	64.2%	76.1%	71.6%
Yes	296	324	620
	35.8%	23.9%	28.4%
Total	826	1354	2180
	100.0%	100.0%	100.0%

The cross-tabulation Table 7-3 showed higher proportion of controls (35.8%) using statins compared to case group (23.9%). Chi-square test **p value <0.001**, showed statistically significant difference in proportion of prostate cancer of case-control group.

The Table 7-4 page 7-129, showed that all statin users has statistically significant reduction risk of prostate cancer at adjusted odds ratio for age, at OR=0.665 (95%CI: 0.546-0.808) and when adjusted for age, education, ethnic and family history of cancer at OR=0.714 (95%CI: 0.580-0.878) when compared to non-user of statin drug.

Table 7-4 Logistic Regression Modelling for Statin User to obtain Odds Ratio (OR) for Univariate/Unadjusted and Adjusted models Prostate Cancer Risk

(n=2180)	Control		Case		OR [a] (95%CI)	p value[a]	OR [b] (95%CI)	p value[b]	OR [c] (95%CI)	p value[c]
Statin Used	Yes (%)	No (%)	Yes (%)	No (%)						
	296 (35.8%)	530 (64.2%)	324 (23.9%)	1030 (76.1%)	0.563 (0.466-0.681)	<0.001	0.665 (0.546-0.808)	<0.001	0.714 (0.580-0.878)	0.001

[a]Unadjusted Regression Models
[b]Adjusted Regression Models for age
[c]Multivariate Adjusted Regression Models for age, education, ethnic and family history of cancer

7.5.4 Duration of Statin Usage

The effect of statin duration of usage on prostate cancer risk in compared with non-statin user was studied by categorizing the users using duration block of 5 years interval.

Table 7-5 Crosstabulation of Statin usage duration of Cases and Controls

Statin Usage Duration	Group		Total
	Control	Case	
	%	%	%
Non user	530	1030	1560
	66.3%	77.7%	73.4%
Less than 5 Years	136	137	273
	17.0%	10.3%	12.8%
5Y or more but less than 10Y	77	105	182
	9.6%	7.9%	8.6%
10Y or more but less than 15Y	39	38	77
	4.9%	2.9%	3.6%
15Y or More	17	16	33
	2.1%	1.2%	1.6%
Total	799	1326	2125
	100.0%	100.0%	100.0%

Table 7-5 presents cross-tabulation of statin duration usage. The results showed higher proportion of longer duration of statin usage among the control group compared to cases. Chi-square test revealed $p<0.001$ suggesting differences in statin usage duration between cases and controls.

Table 7-6 Odds Ratio and Confidence Interval of Statin Duration Block and Prostate Cancer Risk

Statin Usage Duration	Control (%)	Cases (%)	OR[a] (95%CI)	p value[a]	OR[b] (95%CI)	p value[b]	OR[c] (95%CI)	p value[c]
Non user	530 (66.3%)	1030 (77.7%)	-Ref-		-Ref-		-Ref-	
Less than 5 Years	136 (17.0%)	137 (10.3%)	**0.518 (0.400-0.672)**	**<0.001**	**0.585 (0.449-0.764)**	**<0.001**	**0.617 (0.467-0.815)**	**0.001**
5 Years or more but less than 10 Years	77 (9.6%)	105 (7.9%)	**0.702 (0.514-0.959)**	**0.026**	0.819 (0.594-1.129)	0.222	0.947 (0.674-1.330)	0.754
10 Years or more but less than 15 Years	39 (4.9%)	38 (2.9%)	**0.501 (0.317-0.793)**	**0.003**	0.667 (0.416-1.070)	0.093	0.666 (0.407-1.090)	0.106
15 Years or More	17 (2.1%)	16 (1.2%)	**0.484 (0.243-0.966)**	**0.040**	0.625 (0.310-1.262)	0.190	0.629 (0.298-1.327)	0.223

[a]Unadjusted regression model
[b]Age-adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, family history of cancer
P for trend, p<0.001

The table above showed that logistic regression after adjusting for age or also inclusion of education, ethnic and family history variables, only those who reported using statins of less than 5 years appeared to show statistically significant reduced odds ratio of **0.585 (95%CI: 0.449-0.764) and 0.617 (95%CI: 0.467-0.815)** respectively. When further adjusted for hypercholesterolemia status, the OR for 'Less than 5 Years' remains significant at **0.639 (95%CI: 0.455-0.897)**.

Although across other categories of usage duration do not show statistically significant adjusted models, they all displayed risk reductions.

7.5.5 Cumulative Duration Use of Statins

The possibility of cumulative use of statin determining prostate cancer risk as a whole is studied in the following analysis as shown in Table 7-7 page 7-133.

The usage of statins in cumulative duration use of 5, 10, 15 or up to 20 years in compared with non-user, showed statistically significant findings in unadjusted, age-adjusted and fully adjusted models.

Final regression models even after include adjustment for hypercholesterolemia status, the value of odds ratios remained statistically significant (results not shown here).

Table 7-7 Odds Ratios and Confidence Interval for Statin Cumulative Duration Use Prostate Cancer Risk

Statin Cumulative Duration (n=2180)	Control		Case		OR [a] (95%CI)	p value[a]	OR [b] (95%CI)	p value[b]	OR [c] (95%CI)	p value[c]
	No (%)	Yes (%)	No (%)	Yes (%)						
Statin use up to 5 Years	530 (75.4%)	173 (24.6%)	1030 (84.8%)	184 (15.2%)	**0.547 (0.434-0.691)**	**<0.001**	**0.617 (0.486-0.784)**	**<0.001**	**0.665 (0.518-0.854)**	**0.001**
Statin use up to 10 Years	530 (69.1%)	237 (30.9%)	1030 (79.8%)	261 (20.2%)	**0.567 (0.462-0.695)**	**<0.001**	**0.654 (0.529-0.808)**	**<0.001**	**0.712 (0.571-0.889)**	**0.003**
Statin use up to 15 Years	530 (67.2%)	259 (32.8%)	1030 (78.1%)	289 (21.9%)	**0.574 (0.471-0.700)**	**<0.001**	**0.675 (0.550-0.828)**	**<0.001**	**0.725 (0.585-0.899)**	**0.003**
Statin use up to 20 Years	530 (66.4%)	268 (33.6%)	1030 (77.7%)	295 (22.3%)	**0.566 (0.466-0.689)**	**<0.001**	**0.666 (0.544-0.815)**	**<0.001**	**0.712 (0.576-0.881)**	**0.002**

[a]Unadjusted regression model
[b]Age-adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, family history of cancer

7.6 Discussion

7.6.1 Statin use

On the list of statins used by the respondents, Simvastatin was the highest at 63.8%, followed by Atorvastatin (22.4%) and then Pravastatin and Rosuvastatin at 3.2% and 2.9% respectively (see Table 7-1 on page 7-127). There was no indication of reasons for the higher reported use of Simvastatin in this study. The possible explanation could be due to its most commonly available in the pharmacy stores or over the counter drug. Pricing could be another reason because different types of statin have different prices which may affect choices. The amount of dosages needed to have similar effect on lowering cholesterol properties and possible side effects could also potentially affect prescribed drug.

The prevalence of statin usage among the control in this study is 35.8% compared to cases at 23.9%. A study on the prevalence usage of statin among European countries by Walley showed the rate for UK at that time 1997-2002, the average increasing rate on annual of statin amount used daily was 48% (Walley *et al*, 2004). Actual data on prevalence usage of statin is not known however they are prescribed mostly for those with cardiovascular risk. A study in USA on outpatient visits between 1992 - 2002 by Ma et al showed statin usage as lipid-lowering drug rose from 47% to 87% between those years (Ma *et al*, 2005). The use among highest risk patients were between 4 – 19% while moderate risk patients were from 2 -14%.

In our study since the majority of subjects were older, we would expect them to be mostly consisted of higher risk group of hyperlipidemia or had cardiovascular risk. The prevalence of hypercholesterolemia among the subjects in this study is 26.3% and 32.4% in case and control group respectively, whereas the prevalence of ischaemic heart disease is 8.1% and 11.0% also respectively. These confirmed the likelihood reasons for them to be prescribed of statin at one time or continuously during the last 10 years of their history on taking statin medication.

The finding of univariate analysis showed a protective effect on prostate cancer approximately of 43.7% (range: 31.9% to 53.4%) among users of statins. Upon adjustment of age, and further on education, ethnic and family history of cancer, the protective risk of statins remained statistically significant with protection

against prostate cancer at 33.5% (range: 19.2% - 45.4%) and 28.6% (range: 12.2% - 42.0%) respectively (refer Table 7-4 page 7-129). No stratification of statin types was done due to small numbers in each category.

The results suggested that the overall statin use affects prostate cancer risk by reducing the risk approximately of 28.6% compared to those who do not take it. The possibility of different statin types on prostate cancer risk will be discussed in later part of this chapter.

7.6.2 Duration of Statin Usage

Subjects who reported statin used were divided into groups according to their duration of 5 years interval in an ascending order. The univariate analysis showed a significant risk reduction across categories (p for trend <0.001). The results of the unadjusted odds ratios were all statistically significant with value of prostate cancer risk reduction of 48.2%, 29.8%, 49.9% and 51.6% for categories of: less than 5 years, 5 years or more but less than 10 years, 10 years or more but less than 15 years and 15 years or more, respectively. Upon age-adjustment and further multivariate model adjustment, only the category of using statin less than 5 years was found to be statistically significant at OR=0.585 (95%CI: 0.449-0.764) and 0.617 (95%CI: 0.467-0.815) (see Table 7-7, on page 7-133).

The study findings are similar to the study by Jacobs and colleagues. They analysed 3413 cases of incident prostate cancer, upon adjustment for potential confounders, current use of cholesterol lowering drugs for 5 years or more was not associated with overall prostate cancer incidence at rate ratio of 1.06 (95%CI: 0.93-1.20), however the retail pharmaceutical estimation for statin used as cholesterol lowering drug was about 86% at that time, therefore not exclusively for usage of statin drugs alone but analysis included other non-statin cholesterol lowering agents as well (Jacobs *et al*, 2007a).

However, the nested case control study by Flick et al of 69,047 participants in a California Men's Health Study (a prospective cohort) in 2002, identified 888 prostate cancer cases including 131 advance cases, found that use of statins for five or more years was associated with 28% lower risk in prostate cancer (Rate ratio: 0.72 (95%CI: 0.53-0.99) (Flick *et al*, 2007). Another study of cohort subjects ascertainment of 2579 prostate cancer cases, of which 316 were

advanced cases also found risk of advanced disease was lower with longer statin use at p for trend 0.003 compared to never use statin (Platz *et al*, 2006).

Even though our results did not show statistically significant of using statin of more than 5 years onwards, the OR value remained in value <1.0 thus suggestive of protective against risk of prostate cancer.

7.6.3 Cumulative Duration Use of Statins

The cumulative duration use was carried out to investigate cumulative effect of the drug on the prostate cancer risk based on time of the use of up to 5, 10, 15 and 20 years period.

The results displayed in Table 7-7 page 7-133 showed that in the multivariate adjusted modelling, the effect of statin cumulative use remained statistically significant for all categories of up to 5, 10, 15 and 20 years statin use at OR of 0.665 (95%CI: 0.518-0.854), 0.712 (95%CI: 0.571-0.889), 0.725 (95%CI: 0.585-0.899) and 0.712 (95%CI: 0.576-0.881) respectively, suggesting protective effects against prostate cancer.

There are not many studies that have employed this cumulative measurement which was based on duration. Other studies that used a cumulative method were based on cumulative risk as in exposure to substance that can have a *"latent"* effect such as exposure to chemical dye causing cancer, or combined risks of different exposures to risk of developing a condition.

7.6.4 Overall Discussion

Since the findings reported in the literature showed some potential effects of statin lowering cancer incidence whilst other studies did not show such correlation, it was suggested by Sivaprasad et al in their investigation of possible discrepancy of results. They suggested that it could be due to different types of statins on their efficacy in inhibiting prostate cancer cell proliferation when mevastatin (a lovastatin homologue) was used as a control (Sivaprasad *et al*, 2006). They reported that Lovastatin, Fluvastatin and Simvastatin arrest all prostate cancer cells in the G1 phase of cell cycle. Pravastatin needs to be at least 200 times higher concentration of Lovastatin in order to achieve similar

effect and at the same time less efficient in inhibiting HMG-CoA reductase, and high dosage could potentially cause toxic effect.

Since Pravastatin is hydrophilic and also has lower lipophilicity compared to Atorvastatin and Fluvastatin of moderate lipophilicity, or Simvastatin and Lovastatin of highest lipophilicity as HMG-CoA reductase inhibitors, therefore its' uptake into cells is not efficient compared to other statins. Thus, this results in a different efficacy in inhibiting prostate cancer cell proliferation (White, 2002).

The results in-vitro experiments suggest that clinically useful statins such as Lovastatin, Fluvastatin and Simvastatin may have beneficial effect on prostate cancer incidence and progression (Sivaprasad *et al*, 2006).

Browning & Martin conducted a systematic review on the association of statin (HMG-CoA reductase inhibitor) use and cancer risk of 38 individual studies of 26 randomized trials and 12 observation studies (Browning & Martin, 2007). Four trials and one observation studies were on prostate and meta-analysis revealed statin therapy indicate no evidence of association at p=0.38, although there was a high degree of inconsistency between studies. The risk ratio for prostate cancer within the meta-analysis of randomized trials for prostate cancer was of 1.00 (95%CI: 0.85-1.17).

Some of the recent case controls studies focusing on the association between statin effect on prostate cancer risk has shown reduction risk. Besides Flick (Flick *et al*, 2007), Jacobs also reported of reductive risk among statin user in a case control study using 55,454 men from Cancer Prevention Study II Nutrition Cohort, which include prostate cancer cases of 3413 of which 317 cases are of advanced disease (Jacobs *et al*, 2007a). The adjusted rate ratio showed marginal statistically significant prostate cancer risk of advanced type at RR=0.600 (95%CI: 0.36-1.00), although overall prostate cancer risk was not statistically significant. Murtola using data from Finnish Cancer Registry of a large cohort study population, with cases and matched control approach, also found statistically significant risk reduction of advanced type of prostate cancer among users of statin with overall OR=0.75 (95%CI: 0.62-0.91) (Murtola *et al*, 2007). The statin types namely atorvastatin, lovastatin and simvastatin had individual adjusted odds ratios of 0.61 (95%CI: 0.37-0.98), 0.61 (95%CI: 0.43-0.85) and 0.78 (95%CI: 0.61-1.01) respectively.

Solomon & Freeman suggested in their article, that in order to properly study statin as chemoprevention or therapy, there is a need to conduct randomized trial for prostate cancer and it's important to exclude patients on cholesterol-reducing therapy and to exclude those who do anything specifically to reduce cholesterol such as diet or exercise in both arms. The study should be longer than 5 years to be able to assess the true effect of statin (Solomon & Freeman, 2008).

7.7 Conclusions and Recommendations

The findings suggested that statins use has a protective effect against prostate cancer.

It is recommended to study further types of statins and their association with prostate cancer risk, as well as stratification prostate cancer cases according to their clinical manifestations. It is also suggested to look at whether the dosage of statin used would have had any association in the prostate cancer risk.

Chapter 8 NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) & Paracetamol

8.1 Literature Review

8.1.1 NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)

NSAIDs (Non-steroidal anti-inflammatory drugs) are a group of drugs which have properties of analgesia (painkiller), anti-pyretic (reduce fever) and anti-inflammatory effects. Some of the common products include aspirin, ibuprofen, Diclofenac and Indomethacin. They are used for symptomatic relief of pain in general, swelling of joints or body organs and tissues, as well as fever. NSAIDs acts by inhibiting cyclooxygenase (Cox) which is an enzyme responsible in the catalyzing production of prostaglandins (potent mediators of inflammation).

aspirin however can also inhibit platelet aggregation by inhibiting thromboxane A2 and its use in reducing blood clot formation in high risk patients has found to reduce or prevent deaths for myocardial infarct and ischaemic stroke, but increases haemorrhagic stroke and major bleeding when used in primary prevention of cardiovascular diseases, as observed in a meta-analysis of randomized controlled trials by (Raju *et al*, 2011).

Current evidences suggests that inflammation may contribute to the carcinogenesis of prostate cancer as shown by both epidemiological and histopathological studies (De Marzo *et al*, 2007). It was also estimated 20% of prostate cancer cases were as a result of chronic inflammation due to infectious agents and or environmental factors.

In view of cyclo-oxygenase-2 (COX-2) being an important enzyme catalyst to prostaglandins formation from arachidonic acid conversion, which in turn mediates the inflammation process, COX-2 is an important potential target for preventive strategies. As such NSAIDs have been studied to see whether they have any association with prostate cancer risk.

However it is important to bear in mind that genetic variation in the inflammatory pathways itself has been found to be associated with prostate cancer as found in study by Zheng in the large Swedish case-control population (CAPS) (Zheng *et al*, 2006).

NSAIDs have been shown over the recent years to be protective of prostate cancer. Most of this studies showed significant amount use of aspirin of few days a week, over a period of long term, would reduce risk to prostate cancer (Dasgupta *et al*, 2006; Garcia Rodriguez, 2004; Jacobs *et al*, 2005; Jacobs *et al*, 2007b; Mahmud *et al*, 2004; Perron *et al*, 2003; Salinas *et al*, 2010).

However, the specific types of NSAIDs other than aspirin when analysed showed no significant association with prostate cancer in many of these studies except for ibuprofen (Jacobs *et al*, 2005). Analysis involving all types of NSAIDs showed some significant association in some studies (Cheng *et al*, 2007; Dasgupta *et al*, 2006; Jacobs *et al*, 2005; Mahmud *et al*, 2010), while others were not significant (Daniels *et al*, 2009; Stock *et al*, 2008).

8.1.2 Paracetamol

Paracetamol or acetaminophen is widely available as an over the counter drug for its function as an anti-pyretic (reduce fever) and analgesic (pain relieve). It acts through inhibition of cyclooxygenase (COX), and recent findings suggest that it is highly selective for COX2 (Hinz *et al*, 2008). Therefore, it could potentially use similar mechanism as NSAIDs in inhibiting the pathway of inflammatory process, on cancer cell growth (Fris *et al.* 2002)

Paracetamol association with regard to cancer risk has been inconsistent. An earlier study in year 2002 by Friis et al showed that those who received paracetamol prescription over 9 years follow-up in Denmark, had higher standardized incidence ratio (SIR) of overall cancers compared with those who didn't receive same prescription. Significantly higher SIR were found for esophageal and lung cancer. It was not significant for prostate cancer.

A meta-analysis by Bonovas showed an inverse association between paracetamol use and ovarian cancer risk but of marginal statistical significance. It was found also that regular use was statistically significantly 30% reduced in ovarian cancer risk compared to non-users (Bonovas *et al*, 2006).

Another recent study by Walter has shown that high use of paracetamol of more than 4 days per week for 4 years or more was associated with an increased risk for haematologic malignancies with hazard ratio, HR=1.84 (95%CI: 1.35-2.50) and p-trend of 0.004. The statistically significant association was observed for myeloid neoplasms, non-Hodgkin's lymphomas and plasma cell disorders (Walter *et al*, 2011).

8.2 Aims

This study aimed to investigate prostate cancer risk in association with duration of intake of common painkiller of specific types of NSAIDS, as well as acetaminophen:

i. Aspirin
ii. Ibuprofen
iii. Paracetamol

8.3 Method

Data was collected through self administered questionnaire which detailed the individual type of drugs above and entered through a Microsoft access database, before being extracted into excel document.

8.4 Analysis

Subjects were asked to report any uses of Aspirin, Ibuprofen and Paracetamol. Each medication had to be taken regularly within the last 10 years prior to prostate cancer diagnosis for case subjects, or anytime within last 10 years for control at least 1 tablet per week for 3 months or more. Those who completed any of the above drugs used were then asked to provide information on duration using them.

Data of each type of medication was re-coded and analysed to assess the followings.

a) Distribution of each medication used in study subjects
b) Association between drug used as define by Duration Block and prostate cancer risk
c) Association between cumulative years use of up to 5, 10, 15 and 20 years and prostate cancer risk.

For Aspirin and Ibruprofen, 'Duration Block' was classified by 10 years interval block as following:

'0' – None

'1' – use less than 10 years

'2' – use for 10 years or more but less than 20 years

'3' – use for 20 years or more

For paracetamol, 'Duration Block' was classified by 5 years interval block as following:

'0' – None

'1' – use paracetamol less than 10 years

'2' – use paracetamol for 10 years or more but less than 20 years

'3' – use paracetamol for 20 years or more but less than 30 years

'4' – use paracetamol for 30 years or more

Based on this data classification above, p for trend analysis was done for each drug/medication.

The possibility of cumulative use of aspirin, ibuprofen and paracetamol determining prostate cancer risk as a whole is studied by classifying the users into category of cumulative years use of up to 5, 10, 15 and 20 years.

Statistical software SPSS version 17.0 was used to analyse the data for descriptive cross-tabulation and analytical Chi-square, logistic regression and subsequent adjusted logistic regression modelling to obtain odds ratios and confidence intervals

8.5 Results

8.5.1 Aspirin

Distribution of aspirin used among study subjects is shown in Table 8-1.

Table 8-1 Cross-tabulation of Aspirin use among case-control group

	Group		
	Control	Case	Total
Aspirin use	(%)	(%)	(%)
No	660	1139	1799
	79.6%	83.9%	82.3%
Yes	169	218	387
	20.4%	16.1%	17.7%
Total	829	1357	2186
	100.0%	100.0%	100.0%

The results showed that the proportion of users of aspirin (prior to diagnosis in case group or receiving questionnaire in control group) is higher among controls compared to cases (20.4% as compared to 16.1%). Chi-square test **p value = 0.010**, and showed statistically significant difference in proportion of aspirin users in the case and control group.

Table 8.2 shows odds ratios and confidence interval for Aspirin user and prostate cancer risk. There is statistically significant reduced prostate cancer risk in those using aspirin in univariate analysis at **OR=0.747 (95%CI: 0.598-0.934)**, however upon adjustment for age, and further adjustment for education, ethnic and family history of cancer, the association was not significant.

Table 8-2 Odds ratios and confidence interval for Aspirin user and prostate cancer risk

	Control		Case		OR[a] (95%CI)	p value[a]	OR[b] (95%CI)	p value[b]	OR[c] (95%CI)	p value[c]
Aspirin Used	**Yes (%)**	**No (%)**	**Yes (%)**	**No (%)**						
	169 (20.4%)	660 (79.6%)	218 (16.1%)	1139 (83.9%)	**0.747 (0.598-0.934)**	**0.010**	0.797 (0.634-1.002)	0.052	0.814 (0.639-1.037)	0.096

[a]Unadjusted Regression Models
[b]Adjusted Regression Models for age
[c]Multivariate Adjusted Regression Models for age, education, ethnic and family history of cancer

8.5.1.1 Duration Block Aspirin Usage

Table 8-3 Cross tabulation of duration Aspirin usage of cases and controls

Aspirin Duration Block	Group		Total
	Control	Case	
	(%)	(%)	(%)
None	660	1138	1798
	84.4%	88.7%	87.1%
Less than 10 Years	69	76	145
	8.8%	5.9%	7.0%
10 Years or more but less than 20 Years	33	41	74
	4.2%	3.2%	3.6%
20 Years or more	20	28	48
	2.6%	2.2%	2.3%
Total	782	1283	2065
	100.0%	100.0%	100.0%

Table 8-3 shows that overall the control subjects had a higher proportion of duration of aspirin usage in any block duration compared to cases, especially duration of aspirin usage less than 10 years. Chi-square indicates statistically significant differences in proportion between cases and control at p=0.036.

Table 8-4 showed that in a univariate model, aspirin duration showed statistically a significant association with prostate cancer risk. In unadjusted and age-adjusted regression models only category that showed statistically significant association with prostate cancer risk is those who used aspirin for less than 10 years when compared with non-user at OR=0.639 (95%CI: 0.455-0.897) and 0.657 (95%CI: 0.463-0.931). There was no statistically significant OR in the fully adjusted model.

Table 8-4 Odds ratios and confidence interval for Aspirin duration usage and prostate cancer risk

Aspirin Duration Usage (n=2065)	Control (%)	Cases (%)	OR[a] (95%CI)	P value[a]	OR[b] (95%CI)	P value[b]	OR[c] (95%CI)	Pvalue[c]
None	660 (84.4%)	1138 (88.7%)	-Ref-	**0.037**	-Ref-	0.108	-Ref-	0.301
Less than 10 Years	69 (8.8%)	76 5.9%)	**0.639 (0.455-0.897)**	**0.01**	**0.657 (0.463-0.931)**	**0.018**	0.716 (0.496-1.035)	0.076
10 Years or more but less than 20 Years	33 (4.2%)	41 3.2%)	0.721 (0.451-1.151)	0.17	0.897 (0.553-1.455)	0.66	0.817 (0.488-1.370)	0.444
20 Years or more	20 (2.6%)	28 2.2%)	0.812 (0.454-1.453)	0.483	0.794 (0.435-1.450)	0.453	0.897 (0.477-1.686)	0.735

[a]Unadjusted regression model
[b]Age-adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, family history of cancer
P for trend, p=0.030

8.5.1.2 Aspirin Cumulative Duration Use

Table 8-5 page 8-148 shows Odds ratios and confidence interval for Aspirin cumulative duration use and prostate cancer risk. Aspirin non-users was used as a reference category, the results showed that univariate analysis was statistical significantly associated with all categories of cumulative usages of aspirin with reduction in prostate cancer risk. When the regression model was adjusted for age, only aspirin usage of 5 years, 10 years, 15 years and 40 years or more categories remained statistical significant. In the fully adjusted model, all associations were non-significant statistically.

Table 8-5 Odds ratios and confidence interval for Aspirin cumulative duration use and prostate cancer risk

Aspirin Cumulative Duration	Control		Case		OR[a] (95%CI)	p value[a]	OR[b] (95%CI)	p value[b]	OR[c] (95%CI)	p value[c]
	No (%)	Yes (%)	No (%)	Yes (%)						
Aspirin use up to 5 Years	660 (92.2%)	56 (7.8%)	1138 (95.0%)	60 (5.0%)	**0.621 (0.426-0.906)**	**0.013**	**0.631 (0.428-0.929)**	**0.020**	0.702 (0.468-1.053)	0.087
Aspirin use up to 10 Years	660 (88.1%)	89 (11.9%)	1138 (91.6%)	105 (8.4%)	**0.684 (0.508-0.922)**	**0.013**	**0.736 (0.542-1.000)**	**0.050**	0.755 (0.545-1.045)	0.090
Aspirin use up to 15 Years	660 (87.1%)	98 (12.9%)	1138 90.7%)	116 (9.3%)	**0.686 (0.516-0.913)**	**0.010**	**0.743 (0.554-0.997)**	**0.048**	0.764 (0.559-1.042)	0.089
Aspirin use up to 20 Years	660 (86.2%)	106 (13.8%)	1138 (89.8%)	129 (10.2%)	**0.706 (0.537-0.929)**	**0.013**	0.777 (0.586-1.031)	0.081	0.803 (0.595-1.083)	0.150
Aspirin use up to 40 Years	660 (85.1%)	116 (14.9%)	1138 (88.9%)	142 (11.1%)	**0.710 (0.546-0.924)**	**0.011**	**0.759 (0.579-0.996)**	**0.047**	0.781 (0.587-1.041)	0.091

[a]Unadjusted regression model
[b]Age-adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, family history of cancer

8.5.2 Ibuprofen

8.5.2.1 Ibuprofen use

Table 8-6 Cross-tabulation of Ibuprofen use among case-control group

Ibuprofen use	Group		Total
	Control	Case	
	(%)	(%)	(%)
No	707	1175	1882
	85.5%	86.4%	86.1%
Yes	120	185	305
	14.5%	13.6%	13.9%
Total	827	1360	2187
	100.0%	100.0%	100.0%

The cross-tabulation in Table 8-6 showed that there is a similarity in the proportion of ibuprofen users between cases and control groups. Chi-square test p value =0.553, showed a non-statistically significant difference of case-control group of ibuprofen users proportion.

Table 8-7 showed that there was no statistically significant association between ibuprofen ever use compared to non-user in prostate cancer risk, neither in unadjusted nor adjusted models.

Table 8-7 Odds ratios and confidence interval for Ibuprofen user and prostate cancer risk

(n=2180)	Control		Case		OR [a] (95%CI)	p value[a]	OR [b] (95%CI)	p value[b]	OR [c] (95%CI)	p value[c]
Ibuprofen Used	Yes (%)	No (%)	Yes (%)	No (%)						
	120 (14.5%)	707 (85.5%)	185 (13.6%)	1175 (86.4%)	0.928 (0.724-1.189)	p=0.553	0.810 (0.627-1.046)	0.106	0.771 (0.591-1.007)	0.057

[a]Unadjusted Regression Models
[b]Adjusted Regression Models for age
[c]Multivariate Adjusted Regression Models for age, education, ethnic and family history of cancer

8.5.2.2 Duration of Ibuprofen Usage

Table 8-8 Crosstabulation of Ibuprofen duration usage of cases and controls

Ibuprofen Duration	Group		Total
	Control	Case	
	(%)	(%)	(%)
None	707	1175	1882
	90.9%	91.2%	91.1%
Less than 10 Years	36	42	78
	4.6%	3.3%	3.8%
10 Years or more but less than 20 Years	15	43	58
	1.9%	3.3%	2.8%
20 Years or more	20	28	48
	2.6%	2.2%	2.3%
Total	778	1288	2066
	100.0%	100.0%	100.0%

The cross-tabulation table above showed that about 9% of study subjects reported Ibruprofen used. Chi-square indicate non-statistically significant differences in proportion between cases and control at p=0.104.

In studying the association between different durations of usage of ibuprofen and prostate cancer regression models, there was no statistically significant findings on odds ratios although the multivariate adjusted models showed borderline significant finding for ibuprofen use of less than 10 years has odds ratio of 0.616 (95%CI: (0.377-1.004) at p=0.052 when compared to none ibuprofen user (Table 8-9).

Table 8-9 Odds ratios and confidence interval for Ibuprofen duration usage and prostate cancer risk

Ibuprofen Duration Usage (n=2066)	Control (%)	Cases (%)	OR[a] (95%CI)	P value[a]	OR[b] (95%CI)	P value[b]	OR[c] (95%CI)	P value[c]
None	707 (90.90%)	1175 (91.20%)	-Ref-	0.109	-Ref-	0.178	-Ref-	0.118
Less than 10 Years	36 (4.60%)	42 (3.30%)	0.702 (0.445-1.106)	0.127	0.66 (0.413-1.054)	0.082	0.616 (0.377-1.004)	0.052
10 Years or more but less than 20 Years	15 (1.90%)	43 (3.30%)	1.725 (0.951-3.128)	0.073	1.346 (0.735-2.464)	0.336	1.224 (0.661-2.268)	0.521
20 Years or more	20 (2.60%)	28 (2.20%)	0.842 (0.471-1.507)	0.563	0.748 (0.411-1.364)	0.344	0.659 (0.352-1.233)	0.192

[a]Unadjusted regression model
[b]Age-adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, family history of cancer
P for trend, p=0.920

8.5.2.3 Ibuprofen Cumulative Use

Table 8-10 presents Odds ratios and confidence interval for Ibuprofen cumulative duration use and prostate cancer risk. The cumulative duration of ibuprofen when compared with non-user also did not show any statistically significant association with prostate cancer risk, though all ORs fall in value of less than 1.0 which is of protective effect, all CIs included 1.

Table 8-10 Odds ratios and confidence interval for Ibuprofen cumulative duration use and prostate cancer risk

Ibuprofen Cumulative Duration	Control		Case		OR [a] (95%CI)	p value[a]	OR [b] (95%CI)	p value[b]	OR [c] (95%CI)	p value[c]
	No (%)	Yes (%)	No (%)	Yes (%)						
Ibuprofen use up to 5 Years	707 (95.7%)	32 (4.3%)	1175 (96.9%)	38 (3.1%)	0.715 (0.442-1.154)	0.169	0.687 (0.420-1.124)	0.135	0.651 (0.390-1.087)	0.101
Ibuprofen use up to 10 Years	707 (94.0%)	45 (6.0%)	1175 (94.2%)	73 (5.8%)	0.976 (0.666-1.432)	0.901	0.865 (0.583-1.284)	0.472	0.801 (0.531-1.207)	0.288
Ibuprofen use up to 15 Years	707 (93.3%)	51 (6.7%)	1175 (93.4%)	83 (6.6%)	0.979 (0.683-1.405)	0.909	0.850 (0.586-1.233)	0.391	0.787 (0.535-1.157)	0.223
Ibuprofen use up to 20 Years	707 (92.3%)	59 (7.7%)	1175 (92.4%)	96 (7.6%)	0.979 (0.699-1.372)	0.902	0.862 (0.609-1.220)	0.403	0.800 (0.558-1.147)	0.224
Ibuprofen use up to 40 Years	707 (91.2%)	68 (8.8%)	1175 (91.4%)	111 (8.6%)	0.982 (0.716-1.347)	0.911	0.858 (0.620-1.189)	0.358	0.787 (0.561-1.104)	0.165

[a]Unadjusted regression model
[b]Age-adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, family history of cancer

8.5.3 Paracetamol

Paracetamol use

Table 8-11 Cross-tabulation of Paracetamol use among case-control group

Paracetamol use	Group		Total
	Control (%)	Case (%)	(%)
No	653	1094	1747
	78.4%	80.5%	79.7%
Yes	180	265	445
	21.6%	19.5%	20.3%
Total	833	1359	2192
	100.0%	100.0%	100.0%

Table 8-11 showed that there is slight difference in the proportion of paracetamol users between case and control groups. Chi-square test p value =0.233, showed non-statistically significant difference.

Table 8-12 presents the estimated risks of paracetamol use and prostate cancer risk and shows that there was no statistically significant association between paracetamol ever use compared to non-user in prostate cancer risk, neither in unadjusted nor adjusted models, although all OR values are suggestive of protective risk at OR<1.0, all CIs included 1.

Table 8-12 Odds ratios and confidence interval for paracetamol user and prostate cancer risk

(n=2180)	Control		Case		OR[a] (95%CI)	p value[a]	OR[b] (95%CI)	p value[b]	OR[c] (95%CI)	p value[c]
Paracetamol Used	Yes (%)	No (%)	Yes (%)	No (%)						
	180 (21.6%)	653 (78.4%)	265 (19.5%)	1094 (80.5%)	0.979 (0.710-1.087)	0.234	0.828 (0.665-1.031)	0.091	0.800 (0.634-1.009)	0.059

[a]Unadjusted Regression Models
[b]Adjusted Regression Models for age
[c]Multivariate Adjusted Regression Models for age, education, ethnic and family history of cancer

8.5.3.1 Duration of Paracetamol Usage

Table 8-13 Crosstabulation of paracetamol duration usage of cases and controls

Paracetamol Duration Use	Group		Total
	Control	Case	
	(%)	(%)	(%)
None	654	1094	1748
	85.7%	87.7%	86.9%
Less than 10 Years	45	61	106
	5.9%	4.9%	5.3%
10 Years or more but less than 20 Years	19	30	49
	2.5%	2.4%	2.4%
20 Years or more but less than 30 Years	23	23	46
	3.0%	1.8%	2.3%
30 Years or more	22	40	62
	2.9%	3.2%	3.1%
Total	763	1248	2011
	100.0%	100.0%	100.0%

The cross-tabulation table showed that overall there is similar proportion of paracetamol users between different categories of duration. Chi-square indicates non-statistically significant differences in proportion between cases and control at p=0.388.

Table 8-14 Odds ratios and confidence interval for paracetamol duration usage and prostate cancer risk. There were no statistically significant findings on odds ratios in unadjusted regression models. However, the age-adjusted and multivariate adjusted models showed that paracetamol use of '20 years or more but less than 30 years' duration had statistically significant lower odds ratio compared to non-user at OR=0.501 (95%CI: 0.272-0.921) and 0.534 (95%CI: 0.287-0.993) respectively.

Table 8-14 Odds ratios and confidence interval for paracetamol duration usage and prostate cancer risk

Paracetamol Duration Usage (n=2011)	**Control (%)**	**Cases (%)**	**OR[a] (95%CI)**	**p value[a]**	**OR[b] (95%CI)**	**p value[b]**	**OR[c] (95%CI)**	**p value[c]**
None	654 (85.7%)	1094 (87.7%)	-Ref-	0.396	-Ref-	0.166	-Ref-	0.163
Less than 10 Years	45 (5.9%)	61 (4.9%)	0.810 (0.545-1.205)	0.299	0.766 (0.509-1.154)	0.202	0.700 (0.455-1.077)	0.105
10 Years or more but less than 20 Years	19 (2.5%)	30 (2.4%)	0.944 (0.527-1.691)	0.846	0.918 (0.505-1.670)	0.780	0.836 (0.442-1.580)	0.581
20 Years or more but less than 30 Years	23 (3.0%)	23 (1.8%)	0.598 (0.333-1.074)	0.085	**0.501 (0.272-0.921)**	**0.026**	**0.534 (0.287-0.993)**	**0.048**
30 Years or more	22 (2.9%)	40 (3.2%)	1.087 (0.640-1.845)	0.758	1.053 (0.612-1.815)	0.851	1.018 (0.577-1.798)	0.951

[a]Unadjusted regression model
[b]Age-adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, family history of cancer
P for trend, p=0.396

8.5.3.2 Paracetamol Cumulative Use

In the univariate and age-adjustment model, the results did not reveal a statistically significant association. However, upon multivariate adjustment, the association became significant (Table 8-15). The odds ratios and confidence intervals were all less than 1.0 in the categories for paracetamol use cumulative duration of up to 20, 30, 40 and 50 years at OR=0.713 (95%CI: 0.513-0.990), 0.703 (95%CI: 0.518-0.954), 0.720 (95%CI: 0.538-0.965) and 0.745 (95%CI: 0.560-0.991) respectively, all of protective risks.

Table 8-15 Odds ratios and confidence interval for Paracetamol cumulative use prostate cancer risk

Paracetamol Cumulative Duration	Control		Case		OR [a] (95%CI)	p value[a]	OR [b] (95%CI)	p value[b]	OR [c] (95%CI)	p value[c]
	No (%)	Yes (%)	No (%)	Yes (%)						
Paracetamol use up to 10 Years	654 (92.0%)	57 (8.0%)	1094 (92.9%)	84 (7.1%)	0.881 (0.621-1.250)	0.478	0.843 (0.587-1.210)	0.354	0.767 (0.523-1.125)	0.174
Paracetamol use up to 20 Years	654 (89.0%)	81 (11.0%)	1094 (90.9%)	110 (9.1%)	0.812 (0.600-1.099)	0.177	0.759 (0.556-1.038)	0.084	**0.713 (0.513-0.990)**	**0.044**
Paracetamol use up to 30 Years	654 (87.3%)	95 (12.7%)	1094 (89.4%)	130 (10.6%)	0.818 (0.617-1.084)	0.162	0.756 (0.565-1.010)	0.059	**0.703 (0.518-0.954)**	**0.024**
Paracetamol use up to 40 Years	654 (86.3%)	104 (13.7%)	1094 (88.3%)	145 (11.7%)	0.833 (0.636-1.092)	0.186	0.772 (0.585-1.020)	0.069	**0.720 (0.538-0.965)**	**0.028**
Paracetamol use up to 50 Years	654 (85.7%)	109 (14.3%)	1094 (87.7%)	153 (12.3%)	0.839 (0.644-1.093)	0.193	0.787 (0.599-1.033)	0.085	**0.745 (0.560-0.991)**	**0.043**

[a]Unadjusted regression model
[b]Age-adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, family history of cancer.

8.6 Discussion

8.6.1 Aspirin

Aspirin use

Cross-tabulation of aspirin use (see Table 8-1 , page 8-142 and Table 8-2 O, page 8-144) showed that there was higher proportion in the control subjects compared to cases, which was statistically significant and univariate analysis odds ratio of 0.747 (95% CI: 0.598-0.934) indicates that those who reported ever use aspirin at least one tablet per week for more than three months in the last 10 years had a reduced their risk against prostate cancer at approximately 25.3% (range 6.6% -40.2%). After adjusted for age and multivariate confounders into the regression models of aspirin use, the odds ratios were not statistically significant at p=0.052, OR=0.797 (95%CI: 0.634-1.002) and p=0.096, OR=0.814 (95%CI: 0.639-1.037).

The results of this study are similar to some studies looking at relationship of NSAIDs in specific aspirin use and prostate cancer. Platz *et al.* reported results on 1244 males of Baltimore Longitudial Study of Aging. They found that the rate ratio of 0.76 (95%CI: 0.54-1.07) to prostate cancer risk in comparison with never use of aspirin (Platz *et al*, 2005). Menezes] in their case-control study of 1029 men with primary incident of prostate and matched 1029 control of Roswell Park Cancer Institute in Buffalo, New York. Subjects who reported used aspirin regularly (at least once a week for 6 months) was compared to non-regular user. Their findings supported no association with prostate cancer risk (OR 1.05 with 95%CI: 0.89-1.25) (Menezes *et al*, 2006)).

Rodriguez & Gonzalez-Perez conducted a nested case-control study on 2,183 cases and 10,000 controls. Data obtained from General Practice Research Database (GPRD) in the UK. The results showed that ever use of aspirin was associated with prostate cancer risk reduction at OR=0.70 (95%CI: 0.61-0.79) (Garcia Rodriguez, 2004). Another study by Liu on case-control matched of 532 subjects in Ohio, USA found aspirin to be associated with reduction risk of advanced prostate cancer at OR=0.66 (95%CI: 0.51-0.86) (Liu *et al*, 2006). While a study of 4175 subjects in Quebec Canada, using subjects of older age >67 who underwent prostate biopsy to separate cases and control, found protective risk among aspirin users at OR=0.84 (95%CI: 0.74-0.96) (Dasgupta *et al*, 2006).

The definition of aspirin use differs from one study to the others. For example, some studies would use at least continues 120 days use (Dasgupta *et al*, 2006), while others are based on regularity use per week or month (Liu *et al*, 2006; Menezes *et al*, 2006), or some on ever use (Garcia Rodriguez, 2004; Jacobs *et al*, 2005; Murad *et al*, 2011; Salinas *et al*, 2010) which could result in some discrepancy in the reported odds ratios.

8.6.1.1 Duration of Aspirin Usage

The results presented in Table 8-4 (page 8-146) showed a statistical significant difference in the number of years aspirin used between cases and control, with higher % in each duration category among control group. Unadjusted regression model and age-adjusted model to look at number of years usage of aspirin to prostate cancer risk compared to non-user showed statistically significant OR of risk reduction for aspirin users category of less than 10 years. In the fully adjusted model, the results did not support any significant associations.

One case-control study of age-matched hospital-based of 1029 and equally 5 year age group frequency matched control of similar numbers by Menezes , showed similar non-statistical significant adjusted OR for duration of use between 1 to 10 years of aspirin use at 0.97 (95%CI: 0.79-1.19). Duration of more than 10 years also didn't show any statistical significant adjusted OR at 1.17 (95%CI: 0.93-1.46) (Menezes *et al*, 2006).

Other case-control study stratified the number of years use of aspirin showed a statistically significant reduced odds ratio for aspirin usage of less than 4 years but not significant after if 4 years or more (Garcia Rodriguez, 2004). In contrast, a case control study by Salinas of 1001 registry case and 942 age-matched population based control showed statistically significant reduced odds ratio when aspirin was used more than 5 years when compared with non-user at adjusted OR 0.76 (95%CI: 0.61-0.96) but not when used only less than 5 years (Salinas *et al*, 2010).

Cohort studies also supported a statistically significant reduction in odds ratio for prostate cancer when aspirin is used for 5 years or more but not when period of less than that (Jacobs *et al*, 2005; Perron *et al*, 2003).

There are not many large case-control studies that look at longer duration of aspirin usage, most would analyse their data at less than 10 years when stratifying to block duration of aspirin or NSAIDs usage. Our study did look at duration beyond 10 years on the effect of aspirin use on prostate cancer and found non-statistically significant association over long term use.

The p for trend for duration block for aspirin usage was statistically significant at p=0.030 at univariate analysis, however upon adjustment for multivariate analysis became non significant (results not shown here). Study by Rodriguez & Gonzalez-Perez has reported a similar result with p-for trend at 0.220 in their fully adjusted model (Garcia Rodriguez, 2004). However Liu showed that aspirin p-trend was statistically significant at p=0.001 and ORs <1.0 in all categories (Liu *et al*, 2006). Similarly, Perron also reported p for trend at 0.0009 (Perron *et al*, 2003).

In this study an interval of 10 years was used while previous studies used shorter duration, and at the same time the definition of aspirin use is different. Our findings, however, supported that there is no trend of risk reduction over the duration of years aspirin usage and prostate cancer risk.

8.6.1.2 Aspirin Cumulative Duration of Use

The cumulative duration of using aspirin on the prostate cancer risk based on time of the use of up to 5, 10, 15 and 20 years period (as shown in Table 8-5 page 8-148).

The unadjusted odds ratios of aspirin cumulative use of up to 5, 10, 15, 20 and 40 years were all statistically significant at OR = 0.621 (95%CI: 0.426-0.906), 0.684 (95%CI: 0.508-0.922), 0.686 (95%CI: 0.516-0.913), 0.706 (95%CI: 0.537-0.929) and 0.710 (95%CI: 0.546-0.924) respectively, which were all of protective risk against prostate cancer. In age-adjusted model, only aspirin cumulative use of up to 20 years became not statistically significant, while the rest categories remained significant with odds ratio less than 1.0.

The results of fully adjusted model showed that ORs of aspirin cumulative use all categories were less than 1 however all their CIs included 1.

Not many studies reported cumulative effect use of aspirin, however the benefit of using this method is to potentially look at the strength of association between

aspirin longer use to the prostate cancer risk. Our findings suggested no association between cumulative effect of aspirin use and prostate cancer risk.

A study by Platz, the Baltimore Longitudinal Study of Aging subjects reported a non statistically significant rate ratios of aspirin use of 4 years or more at RR=1.27 (95%CI: 0.38-4.18), on prostate cancer risk (Platz *et al*, 2005). Menenez demonstrated non-statistically significant finding for both duration use of less than 10 years or more than 10 years in comparison of non-users of aspirin on prostate cancer risk at adjusted OR =0.92 (95%CI: 0.65-1.29) and 1.14 (95%CI: 0.79-1.65) respectively (Menezes *et al*, 2006).

On the other hand, a case control study by Perron using data from Quebec health insurance database of 2,221 cases and 11,105 control subjects, showed that aspirin use was associated with protection against prostate cancer after usage for 5 years or more with OR=0.70 (95%CI: 0.520-0.950) Jacobs et al. (2005). in their American Cancer Society's Cancer Prevention Study II Nutrition Cohort of 70,144 men, found the association only statistically significant after 5 years use at rate ratio (RR) at 0.85 (95% CI: 0.73-0.99) (Perron *et al*, 2003).

Similarly, Liu found 6 years or more of aspirin usage reduced risk of prostate cancer by almost 50% (OR= 0.54, with 95%CI: 0.37-0.78) (Liu *et al*, 2006). The protective effect was also reported by Dasgupta. They collected data from Canadian Quebec population and found a 20% risk reduction with aspirin used more than 120 days (OR=0.84, with 95%CI: 0.74-0.96) (Dasgupta *et al*, 2006) .

Another study by Jacob reported using aspirin dosage of adult-strength of 325mg minimum per day of 5 years or more had statistically rate ratio, RR at 0.81 (95%CI: 0.70-0.94) (Jacobs *et al*, 2007b). Similar finding was reported by Salinas in their Washington population. They reported only those using aspirin more than 5 years had statistically significant protective risk of prostate cancer at adjusted OR=0.76 (95%CI: 0.61-0.96) (Salinas *et al*, 2010).

Most studies have indicated that long term use of aspirin was statistically significantly associated with reduction in prostate cancer risk. However these studies defined long term as 4 -6 years onwards as long term.

8.6.1.3 Conclusions and Recommendations

Our study using the fully adjusted multivariate regression model did not show a statistically significant association between usage of aspirin and prostate cancer risk although the OR values are less than 1.0. There was also no indication that longer use of aspirin would have any beneficial effect on reduction on prostate cancer risk, p-trend value was at 0.196

Some of the limitations in this study is the lack of data on aspirin actual dosage and regularity, as well as small number of subjects of exposure compared to non-exposed. Furthermore, the information of whether the current usage of aspirin should be taken into account in analysis as there are studies that have shown the need to differentiate the regularity of previous or recent duration. Even if data of regularity and doses are obtained, it would probably be data based on most recent dosage and regularity, which is recallable, compared to say five or ten years back. Further study should be made in looking at whether minimal dosage daily or regularity of aspirin usage as definition to ever use of aspirin, more specific history on aspirin consumption and reasoning of taking it, as well as usage of aspirin prescription from the medical record as a better choice indication of ever use aspirin and dosage wherever possible.

8.6.2 Ibuprofen

Ibuprofen use

The distribution of ibuprofen use (refer Table 8-6 on page 8-149) showed that there was no differences in the proportions between cases and control subjects with chi square p value of 0.55 and univariate analysis odds ratio of 0.93 (95% CI: 0.72-1.19) indicates that by taking ibuprofen at least one tablet per week for more than three months in the last 10 years did not associate with prostate cancer risk Table 8-7 page 8-150. In the age adjusted model, the odds ratio remained not statistically significant at p=0.106, OR=0.810 (95%CI: 0.627-1.046). However with full adjustment of multivariate confounders, the odds ratio became borderline statistical significant at p=0.057 (OR = 0.771, 95%CI: 0.591-1.01) suggesting a protective effect of prostate cancer among ibuprofen user.

There are not many studies that identify ibuprofen specifically in the NSAIDs group of drugs when trying to associate it with prostate cancer risk. In a case-control study by Liu in Cleveland Ohio of 1012 subjects, showed ibuprofen use was not associated with advanced prostate cancer risk at p value 0.22 and adjusted OR=0.79 (95%CI: 0.54-1.16) (Liu *et al*, 2006). Another study by Salinas which was population based case control using 1001 cases and 942 age-matched control subjects from King County in Washington, also reported no association between non-aspirin NSAIDs (approximately half of subjects used ibuprofen) and prostate cancer risk (OR 1.05, 95%CI: 0.84-1.32). The estimated risks for former user and current user in comparison with non-aspirin NSAIDs user also were also not statistically significant (Salinas *et al*, 2010).

Other studies of non-aspirin NSAIDs which did not specify the types used showed non-statistical significant association with prostate cancer risk include Rodriguez & Gonzalez-Perez (data based on current use, OR=1.14 (95%CI: 1.00-1.29) (Garcia Rodriguez, 2004), and also Daniels but no specific p value given (Daniels *et al*, 2009).

However some studies indicated a risk reduction against prostate cancer with usage of non-aspirin NSAIDs. Dasgupta using Quebec Canada population of nested case control study, found statistically significant OR of 0.71 (95%CI: 0.58-0.86) suggesting risk reduction of prostate cancer among non-aspirin NSAIDs users (Dasgupta *et al*, 2006).

In contrast, an earlier study by Langman on the UK population using general practice database of Department of Health of 1813 cases and 5354 control subjects found increased risk to prostate cancer among NSAIDs (mixed with aspirin) users (Langman *et al*, 2000).

The limitation in this study is the number of ibuprofen users in study subjects was small. There was also possible that ibuprofen users are also users of other types of non-aspirin NSAIDs thus suggesting difficulties in studying just a specific type of NSAIDs. The different findings across studies could also possibly due to different definition for user between studies.

8.6.2.1 Duration of Ibuprofen usage

Results from Table 8-8 on page 8-151, showed univariate and adjusted model analysis in this study did not show any statistical significant trend association between duration usages of ibuprofen to prostate cancer risk. Data from literature suggested not many studies investigated ibuprofen in association with prostate cancer risk. One case-control study comprised of 1012 men with 506 cases and 506 age & ethnic matched controls in Ohio, USA showed non-statistical significant when ibuprofen was used for less than 4 pill-years period, however ibuprofen used beyond 4 years was statistically significant with protective effect against prostate cancer (OR=0.44 with 95%CI: 0.22-0.87). Most studies would describe ibuprofen as a group of non-aspirin NSAIDS, and these studies have shown the mixed effect of non-aspirin NSAIDS on prostate cancer. Long term exposure on non-aspirin NSAIDs in study by Dasgupta showed protective effect against prostate cancer at OR=0.71 (95%CI: 0.58-0.86) (Dasgupta *et al*, 2006), while Rodriguez & Gonzalez-Perez found significant association at any duration of usage (Garcia Rodriguez, 2004).

P for trend in our study on usage duration of ibuprofen was not significant at p=0.920. Similar results were also reported in other studies. Perron reported non-aspirin NSAIDs p-trend with duration of exposure at p=0.152 (Perron *et al*, 2003), while Rodriguez & Gonzalez-Perez showed p-trend value of 0.12 (Garcia Rodriguez, 2004). Another study on ibuprofen also showed p for trend at 0.08 (Liu *et al*, 2006).

8.6.2.2 Ibuprofen Cumulative Duration of Use

The cumulative duration of use results (time of the use of up to 5, 10, 15, 20 and 40 years period) showed no statistically significant association between each category of cumulative usage of ibuprofen to prostate cancer risk, although all ORs values were less than 1.0 (Table 8-10, page 8-154).

The findings suggested that cumulative use of ibuprofen doesn't provide any protection against prostate cancer.

A study by Perron on non-aspirin NSAIDs usage of 1 year or more and subsequent interval increase of 1 year in each category also found all association with prostate cancer as not statistically significant (Perron *et al*, 2003). Similar non-statistically significant findings in association prostate cancer risk were also reported in studies by Rodriguez & Gonzalez-Perez and Salinas when trying to look at different categories of numbers of years exposure to ibuprofen or non-aspirin NSAIDs (Garcia Rodriguez, 2004; Salinas *et al*, 2010).

In contrast, Dasgupta found that non-aspirin NSAIDs categories use of 60 days or higher was statistically significantly associated with reduced risk of prostate cancer at OR=0.77 (95%CI: 0.60-0.98) (Dasgupta *et al*, 2006). Liu also found protective effect against advanced prostate cancer for those who use ibuprofen 4 years or more at p=0.02 and OR=0.44 (95%CI: 0.22-0.87) (Liu *et al*, 2006).

One of the limitations in our study includes the lack of information on details of ibuprofen use to enable stratification of data as current users or former users. Our definition for 'ibuprofen user' may not be comparable with other studies.

The fact that there are a number of various types of non-aspirin NSAIDs, it is impossible to isolate the effect of ibuprofen with prostate cancer as the data collected could be mixed with other NSAIDs and not just ibuprofen alone.

8.6.2.3 Conclusions and Recommendations

There is no association between ibuprofen use and prostate cancer risk in this study. Suggestion would be to collect the types of NSAIDs in more detail manner with specific classifying recent or former user, as well as dosage and regularity of

consuming them. These further information would allow the analysis of true effect of the drug on prostate cancer risk.

8.6.3 Paracetamol

Paracetamol use

The results from cross-tabulation table (see Table 8-11 page 8-155) showed a slightly higher proportion of paracetamol users among controls as compared to cases (Chi-square test p value 0.233). The regression model adjusted for age and potential multivariate confounders did not show any statistical significances (OR=0.828, 95%CI: 0.665-1.031 and OR=0.800, 95%CI: 0.634-1.009, respectively).

Our findings are in agreement with most studies in the literature that investigated paracetamol use and prostate cancer risk. A large cohort study on paracetamol in North Jutland county in Denmark using Pharmacoepidemiologic Prescription Database of 51,935 which represented 9% of the county population by Friis on many types of cancers including prostate cancer reported the standardized incidence ratio (SIR) for prostate cancer among paracetamol users was 1.0 (95%CI: 0.9-1.3). Further exclusion of those who received prescription of Aspirin/NSAIDs prior or within one year after receiving to first prescription of paracetamol analysis also revealed SIR of non-statistically significant at 0.8 (95%CI: 0.5-1.3) to prostate cancer risks among paracetamol users (Friis *et al*, 2002).

Platz also using prescriptions to assess exposure on 1244 males of Baltimore Longitudinal Study of Aging population showed non-statistical significant association between paracetamol use and prostate cancer at rate ratio, RR=0.89 (95%CI: 0.59-1.34) of ever use and 0.69 (95%CI: 0.39-1.20) for current use of paracetamol (Platz *et al*, 2005). While Murad in their nested case control within ProtecT study (an on-going multicentre randomized controlled trial across UK) reported no association at OR=1.15 (95%CI: 0.86-1.53) after adjusted for any aspirin or non-aspirin NSAIDs used (Murad *et al*, 2011).

8.6.3.1 Duration of Paracetamol Usage

The results suggested that only those who used paracetamol for a period of between 20 years or more but less than 30 years would benefit a protective effect

against prostate cancer, as reported in the age-adjusted and multivariate-adjusted regression models at OR 0.501 (95%CI: 0.272-0.921) and 0.534 (95%CI: 0.287-0.993) respectively (Table 8-14 page 8-158).

Previous case-control studies on acetaminophen effect on prostate cancer did not show any statistically significant association (Murad *et al*, 2011; Salinas *et al*, 2010). Similarly results also reported in cohort and incidence studies (Friis *et al*, 2002; Platz *et al*, 2005). These studies defined paracetamol as 'ever use'.

There was no significant trend across categories. The fully adjusted model with potential multivariate confounders also showed a non significant p trend = 0.165 and OR=0.925 (95%CI: 0.830-1.032) (result not presented in this thesis).

There is one study in the literature that disagrees with our findings. The study by Rodriguez & Gonzalez-Perez used data from the UK General Practice Research Database (GPRD) and had shown p trend value of 0.02. Although the current use compared to non-user of paracetamol has non-statistically significant OR of 0.95 (95%CI: 0.84-1.07), their study however showed the categories of longer duration of paracetamol usage showed reduction in prostate cancer (Garcia Rodriguez, 2004).

Most other studies did not perform p-trend value for paracetamol probably because of the inconsistence OR value with each category of duration use.

8.6.3.2Paracetamol Cumulative Duration of Use

The result of univariate analysis of the different categories of duration usage of paracetamol in comparison with those who are non-user did not show any statistical significance, all the OR values were less than 1.0, all CIs included 1.

However in the multivariate adjustment of all potential confounders, the estimated risks for paracetamol use of up to 20, 30, 40 and 50 years became statistically significant at OR=0.713 (95%CI: 0.513-0.990), 0.703 (95%CI: 0.518-0.954), 0.720 (95%CI: 0.538-0.965) and 0.745 (95%CI: 0.560-0.991) respectively (Table 8-15 page 8-160). These results suggested that longer term paracetamol use reduce prostate cancer risk among users as compared to non-users.

Other studies on duration use of paracetamol on prostate cancer risk showed mixed results. For example, a study by Platz reported non-statistical significance at RR=0.93 (95%CI: 0.61-1.44) and 0.88 (95%CI: 0.34-2.33) for less than 4 years and 4 years or more respectively (Platz *et al*, 2005). Rodriguez & Gonzalez-Perez however found that paracetamol at 1-2 years and 4 years or more showed statistically significant risk reduction (OR=0.67, 95%CI: 0.49-0.92) and 0.50, 95%CI: 0.38-0.65 respectively) (Garcia Rodriguez, 2004).

8.6.3.3 Conclusions and Recommendations

In this study, paracetamol use was not associated with prostate cancer risk. There was also no indication of trend across increase duration. However the cumulative odds ratios for usage of paracetamol use of up to 20, 30, 40 and 50 years were statistically significant in multivariate adjusted model with reduction in prostate cancer risk.

In order to interpret the result validly, it is important to further look at possible existence of confounders due to other painkiller medication such as NSAIDs because their similarity in mechanism of action.

Among three drugs, paracetamol is the most frequent use as compared to others. It would be difficult to conclude that this is a true effect because we are unable to identify subjects who only used paracetamol not other pills (due to small numbers making estimated risk less precise).

Further study would need to use reporting using prescription as such. Since paracetamol is widely available over the counter and many brands existed and probably not monitored properly, would result in mixed efficacy at its function as COX inhibitors for inflammatory process.

Chapter 9 Skin Complexion, Colour, Sun effect and Sunlight Exposure

9.1 Literature Review

9.1.1 Skin type, sun effect, sun protection behaviour & Prostate cancer

The study of skin type and prostate cancer are scarce in literature however the association of skin type and other cancers such as skin cancer i.e. basal cell carcinoma and melanoma are many due to the fact for its organ related. The type of skin complexion and colour were found to be of relevant to the manner of skin reaction towards exposure such as how well individuals sunburn or suntan (Astner & Anderson, 2004). Fitzpatrick Skin Phototypes is widely used for estimating UV (ultraviolet), photochemotherapy and ultraviolet A radiation (PUVA) laser treatment doses.

Different skin phototype and complexion would react differently towards long hours of exposure to sunlight. Skin phototype was used in studying the risk of skin cancer with highest risk among type I and lowest risk in type VI. Astner & Anderson also described based on the table below that skin phototype I to VI are constitutive of colour from Ivory white to White, then Beige-Olive to moderate brown, and lastly dark brown to black (Astner & Anderson, 2004). Burns occur mostly among the fairer skin, while tanning occur best among the darker skin, with in-between having both processes.

Table 9-1 Skin Phototype based on susceptibility to sunburn in sunlight and tanning ability

Skin Phototype	Sunburn Susceptibility	Tanning Ability
I	High	None
II	High	Poor
III	Moderate	Good
IV	Low	Very Good
V	Very Low	Excellent
VI	Very Low	Excellent

Adapted from: Fitzpatrick's Dermatology in General Medicine, 7th Edition. 2008 (Fitzpatrick & Wolff, 2008)

Sunburn and tanning are the most obvious effects of ultraviolet radiation (UVR) acute clinical effects (Fitzpatrick & Wolff, 2008). This was useful in describing the sun-sensitivity according to skin phototype as shown in Table 9-1 above. Most human ultraviolet radiation comes from sunlight but use of tanning devices is increasingly popular. Sun ultraviolet radiation exposure could be intentional or unavoidable and much is depended on behaviours and time spent outdoors, as well as any usage of photoprotection strategies.

Although ultraviolet radiation (UVR) was recognized as a risk to skin cancer (Fitzpatrick & Wolff, 2008), there is interest that sunlight UVR interaction with skin type might show association towards internal cancers such as lymphoid malignancies . There are studies suggesting a positive association between most reactive and palest skin types with non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) (Grandin *et al*, 2008).

The mechanism on how skin type and internal cancers such as prostate cancer were related is still unclear although Vitamin D was implicated through its synthesis by sunlight (Bodiwala *et al*, 2003a). A case-control study was conducted on 453 prostatic adenocarcinoma cases and 312 benign prostatic hypertrophy (BPH) control subjects by Bodhiwala to look at how the ability to pigment as assessed by skin type, influences the extent of exposure to UVR and whether skin type is associated with prostate cancer susceptibility. The results showed that prostate cancer subjects with sensitive to sun i.e. skin type type 1 (always burn or never tan), had lower cumulative exposure of sunlight per year at statistically significant $p=0.0014$ and lower sunbathing score ($p<0.0001$) in comparison with type 4 (rarely burn or easily tan), possibly due to tendency to avoid exposure. The study also showed that cumulative exposure to sunlight per year and sunbathing score were significantly lower in cancer cases than BPH control at $p<0.001$ and $p<0.001$ respectively. However there was no association between skin type 1 versus type 4 and prostate cancer risk.

The usage of childhood sunburn history was also associated with reduced prostate cancer risk in some studies (Bodiwala *et al*, 2003a; Bodiwala *et al*, 2003b; Luscombe *et al*, 2001).

The author has not yet found articles that described specifically the habits use of protective clothing from the sun with the prostate cancer risk. It is possible at

this time, more studies has been carried out to see using variables on usage of protective clothing against long exposure of daylight towards confounding the affect of sunlight exposure on subject by reducing the actual amount of sunlight received and consecutively of lesser Vitamin D production than intended.

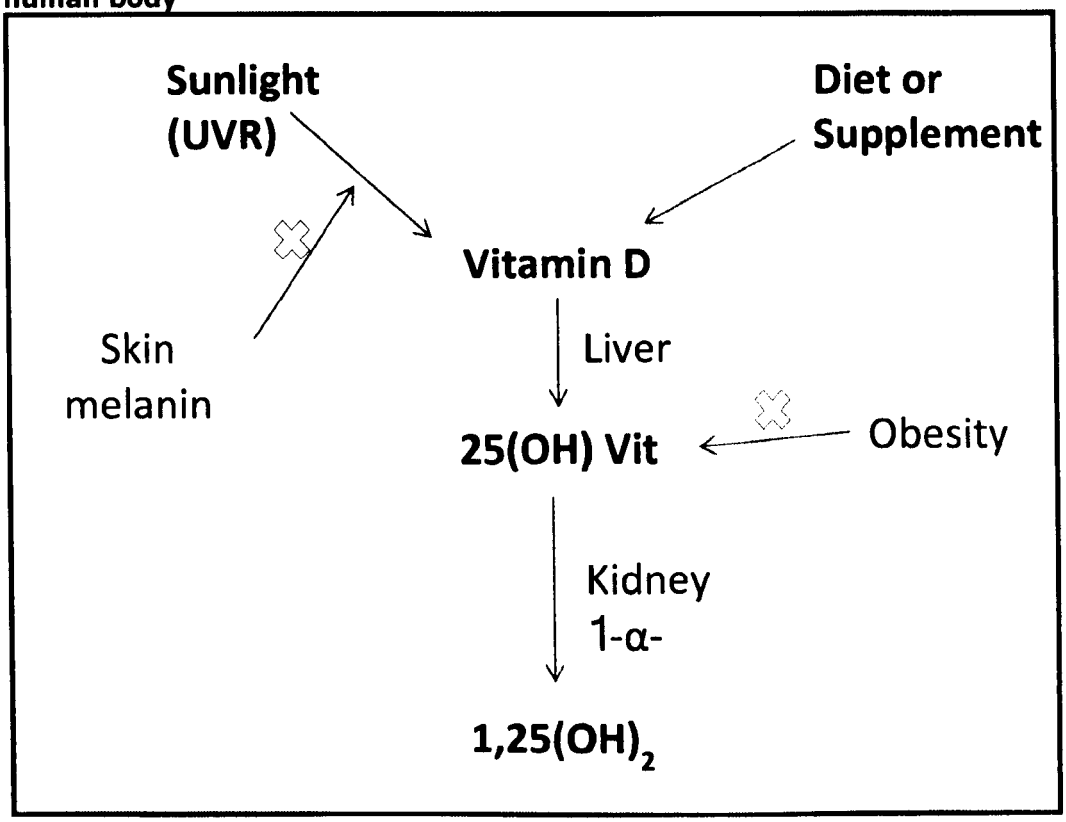
In terms of suntan cream usage habit to avoid getting sunburn or reduce skin reactions due to long exposure under the sun, the author did not find direct any study association with prostate cancer, although it was reported higher SPF (sun-protection factor) seems to increase duration of recreational sun exposure of young Europeans (Autier *et al*, 1999).

9.1.2 Sunlight, Vitamin D & Prostate cancer

The study of relationship of sunlight or ultraviolet radiation exposure and prostate cancer in the last decade has been of interest especially when trying to investigate how sunlight and vitamin D could be related. Proposed mechanisms of how sunlight exposure and vitamin D are related to cancer has been described in literature.

Giovannucci described (refer Figure 9-1, page 9-175) how ultraviolet radiation (UVR) is required to convert 7-dehydrocholesterol into vitamin D (cholecalciferol) in the skin. Vitamin D main sources are sunlight and diet or supplements. Vitamin D are then hydroxylated in the liver to produce 25(OH)D which in the blood circulation concentration is the best indicator for vitamin D status. 25(OH)D may be converted into $1,25(OH)_2D$ by kidney 1-alpha-hydroxylase regulation activity. Darker skin due to melanin, aging and obesity has been associated with reduction production of 25(OH)D (Giovannucci, 2005).

Figure 9-1 Proposed pathways Vitamin D production and metabolism in human body[1]



Through circulation, various cells are exposed to either 25(OH)D or $1,25(OH)_2D$. It was through this mechanism that levels either one or both types of vitamin D could affect cancer risk by inhibiting tumour growth by controlling cell differentiation and proliferation (Schwartz, 2005). However the levels or concentration of these hydroxylated forms of vitamin D could be directly associated with amount of sources of vitamin D such as sunlight UVR, diet/supplements, and regulation of activity of enzymes or hormones of liver, kidney and parathyroid such as 1-alpha-hydroxylase, parathyroid hormone, as well levels of calcium, phosphorus etc.

[1] Adapted from Giovannucci E (2005) The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). *Cancer Causes Control* **16**(2): 83-95.

Several studies have shown that increased cumulative sunlight or ultraviolet radiation exposure has been associated with reduced risk in prostate cancer (Bodiwala *et al*, 2003a; Bodiwala *et al*, 2003b; John *et al*, 2004; John *et al*, 2007; Rukin *et al*, 2007).

Ecological studies use trend surface analysis or mapping to define the residence amount of ultraviolet (UV) sunlight exposure or residential sunlight for early life (Freedman *et al*, 2002; John *et al*, 2004; John *et al*, 2007; Schwartz & Hanchette, 2006). Most of these studies were American studies therefore the results somewhat share the similar conclusions. Those who reside or longest reside in the South (nearer to earth Equator) or born in the state with the highest solar radiation have reduced relative risk for prostate cancer (John *et al*, 2004; John *et al*, 2007) or reduce mortality rate for prostate cancer (Freedman *et al*, 2002; Schwartz & Hanchette, 2006).

Similarly studies assessed history of regular sunbathing and foreign holidays were also showed association with reduction in prostate cancer risk (Bodiwala *et al*, 2003a; Bodiwala *et al*, 2003b; John *et al*, 2007; Luscombe *et al*, 2001). While some use place of birth as a measure of UVR level and also showed decreased risk in prostate cancer with lower latitude area (John *et al*, 2004; John *et al*, 2007).

However, when circulation plasma levels of vitamin D such as 25(OH)D are used, it was not associated with prostate cancer risk (Ahn *et al*, 2008; Barnett *et al*, 2010; Park *et al*, 2010).

9.2 Aims

The aims of this chapter are to investigate the relationship of the following factors with prostate cancer risk:

i. Skin complexion
ii. Skin colour
iii. Types of sun effect reactions
iv. Sunlight exposure time during outworking
v. Sunlight exposure time during non-working
vi. Habits of protection when exposed to sunlight
vii. Frequency usage of suntan cream

The above factors are used as surrogate marker for vitamin D sources from sunlight exposure and prostate cancer risk was also reviewed. The dietary intake of vitamin D in association with prostate cancer would be discussed in another chapter of this thesis in the diet topic.

We proposed a scoring method for prostate cancer risk, by combining the above variables as surrogate markers for Vitamin D production through skin and sunlight exposure.

9.3 Methodology

Only data collected in Phase II of the study was used in all analyses. The total number of subjects is 2209. Data were self reported on:

i. Skin complexion type
ii. Skin colour when not sun tanned
iii. Effect of too long under the sun on skin
iv. Amount of hours outdoor during daytime working or non-working at age 20's, 30's, 40's, and last 5 years
v. Habits of protection when outdoors in the day time at age 20's, 30's, 40's, and last 5 years
vi. Frequency usage of suntan oil, lotion or cream to protect skin when out in the sun at age 20's, 30's, 40's, and last 5 years
vii. Scoring for each aspect in proposed table scoring method for prostate cancer risk

9.3.1 Definition

Skin complexion choice of answers was of oily, dry, combination or normal. Skin colour when not sun tanned and effect of too long under the sun on skin, were choice answers loosely based on Fitzpatrick classification scale that was developed in 1975 by Harvard Medical School dermatologist, Thomas Fitzpatrick. The scale classifies a person's skin and their tolerance to sunlight as shown in Table 9-2 on page 9-178:

Table 9-2 Fitzpatrick Skin Classification (1975)

Skin Type	Skin Colour	Characteristics
I	White; Fair	Always burn, never tans
II	White; Fair	Usually burns, tans with difficulty
III	Cream white; fair	Sometimes mild burn, gradually tans
IV	Brown; typical Mediterranean skin	Rarely burns, tans with ease
V	Dark brown; mid-eastern skin	Very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

For skin colour, choices provided in the study questionnaire are very fair, fair, medium, olive and very dark. For sun effect on skin, answer choices are painful bad blistering peeling, blistering followed by peeling, burns sometimes, rarely burns and never had bourns.

The subjects were further asked to identify on average number of hours they were spent time outdoor during working and non-working hours at various stages in life as markers of probable sunlight exposure. The ranges are from less than 1 hour, 1-2 hours, 3-4 hours and 5 hours or more. They were also asked to record if they used any protection from the sun when they were outdoor with choices of answer ranging from; always seek a sun tan, wear very little, wear normal summer clothing, try to cover oneself up from the sun, and did not spend time outdoors at all.

Lastly the frequency of using suntan oil, lotion or cream when they were out in the sun; from always, sometimes to rarely or never.

9.3.2 Analysis

Data were analyzed descriptively and p value for trend analysis was performed with variables of ordinal scales. Chi-square test was carried out to see any differences in the distributions of answers between cases and controls.

Logistic regressions are carried out to yield risk estimates and their confident intervals. The models include univariate, followed by age-adjusted modelling and lastly fully adjusted multivariate potential confounders including education, ethnic and family history of cancer with a-priori variable of age and skin colour.

For outdoor daylight exposure during working and non-working, duration of 'less than 1 hour' daily was used as reference. Whereas for protection habits when under the sun, 'always seek a sun tan' was used as reference category, and regression modelling for suntan cream frequency usage, 'never use suntan' was the reference category.

Proposed Scoring Method for Vitamin D and Prostate Cancer Risk

Since vitamin D exposure can be affected by factors relevant to skin and sunshine exposure, as well as diet, therefore we proposed a scoring method by applying a surrogate score to each of the factors for each individual. The scores were then summed to obtain a total single score of probable vitamin D exposure at various stages in life. The scoring table is summarized in Table 9-3 page 9-181. The factors in the study questionnaire were put together in the table.

The fact that more than 90% of vitamin D requirement comes from source of casual exposure to sunlight (Gillie, 2006). Dietary intake of vitamin D source is probably the balance of 10%. Ideally, the calculation of total sum scores should apply this principal of ratio 90%:10% between vitamin D source from skin and sunlight and dietary intake. However the study only collected diet history over the last 5 year whilst skin and sunlight exposure was available throughout lifetime (20s, 30s, 40s and during the last 5 years) thus limit the application of scoring method throughout lifetime exposure. The total sum score of vitamin D exposure at age 20s, 30s and 40s was calculated from skin and sunlight exposures. The total sum score of vitamin D exposure during the last 5 years was calculated from skin/sunlight exposure and dietary intake of vitamin D during the last 5 years.

Vitamin D exposure during the last 5 years

The skin and sunlight exposures consist of 7 variables and total vitamin D intake is a single variable. 7 out of 8 aspects of scoring is equivalent to proportion of 87.5%. Similarly, the possible maximum total score obtained from skin and sunlight source of vitamin D is 30. Dietary vitamin D maximum score is 4 making a total possible maximum score of 34 (when combining skin/sunlight vitamin D and dietary intake vitamin D) therefore at score of 30 from sunlight and skin exposure alone (30 out of maximum 34) is equivalent to proportion of 88.2%. The maximum score of 4 from diet alone is equivalent to 11.8%.

Possible derived score

For vitamin D exposure during the last 5 years, the lowest and highest possible total score is 8 and 34 respectively. For vitamin D at age 20s, 30s and 40s, the possible score range from 8-30.

The sum score of each individual at each period in life was then assigned into quartile range based on control scores. The total score would be greater for those who have more sunlight exposure and Vitamin D production by skin or highest quartile dietary intake of vitamin D. The hypothesis is that higher score leads to lower risk for prostate cancer, at the same time, lower score means higher risk to prostate cancer.

Logistic regression was carried out to obtain odds ratios and confidence intervals and trend of risk across quartiles was also assessed.

Table 9-3 Proposed Scoring Method for aspects of Skin complexion, colour, Sun effect, Working & non-working Sunlight exposure, Protection clothing used and Suntan cream usage affecting habits to be under the sun, for subsequent effects on Vitamin D Production by Skin, and Dietary Vitamin D

Aspects	Score					
	5	4	3	2	1	Aspect Score
Skin Complexion		Normal	Combination	Dry	Oily	
Skin Colour	Very dark	Olive	Medium	Fair	Very Fair	
Sun effect	Never burns	Rarely burns	Burn sometimes	Blister with peeling	Painful blister and peeling	
Working Sunlight exposure daily	-	5 hours or more	3 to 4 hours	1 to 2 hours	<1 hour	
Non-working Sunlight exposure daily	-	5 hours or more	3 to 4 hours	1 to 2 hours	<1 hour	
Protection habits	-	Always seek a sun tan	Wear very little	Wear normal summer clothing	Try to cover up from the sun or did not spend time outdoors at all	
Suntan cream usage	-	Always	Sometimes	Rarely	Never	
Dietary Intake Vitamin D Amount*		4th Quartile	3rd Quartile	2nd Quartile	1st Quartile	
					Total Score	

Example:
A White man at age 20's with dry skin complexion, fair skin colour, who experienced blister with peeling when spend a few hours under sunlight with less than 1 hour under the sun while working but spend 3 to 4 hours under sunlight when not working, and habits of wearing normal summer clothing when exposed to sunlight, sometimes use suntan cream and dietary intake of Vitamin D at 2nd quartile, would score = 2+2+2+1+3+2+3 + 2= **17**

Score **17** is the possible amount of Total Vitamin D production by skin and dietary intake at age 20's for association study for prostate cancer risk.

*Dietary Intake Vitamin D amount was taken only for last 5 years, therefore only used when scoring for age period 'last 5 years'.

9.4 Results

9.4.1 Skin Complexion

Table 9-4 Skin Complexion characteristics between Case-Control Group

Complexion	Group		Total
	Control	Case	
	%	%	%
Oily	86	146	232
	10.4%	10.7%	10.6%
Dry	90	159	249
	10.9%	11.7%	11.4%
Combination	90	186	276
	10.9%	13.7%	12.6%
Normal	562	869	1431
	67.9%	63.9%	65.4%
Total	828	1360	2188
	100.0%	100.0%	100.0%

'Normal' skin complexion is the most common skin type among case and control groups at approximately two-thirds. The percentage of cases and controls reported oily, dry and combination are similar. Chi-square test (p value=0.185) did not show any statistical significant difference between skin types of case and control group.

The logistic regression models displayed on Table 9-5 page 9-183 did not reveal any statistical significant association between different skin complexion with prostate cancer when compared to 'normal' skin.

Table 9-5 Odds ratios and 95% Confidence Interval of Skin complexion and Prostate Cancer Risk

Skin Complexion	Control	Cases	OR[a] (95%CI)	P value[a]	OR[b] (95%CI)	P value[b]	OR[c] (95%CI)	p value[c]
Normal	562	869	-Ref-	-	-Ref-	-	-Ref-	-
	67.9%	63.9%						
Oily	86	146	1.098 (0.824-1.463)	0.523	0.983 (0.733-1.320)	0.911	0.898 (0.660-1.223)	0.496
	10.4%	10.7%						
Dry	90	159	1.143 (0.864-1.511)	0.350	1.136 (0.853-1.513)	0.382	1.133 (0.839-1.529)	0.416
	10.9%	11.7%						
Combination	90	186	**1.337 (1.017-1.756)**	**0.037**	1.110 (0.838-1.470)	0.469	0.985 (0.735-1.321)	0.922
	10.9%	13.7%						

[a]Unadjusted regression model
[b]Age-adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, and family history of cancer
P for trend = 0.231

9.4.2 Skin Colour

Table 9-6 Distribution of skin colour in study subjects

Colour	Group		Total
	Control	Case	
	%	%	%
Very Fair	39	77	116
	4.7%	5.6%	5.3%
Fair	313	510	823
	37.8%	37.4%	37.6%
Medium	443	695	1138
	53.6%	51.0%	52.0%
Olive	29	61	90
	3.5%	4.5%	4.1%
Very Dark	3	20	23
	0.4%	1.5%	1.1%
Total	827	1363	2190
	100.0%	100.0%	100.0%

'Medium' skin colour was the most common reported at approximately 52%, followed by 'fair skin' at 37%. There is no difference in skin colour between both cases and controls (Chi-square test p value of 0.069). The odds ratios results of logistic regression models of skin colour on prostate cancer risk did not show any statistically significant association (refer Table 9-7 page 9-185). P for trend also was not statistically significant at 0.574

Table 9-7 Odds ratios and 95% Confidence Interval of Skin Colour and Prostate Cancer Risk

Skin Colour	Control	Cases	OR[a] (95%CI)	P value[a]	OR[b] (95%CI)	P value[b]	OR[c] (95%CI)	p value[c]
Very Fair	39	77	Ref	-	Ref	-	Ref	-
	4.7%	5.6%						
Fair	313	510	0.825 (0.548-1.244)	0.359	0.929 (0.610-1.413)	0.730	0.917 (0.590-1.427)	0.702
	37.8%	37.4%						
Medium	443	695	0.795 (0.531-1.189)	0.264	0.859 (0.569-1.298)	0.470	0.812 (0.526-1.253)	0.346
	53.6%	51.0%						
Olive	29	61	1.065 (0.593-1.915)	0.832	1.099 (0.603-2.000)	0.758	0.920 (0.482-1.756)	0.801
	3.5%	4.5%						
Very Dark	3	20	3.377 (0.945-12.062)	0.061	3.584 (0.989-12.984)	0.052	1.905 (0.454-7.994)	0.378
	0.4%	1.5%						

[a]Unadjusted regression model
[b]Age-adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, and family history of cancer
P for trend = 0.574

9.4.3 Sun Effect reaction on skin

Table 9-8 Sun Effect reactions on skin between case-control group

Sun effect	Group		Total
	Control	Case	
	%	%	%
Painful bad blister & peel	52	87	139
	6.3%	6.4%	6.4%
Blister with peel	118	235	353
	14.3%	17.3%	16.2%
Burns sometimes	426	684	1110
	51.8%	50.5%	51.0%
Rarely burns	185	278	463
	22.5%	20.5%	21.3%
Never had burns	42	71	113
	5.1%	5.2%	5.2%
Total	823	1355	2178
	100.0%	100.0%	100.0%

Chi-square test p value=0.410

Half of the subjects in case and control group reported having had burns sometimes when exposed to the sun under long duration. Second most common answer was 'rarely burns' at approximately 21% followed by 'blister with peel' at 16%. Chi-square test did not show any statistically significant difference in the characteristics of sun effect reaction on skin between case and control group (p value=0.410).

Results showed in Table 9-9 on page 9-187, suggested that different types of sun effect on skin did not associate with prostate cancer risk. P for trend also was not statistically significant.

Table 9-9 Odds ratios and 95% Confidence Interval of Sun Effect on Skin and Prostate Cancer Risk

Sun Effect on Skin	Control	Cases	OR[a] (95%CI)	P value[a]	OR[b] (95%CI)	P value[b]	OR[c] (95%CI)	p value[c]
Painful bad blister & peel	52	87	Ref	-	Ref	-	Ref	-
	6.3%	6.4%						
Blister with peel	118	235	1.190 (0.791-1.791)	0.403	1.340 (0.882-2.035)	0.170	1.350 (0.870-2.094)	0.181
	14.3%	17.3%						
Burns sometimes	426	684	0.960 (0.667-1.381)	0.825	1.015 (0.700-1.472)	0.937	1.024 (0.692-1.516)	0.905
	51.8%	50.5%						
Rarely burns	185	278	0.898 (0.608-1.327)	0.590	1.042 (0.699-1.555)	0.839	1.090 (0.715-1.664)	0.688
	22.5%	20.5%						
Never had burns	42	71	1.010 (0.605-1.688)	0.968	1.221 (0.720-2.069)	0.459	1.090 (0.611-1.943)	0.771
	5.1%	5.2%						

[a]Unadjusted regression model
[b]Age-adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, and family history of cancer
P for trend = 0.226

9.4.4 Outdoor sunlight exposure while working

Between ages 20s to 40s and over the last 5 years prior to case diagnosis or control to receiving their questionnaire (refer to Table 9-10 on page 9-188, Table 9-11 on page 9-189, Table 9-12 on page 9-189, and Table 9-13 on page 9-190), the figures showed that almost half of subjects in both case and control groups reported exposed to the sunlight less than 1 hour while at work, while between 20% to 23% worked between 1-2 hours outdoor, and less proportion exposed for more than 3 hours. With progression of age, it was observed that a smaller proportion of subjects of both cases and controls spent time working outdoor for 5 hours or more, starting at 21% at age 20s down to 15% in the last 5 years.

Table 9-10 Time spent outside at age 20's among Case-control group

Working outside with sunlight exposure at age 20's	Group		Total
	Control	Case	
	%	%	%
Less than 1 hour	352	607	959
	44.7%	47.6%	46.5%
1-2 hours	175	246	421
	22.2%	19.3%	20.4%
3-4 hours	94	147	241
	11.9%	11.5%	11.7%
5 hours or more	166	274	440
	21.1%	21.5%	21.3%
Total	787	1274	2061
	100.0%	100.0%	100.0%

Chi-square test p value=0.386

Table 9-11 Time spent outside at age 30's among Case-control group

Working outside with sunlight exposure at age 30's	Group		Total
	Control	Case	
	%	%	%
Less than 1 hour	355	600	955
	45.3%	47.2%	46.5%
1-2 hours	175	286	461
	22.3%	22.5%	22.5%
3-4 hours	111	153	264
	14.2%	12.0%	12.9%
5 hours or more	142	231	373
	18.1%	18.2%	18.2%
Total	783	1270	2053
	100.0%	100.0%	100.0%

Chi-square test p value=0.553

Table 9-12 Time spent outside at age 40's among Case-control group

Working outside with sunlight exposure at age 40's	Group		Total
	Control	Case	
	%	%	%
Less than 1 hour	349	637	986
	44.9%	50.6%	48.4%
1-2 hours	202	276	478
	26.0%	21.9%	23.5%
3-4 hours	100	149	249
	12.9%	11.8%	12.2%
5 hours or more	126	198	324
	16.2%	15.7%	15.9%
Total	777	1260	2037
	100.0%	100.0%	100.0%

Chi-square test p value=0.069

Table 9-13 Time spent outside in the last 5 years among Case-control group

Working outside with sunlight exposure in last 5 years	Group		Total
	Control	Case	
	%	%	%
Less than 1 hour	251	493	744
	44.9%	49.8%	48.1%
1-2 hours	137	210	347
	24.5%	21.2%	22.4%
3-4 hours	85	131	216
	15.2%	13.2%	14.0%
5 hours or more	86	155	241
	15.4%	15.7%	15.6%
Total	559	989	1548
	100.0%	100.0%	100.0%

Chi-square test p value=0.210

All Chi-square tests for different decades of age did not reveal any statistically significant difference in number of hours working outside between cases and controls.

The p values for trend at all decades of age didn't reveal any statistically significant findings (P for trend at 20's p=0.645, at 30's p= 0.452, at 40's p=0.130 and last 5 years, p=0.283).

The results of regression models for sunlight exposure when working outdoor are shown in Table 9-14 page 9-191). Univariate regression analysis showed statistically significant odds ratio (OR= 0.749, 95%CI: 0.599-0.936) in '1-2 hours' category when compared with those 'less than 1 hour' of outdoor sunlight exposure while working during age 40's.

For age-adjusted modelling, only '1-2 hours' category of outdoor sunlight exposure at age 20's was found to be statistically significant or prostate cancer risk association at OR=0.776 (95%CI: 0.610-0.988). All other regression models did not reveal any association between sunlight outdoor exposures while working with prostate cancer risk.

Table 9-14 Odds ratios and 95% Confidence Interval of hours working outside at age 20's, 30's, 40's and last 5 years on Prostate Cancer Risk

Age	Amount of time	Control	Cases	OR[a] (95%CI)	p value[a]	OR[b] (95%CI)	p value[b]	OR[c] (95%CI)	p value[c]
20's	Less than 1 hour	352	607	-Ref-		-Ref-		-Ref-	
		44.7%	47.6%						
	1-2 hours	175	246	0.815	0.087	**0.776**	**0.039**	0.803	0.089
		22.2%	19.3%	(0.645-1.030)		**(0.610-0.988)**		(0.623-1.034)	
	3-4 hours	94	147	0.907	0.509	0.940	0.685	0.954	0.768
		11.9%	11.5%	(0.678-1.212)		(0.697-1.267)		(0.698-1.304)	
	5 hours or more	166	274	0.957	0.713	1.024	0.847	1.006	0.965
		21.1%	21.5%	(0.758-1.209)		(0.805-1.302)		(0.774-1.307)	
30's	Less than 1 hour	355	600	-Ref-		-Ref-		-Ref-	
		45.3%	47.2%						
	1-2 hours	175	286	0.967	0.774	0.997	0.977	1.014	0.912
		22.3%	22.5%	(0.769-1.216)		(0.787-1.261)		(0.793-1.297)	
	3-4 hours	111	153	0.816	0.150	0.876	0.364	0.905	0.516
		14.2%	12.0%	(0.618-1.076)		(0.659-1.166)		(0.669-1.224)	
	5 hours or more	142	231	0.963	0.761	1.025	0.851	1.026	0.860
		18.1%	18.2%	(0.752-1.232)		(0.795-1.321)		(0.774-1.358)	
40's	Less than 1 hour	349	637	-Ref-		-Ref-		-Ref-	
		44.9%	50.6%						
	1-2 hours	202	276	**0.749**	**0.011**	0.800	0.057	0.832	0.136
		26.0%	21.9%	**(0.599-0.936)**		(0.635-1.007)		(0.654-1.059)	
	3-4 hours	100	149	0.816	0.163	0.869	0.348	0.870	0.378
		12.9%	11.8%	(0.614-1.086)		(0.649-1.165)		(0.638-1.186)	
	5 hours or more	126	198	0.861	0.257	0.910	0.485	0.911	0.543
		16.2%	15.7%	(0.665-1.115)		(0.698-1.187)		(0.675-1.229)	
Last 5 Years	Less than 1 hour	251	493	-Ref-		-Ref-		-Ref-	
		44.9%	49.8%						
	1-2 hours	137	210	0.780	0.065	0.815	0.134	0.856	0.282
		24.5%	21.2%	(0.600-1.016)		(0.623-1.065)		(0.646-1.136)	
	3-4 hours	85	131	0.785	0.128	0.857	0.342	0.929	0.672
		15.2%	13.2%	(0.574-1.072)		(0.623-1.179)		(0.661-1.306)	
	5 hours or more	86	155	0.918	0.580	0.990	0.949	1.087	0.639
		15.4%	15.7%	(0.677-1.244)		(0.726-1.350)		(0.767-1.541)	

[a]Unadjusted regression model
[b]Age-adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, family history of cancer and skin colour

9.4.5 Outdoor sunlight exposure while not working

The results are shown in Table 9-15 page 9-192, Table 9-16 page 9-193, Table 9-17 page 9-193 and Table 9-18 page 9-194. There are trends that control group spend longer hours (3 hours or more categories) outdoor to sunlight exposure on non-working setting, compared to case group who tended to spend 2 hours or less for sunlight exposure in all stage of age decades.

Chi-square tests revealed all statistically significant p value of **<0.001** which suggested that there is difference in the numbers of sunlight outdoor exposure while not-working at age 20's, 30's, 40's and last 5 years between case and control group.

Table 9-15 Time spent outside when not working at age 20's among Case-control group

Non-working outside with sunlight exposure at age 20's	Group		Total
	Control	Case	
	%	%	%
Less than 1 hour	45	128	173
	6.0%	10.7%	8.9%
1-2 hours	306	533	839
	41.1%	44.5%	43.2%
3-4 hours	265	360	625
	35.6%	30.0%	32.2%
5 hours or more	128	178	306
	17.2%	14.8%	15.7%
Total	744	1199	1943
	100.0%	100.0%	100.0%

Chi-square test **p<0.001**

Table 9-16 Time spent outside when not working at age 30's among Case-control group

Non-working outside with sunlight exposure at age 30's	Group		Total
	Control	Case	
	%	%	%
Less than 1 hour	43	123	166
	5.7%	10.2%	8.5%
1-2 hours	306	540	846
	40.9%	44.9%	43.4%
3-4 hours	272	382	654
	36.4%	31.8%	33.5%
5 hours or more	127	157	284
	17.0%	13.1%	14.6%
Total	748	1202	1950
	100.0%	100.0%	100.0%

Chi-square test **p<0.001**

Table 9-17 Time spent outside when not working at age 40's among Case-control group

Non-working outside with sunlight exposure at age 40's	Group		Total
	Control	Case	
	%	%	%
Less than 1 hour	49	137	186
	6.6%	11.4%	9.6%
1-2 hours	302	541	843
	40.8%	45.2%	43.5%
3-4 hours	275	366	641
	37.2%	30.6%	33.1%
5 hours or more	114	153	267
	15.4%	12.8%	13.8%
Total	740	1197	1937
	100.0%	100.0%	100.0%

Chi-square test **p<0.001**

Table 9-18 Time spent outside when not working in last 5 years among Case-control group

Non-working outside with sunlight exposure in last 5 years	Group		Total
	Control	Case	
	%	%	%
Less than 1 hour	53	160	213
	6.9%	12.9%	10.6%
1-2 hours	242	475	717
	31.4%	38.3%	35.7%
3-4 hours	279	401	680
	36.2%	32.3%	33.8%
5 hours or more	196	204	400
	25.5%	16.5%	19.9%
Total	770	1240	2010
	100.0%	100.0%	100.0%

Chi-square test **p<0.001**

The estimated risks for prostate cancer risk with history of sunlight exposure while not working are shown in Table 9-19 page 9-195. The results suggested statistically significant throughout age decades at 20's, 30's, 40's and last 5 years in all univariate, age-adjusted and fully adjusted multivariate potential confounders and a-priori variables when all the categories of hours exposure to sunlight while they were outdoor being compared with those of 'less than 1 hour' with exception for multivariate adjusted model at age 30's for exposure of '1-2 hours'. The P for trend also showed in each stage of age decade showed statistically significant **p<0.001**.

Table 9-19 Odds ratios and 95% Confidence Interval of time spent outside when not working at age 20's, 30's, 40's and last 5 years on Prostate Cancer Risk

Age	Amount of time	Control	Cases	OR[a] (95%CI)	P value[a]	OR[b] (95%CI)	P value[b]	OR[c] (95%CI)	p value[c]
20's	**Less than 1 hour**	45	128	-Ref-		-Ref-		-Ref-	
		6.0%	10.7%						
	1-2 hours	306	533	**0.612**	**0.009**	**0.629**	**0.016**	**0.671**	**0.045**
		41.1%	44.5%	**(0.424-0.884)**		**(0.432-0.917)**		**(0.454-0.992)**	
	3-4 hours	265	360	**0.478**	**<0.001**	**0.498**	**<0.001**	**0.541**	**0.003**
		35.6%	30.0%	**(0.328-0.695)**		**(0.339-0.731)**		**(0.363-0.806)**	
	5 hours or more	128	178	**0.489**	**0.001**	**0.501**	**0.001**	**0.534**	**0.005**
		17.2%	14.8%	**(0.325-0.736)**		**(0.330-0.762)**		**(0.345-0.828)**	
30's	**Less than 1 hour**	43	123	-Ref-		-Ref-		-Ref-	
		5.7%	10.2%						
	1-2 hours	306	540	**0.617**	**0.011**	**0.651**	**0.029**	0.704	0.087
		40.9%	44.9%	**(0.424-0.897)**		**(0.444-0.956)**		(0.471-1.052)	
	3-4 hours	272	382	**0.491**	**<0.001**	**0.530**	**0.001**	**0.584**	**0.010**
		36.4%	31.8%	**(0.336-0.718)**		**(0.359-0.783)**		**(0.389-0.879)**	
	5 hours or more	127	157	**0.432**	**<0.001**	**0.447**	**<0.001**	**0.469**	**0.001**
		17.0%	13.1%	**(0.284-0.657)**		**(0.291-0.687)**		**(0.298-0.736)**	
40's	**Less than 1 hour**	49	137	-Ref-		-Ref-		-Ref-	
		6.6%	11.4%						
	1-2 hours	302	541	**0.641**	**0.014**	**0.663**	**0.028**	**0.669**	**0.039**
		40.8%	45.2%	**(0.449-0.914)**		**(0.460-0.956)**		**(0.458-0.979)**	
	3-4 hours	275	366	**0.476**	**<0.001**	**0.497**	**<0.001**	**0.505**	**0.001**
		37.2%	30.6%	**(0.332-0.684)**		**(0.342-0.721)**		**(0.342-0.744)**	
	5 hours or more	114	153	**0.480**	**<0.001**	**0.476**	**<0.001**	**0.469**	**0.001**
		15.4%	12.8%	**(0.320-0.721)**		**(0.313-0.723)**		**(0.302-0.728)**	
Last 5 Years	**Less than 1 hour**	53	160	-Ref-		-Ref-		-Ref-	
		6.9%	12.9%						
	1-2 hours	242	475	**0.650**	**0.015**	**0.615**	**0.007**	**0.613**	**0.010**
		31.4%	38.3%	**(0.460-0.920)**		**(0.430-0.878)**		**(0.423-0.888)**	
	3-4 hours	279	401	**0.476**	**<0.001**	**0.498**	**<0.001**	**0.499**	**<0.001**
		36.2%	32.3%	**(0.337-0.673)**		**(0.349-0.711)**		**(0.345-0.722)**	
	5 hours or more	196	204	**0.345**	**<0.001**	**0.367**	**<0.001**	**0.380**	**<0.001**
		25.5%	16.5%	**(0.239-0.498)**		**(0.252-0.535)**		**(0.256-0.565)**	

[a]Unadjusted regression model
[b]Age-adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, family history of cancer and skin colour

9.4.6 Protection habits while outdoor under the sun

There is no difference over the habits of wearing protection when they spent time outdoor under the sun between cases and controls as indicative by Chi-square results (all p values are greater than 0.05) for all age decades (refer Table 9-20 page 9-196, Table 9-21 page 9-197, Table 9-22 page 9-197 and Table 9-23 page 9-198). However, it is evident that there are trends of protection habits change from less protection categories (as in 'always seek a sun tan' or 'wear very little') to more protection from the sun (as in 'wear normal summer clothing' or 'try to cover up from the sun') as subjects aged. The majority of the subjects in all decades reported 'wear normal summer clothing'.

Table 9-20 Types of protection habits when spent time outdoor at age 20's among case-control group

Protection habits when outdoor at age 20's	Group		Total
	Control	Case	
	%	%	%
Always seek a sun tan	126	196	322
	15.2%	14.5%	14.8%
Wear very little	168	277	445
	20.3%	20.4%	20.4%
Wear normal summer clothing	480	782	1262
	58.0%	57.7%	57.8%
Try to cover up from the sun or did not spend time outdoors at all	53	101	154
	6.4%	7.4%	7.1%
Total	827	1356	2183
	100.0%	100.0%	100.0%

Chi-square test, p=0.798

Table 9-21 Types of protection habits when spent time outdoor at age 30's among case-control group

Protection habits when outdoor at age 30's	Group		Total
	Control	Case	
	%	%	%
Always seek a sun tan	73	117	190
	8.9%	8.6%	8.7%
Wear very little	151	281	432
	18.3%	20.7%	19.8%
Wear normal summer clothing	531	828	1359
	64.40%	61.1%	62.3%
Try to cover up from the sun or did not spend time outdoors at all	69	130	199
	8.4%	9.6%	9.1%
Total	824	1356	2180
	100.0%	100.0%	100.0%

Chi-square test, p=0.350

Table 9-22 Types of protection habits when spent time outdoor at age 40's among case-control group

Protection habits when outdoor at age 40's	Group		Total
	Control	Case	
	%	%	%
Always seek a sun tan	48	76	124
	5.8%	5.6%	5.7%
Wear very little	125	206	331
	15.2%	15.2%	15.2%
Wear normal summer clothing	540	848	1388
	65.5%	62.6%	63.7%
Try to cover up from the sun or did not spend time outdoors at all	112	225	337
	13.6%	16.6%	15.5%
Total	825	1355	2180
	100.0%	100.0%	100.0%

Chi-square test, p=0.290

Table 9-23 Types of protection habits when spent time outdoor over the last 5 years among case-control group

Protection habits when outdoor last 5 years	Group		Total
	Control	Case	
	%	%	%
Always seek a sun tan	41	70	111
	5.0%	5.2%	5.1%
Wear very little	90	145	235
	10.9%	10.8%	10.9%
Wear normal summer clothing	453	732	1185
	55.0%	54.7%	54.8%
Try to cover up from the sun or did not spend time outdoors at all	240	390	630
	29.1%	29.2%	29.2%
Total	824	1337	2161
	100.0%	100.0%	100.0%

Chi-square test, p=0.995

The p for trend for all age decades was not statistically significant (P for trend at 20's= 0.494, at 30's= 0.827, at 40's == 0.287 and last 5 years P for trend = 0.907). The estimated risks of protection habits at different age decades when outdoor under the sun and prostate cancer did not show any statistically significant findings even in the adjusted models (Table 9-24 page 9-199).

Table 9-24 Odds ratios and 95% Confidence Interval of Protection habits when exposed to sunlight at age 20's, 30's, 40's and last 5 years on Prostate Cancer Risk

Age	Protection Habits	Control	Cases	OR[a] (95%CI)	P value[a]	OR[b] (95%CI)	P value[b]	OR[c] (95%CI)	P value[c]
20's	Always seek a sun tan	126	196	Ref	-	Ref	-	Ref	-
	Wear very little	168	277	1.060 (0.789-1.423)	0.699	1.008 (0.745-1.364)	0.957	0.941 (0.684-1.293)	0.706
	Wear normal summer clothing	480	782	1.047 (0.815-1.346)	0.718	1.084 (0.838-1.403)	0.537	1.006 (0.766-1.322)	0.966
	Try to cover up from the sun or did not spend time outdoors at all	53	101	1.225 (0.821-1.829)	0.321	1.312 (0.871-1.977)	0.194	1.221 (0.782-1.907)	0.380
30's	Always seek a sun tan	73	117	Ref	-	Ref	-	Ref	-
	Wear very little	151	281	1.161 (0.816-1.653)	0.407	1.160 (0.808-1.665)	0.420	1.126 (0.770-1.646)	0.542
	Wear normal summer clothing	531	828	0.973 (0.712-1.329)	0.863	1.017 (0.739-1.400)	0.917	0.988 (0.704-1.387)	0.946
	Try to cover up from the sun or did not spend time outdoors at all	69	130	1.176 (0.778-1.777)	0.443	1.260 (0.825-1.923)	0.285	1.147 (0.725-1.813)	0.559
40's	Always seek a sun tan	48	76	Ref	-	Ref	-	Ref	-
	Wear very little	125	206	1.041 (0.681-1.591)	0.853	1.074 (0.696-1.657)	0.747	1.177 (0.746-1.855)	0.484
	Wear normal summer clothing	540	848	0.992 (0.680-1.446)	0.966	1.040 (0.707-1.529)	0.842	1.100 (0.733-1.651)	0.645
	Try to cover up from the sun or did not spend time outdoors at all	112	225	1.269 (0.828-1.944)	0.274	1.273 (0.823-1.969)	0.278	1.322 (0.831-2.103)	0.239
Last 5 Years	Always seek a sun tan	41	70	Ref	-	Ref	-	Ref	-
	Wear very little	90	145	0.944 (0.592-1.505)	0.808	0.994 (0.618-1.600)	0.982	1.110 (0.676-1.825)	0.679
	Wear normal summer clothing	453	732	0.946 (0.633-1.416)	0.789	1.020 (0.676-1.538)	0.925	1.066 (0.692-1.640)	0.773
	Try to cover up from the sun or did not spend time outdoors at all	240	390	0.952 (0.627-1.445)	0.817	1.091 (0.712-1.670)	0.690	1.075 (0.686-1.685)	0.753

[a]Unadjusted regression model
[b]Age-adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, family history of cancer and skin colour

9.4.7 Frequency using suntan cream while spent time outdoor

The results are shown in Table 9-25 page 9-200, Table 9-26 page 9-201, Table 9-27 page 9-201 and Table 9-28 page 9-202). For frequency of suntan cream usage at age 20's, 30's, 40's and last 5 years, there appear to be higher proportion of control group reporting using suntan cream as 'always' or 'sometimes', while cases use suntan cream rarely or never compared to control group.

Chi-square test however did not show statistically significant difference in the distribution of cases and controls.

P for trend was only statistically significant at age 20's (p value of **0.027,** Table 9-25) and marginally non-significant p=0.052 during the last 5 years (Table 9-28), while at age 30's and 40's, there is no trend across categories (p=0.253 and 0.148 respectively Table 9-26 and Table 9-27).

Table 9-25 Frequency using suntan cream when outdoor at age 20's

Suntan cream usage	Group		Total
	Control	Case	
	%	%	%
Always	60	72	132
	7.3%	5.3%	6.1%
Sometimes	313	483	796
	38.0%	35.7%	36.6%
Rarely	253	438	691
	30.7%	32.4%	31.7%
Never	198	360	558
	24.0%	26.6%	25.6%
Total	824	1353	2177
	100.0%	100.0%	100.0%

Chi-square test, p=0.124

Table 9-26 Frequency using suntan cream when outdoor at age 30's

Suntan cream usage	Group		
	Control	Case	Total
	%	%	%
Always	108	162	270
	13.2%	11.9%	12.4%
Sometimes	346	576	922
	42.1%	42.4%	42.3%
Rarely	217	335	552
	26.4%	24.7%	25.3%
Never	150	284	434
	18.3%	20.9%	19.9%
Total	821	1357	2178
	100.0%	100.0%	100.0%

Chi-square test, p=0.384

Table 9-27 Frequency using suntan cream when outdoor at age 40's

Suntan cream usage	Group		
	Control	Case	Total
	%	%	%
Always	182	288	470
	22.1%	21.2%	21.6%
Sometimes	354	554	908
	43.1%	40.9%	41.7%
Rarely	162	278	440
	19.7%	20.5%	20.2%
Never	124	236	360
	15.1%	17.4%	16.5%
Total	822	1356	2178
	100.0%	100.0%	100.0%

Chi-square test, p=0.454

Table 9-28 Frequency using suntan cream when outdoor in last 5 years

Suntan cream usage	Group		Total
	Control	Case	
	%	%	%
Always	290	440	730
	35.3%	32.9%	33.8%
Sometimes	300	472	772
	36.5%	35.3%	35.8%
Rarely	124	209	333
	15.1%	15.6%	15.4%
Never	108	216	324
	13.1%	16.2%	15.0%
Total	822	1337	2159
	100.0%	100.0%	100.0%

Chi-square test, p=0.237

The results of the association between prostate cancer risks and different suntan cream usage habits at each decade of life are shown in Table 9-29 page 9-203.

At age 20's, the estimated risks derived from univariate, age-adjusted and fully adjusted models were statistically significant. Subjects who reported 'always' use suntan cream were at 38% risk reduction when compared with subjects who reported 'never use' suntan cream. Subjects who reported use of suntan cream 'sometimes' was at 26% prostate cancer risk reduction.

At age 30's, only subjects who used suntan cream 'sometimes' were at 42% risk reduction (OR of fully adjusted model 0.762, 95%CI: 0.582-0.997).

At age 40's, the results showed that 'always' and 'sometimes' category was inversely associated with prostate cancer risk (OR 0.678, 95% CI 0.490-0.936 and OR 0.740, 95% CI 0.555-0.986, respectively)

In last 5 years, the results also suggested that 'always' and 'sometimes' category was inversely associated with prostate cancer risk (OR 0.613, 95% CI 0.449-0.837 and OR 0.632, 95% CI 0.465-0.861, respectively).

Table 9-29 Odds ratios and 95% Confidence Interval of Suntan cream frequency use at age 20's, 30's, 40's and last 5 years on Prostate Cancer Risk

Age	Suntan cream frequency use	Control	Cases	OR[a] (95%CI)	P value[a]	OR[b] (95%CI)	P value[b]	OR[c] (95%CI)	P value[c]
20's	Never	198	360	-Ref-		-Ref-		-Ref-	
		24.0%	26.6%						
	Always	60	72	**0.660**	**0.034**	**0.539**	**0.002**	**0.615**	**0.022**
		7.3%	5.3%	**(0.450-0.969)**		**(0.362-0.800)**		**(0.405-0.934)**	
	Sometimes	313	483	0.849	0.152	**0.719**	**0.006**	**0.742**	**0.020**
		38.0%	35.7%	(0.678-1.062)		**(0.570-0.908)**		**(0.578-0.953)**	
	Rarely	253	438	0.952	0.679	0.867	0.243	0.896	0.399
		30.7%	32.4%	(0.755-1.201)		(0.682-1.102)		(0.693-1.157)	
30's	Never	150	284	-Ref-		-Ref-		-Ref-	
		18.3%	20.9%						
	Always	108	162	0.792	0.146	**0.594**	**0.002**	0.707	0.053
		13.2%	11.9%	(0.579-1.084)		**(0.428-0.824)**		(0.497-1.004)	
	Sometimes	346	576	0.879	0.290	**0.723**	**0.010**	**0.762**	**0.048**
		42.1%	42.4%	(0.693-1.116)		**(0.563-0.927)**		**(0.582-0.997)**	
	Rarely	217	335	0.815	0.126	**0.746**	**0.033**	0.849	0.267
		26.4%	24.7%	(0.628-1.059)		**(0.570-0.977)**		(0.636-1.133)	
40's	Never	124	236	-Ref-		-Ref-		-Ref-	
		15.1%	17.4%						
	Always	182	288	0.831	0.206	**0.617**	**0.002**	**0.678**	**0.018**
		22.1%	21.2%	(0.625-1.107)		**(0.457-0.833)**		**(0.490-0.936)**	
	Sometimes	354	554	0.822	0.133	**0.679**	**0.004**	**0.740**	**0.040**
		43.1%	40.9%	(0.637-1.061)		**(0.521-0.886)**		**(0.555-0.986)**	
	Rarely	162	278	0.902	0.486	0.818	0.190	0.923	0.625
		19.7%	20.5%	(0.674-1.206)		(0.605-1.105)		(0.669-1.273)	
Last 5 Years	Never	108	216	-Ref-		-Ref-		-Ref-	
		13.1%	16.2%						
	Always	290	440	**0.759**	**0.049**	**0.599**	**<0.001**	**0.613**	**0.002**
		35.3%	32.9%	**(0.577-0.998)**		**(0.449-0.798)**		**(0.449-0.837)**	
	Sometimes	300	472	0.787	0.084	**0.626**	**0.001**	**0.632**	**0.004**
		36.5%	35.3%	(0.599-1.033)		**(0.471-0.833)**		**(0.465-0.861)**	
	Rarely	124	209	0.843	0.295	0.726	0.059	0.777	0.165
		15.1%	15.6%	(0.612-1.161)		(0.521-1.012)		(0.545-1.109)	

[a]Unadjusted regression model
[b]Age-adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, family history of cancer and skin colour

9.4.8 Scoring Method for Vitamin D towards association with prostate cancer risk

Table 9-30 page 9-205 shows the results of analysis of the proposed scoring method for prostate cancer risk. The total scoring of individual subject were based on study subjects' characteristics of their skin, reaction to sun, as well as amount of exposure to sunlight, protection habits using clothes, suntan cream and Vitamin D dietary intake of are true extraction from the database. However for age period of 20's, 30's and 40's total score did not take account of dietary vitamin D, due to data available only for last 5 years.

The results showed the distribution of cases and control group based on the scoring which has been regrouped into quartiles from lowest to highest score using controls' score as the reference. The results also display the odds ratios and regression modeling of univariate, age-adjusted and multivariate adjusted OR of the total score (possible amount of vitamin D production from sunlight and dietary intake) towards prostate cancer.

At age 20's, the total score based on 7 aspects as in Table 9-30 page 9-205, showed all quartiles of higher score (Q2, Q3 and Q4) gave statistically significant protective risk odds ratios when compared to lowest score quartile even at multivariate-adjusted regression model with OR = 0.730 (95%CI: 0.544-0.981), 0.668 (95%CI: 0.516-0.864) and 0.740 (95%CI: 0.554-0.989) respectively. While at age 30's and 40's, only the 3rd and 4th quartiles showed statistically significant but still reduced risk for prostate cancer. As for the last 5 years, at multivariate-adjusted models, odds ratios were not statistically significant.

Chi-square test at 20's, 30's, 40's and last 5 years are 0.007, 0.029, 0.006 and 0.337 respectively, while P for trend at 20's, 30's, 40's and last 5 years are 0.006, 0.005, 0.002 and 0.103 respectively.

Table 9-30 Odds ratios and 95% CI Skin & Sunshine Score at age 20's, 30's, 40's and last 5 years on Prostate Cancer Risk

Age	Quartile (Total Score)	Control	Cases	OR[a] (95%CI)	P value[a]	OR[b] (95%CI)	p value[b]	OR[c] (95%CI)	p value[c]
20's	Q1 (16 and below)	244 35.1%	483 43.2%	-Ref-	-	-Ref-	-	-Ref-	-
	Q2 (17)	125 18.0%	176 15.8%	**0.711 (0.540-0.938)**	**0.016**	**0.745 (0.560-0.990)**	**0.043**	**0.730 (0.544-0.981)**	**0.037**
	Q3 (18 - 19)	195 28.1%	263 23.5%	**0.681 (0.536-0.867)**	**0.002**	**0.673 (0.525-0.863)**	**0.002**	**0.668 (0.516-0.864)**	**0.002**
	Q4 (20 and above)	131 18.8%	195 17.5%	**0.752 (0.574-0.985)**	**0.038**	**0.742 (0.562-0.980)**	**0.035**	**0.740 (0.554-0.989)**	**0.042**
30's	Q1 (16 and below)	237 34.2%	450 40.3%	-Ref-	-	-Ref-	-	-Ref-	-
	Q2 (17)	117 16.9%	200 17.9%	0.900 (0.682-1.188)	0.457	0.928 (0.697-1.235)	0.607	0.957 (0.711-1.287)	0.770
	Q3 (18 - 19)	204 29.5%	278 24.9%	**0.718 (0.565-0.912)**	**0.007**	**0.719 (0.562-0.921)**	**0.009**	**0.700 (0.541-0.905)**	**0.006**
	Q4 (20 and above)	134 19.4%	190 17.0%	**0.747 (0.569-0.980)**	**0.035**	**0.715 (0.540-0.945)**	**0.019**	**0.725 (0.540-0.972)**	**0.032**
40's	Q1 (16 and below)	252 36.7%	470 42.5%	-Ref-	-	-Ref-	-	-Ref-	-
	Q2 (17)	96 14.0%	185 16.7%	1.033 (0.773-1.381)	0.825	1.093 (0.810-1.474)	0.561	1.081 (0.793-1.472)	0.623
	Q3 (18 - 19)	207 30.1%	274 24.8%	**0.710 (0.560-0.899)**	**0.005**	**0.691 (0.541-0.882)**	**0.003**	**0.675 (0.523-0.870)**	**0.002**
	Q4 (20 and above)	132 19.2%	178 16.1%	**0.723 (0.551-0.949)**	**0.020**	**0.704 (0.532-0.932)**	**0.014**	**0.696 (0.518-0.936)**	**0.016**
Last 5 Years*	Q1 (18 and below)	149 31.5%	301 36.2%	-Ref-	-	-Ref-	-	-Ref-	-
	Q2 (19-20)	120 25.4%	198 23.8%	0.817 (0.605-1.102)	0.186	0.800 (0.589-1.085)	0.151	0.791 (0.575-1.087)	0.148
	Q3 (21-22)	113 23.9%	193 23.2%	0.845 (0.624-1.146)	0.279	0.847 (0.622-1.154)	0.293	0.801 (0.580-1.107)	0.179
	Q4 (23 and above)	91 19.2%	139 16.7%	0.756 (0.544-1.051)	0.096	0.754 (0.539-1.054)	0.098	0.780 (0.549-1.108)	0.166

[a]Unadjusted regression model
[b]Age-adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, and family history of cancer
*Include score for dietary intake of Vitamin D

9.5 Discussion

9.5.1 Skin Complexion

The result did not show any differences in the types of skin complexion between cases and controls. There is no available statistics to compare the findings. Based on the study findings, types of skin complexion of oily, dry or combination when compared with normal complexion did not give any statistical significance odds ratio with prostate cancer risk (refer Table 9-5 page 9-183).

9.5.2 Skin Colour

'Medium' skin colour is the median skin colour in this study and 'fair' skin colour come as second most common skin colour among our study subjects who are majority 'White' in ethnic group (approximately 97%) (Refer Table 9-6 and page 9-184). Our findings are in agreement with a study on self reporting phototype versus physician diagnosed skin phototype (Chan *et al*, 2005a). Subjects who are 'white' subjects mostly rated themselves as 'medium', whilst physicians as the 'gold standard' scored them as 'fair' skin phototype.

Chen and colleagues studied whether skin colour correlates well with race or ethnic group (Chan *et al*, 2005a). Skin phototype is best characterised by physician when correlating with race. The higher correlation was observed at $r=0.55$ ($p<0.01$) as compared to subjects' self reported skin phototype at $r=0.28$ ($p<0.01$). Association between skin colour and race didn't show much correlation among 'whites' at correlation, $r=0.40$, however associations between race and skin phototype is better with darker skin colour at $r=0.60$.

The study results did not show any statistically significant difference in the characteristics of skin colour between cases and control group. Similarly odds ratio value and confidence intervals for logistic regression models for skin colour did not reveal any association with prostate cancer (refer Table 9-7 page 9-185).

9.5.3 Sun effect reaction on skin

Due to non-statistically significant findings earlier in the association between skin colour and prostate cancer risk, we expected that sun effect reactions on skin between cases and control group should also be not statistically significant, because susceptibility to sunburn in sunlight and tanning ability is based on skin phototype as explained earlier in Table 9-1, page 9-172. The association between prostate cancer and different types of sun effect reaction on skin, the odds ratios in logistic regression were not equally statistically significant (refer Table 9-9 page 9-187).

9.5.4 Outdoor sunlight exposure while working

With progression of age, it was observed less proportion of subjects of both cases and control spent outdoor for 5 hours or more while working, starting at 21% at age 20s to 15% in the last 5 years (refer Table 9-10 page 9-188, Table 9-11 page 9-189, Table 9-12 page 9-189, and Table 9-13 page 9-190). There was however no statistical significant difference in the proportion of number of hours with outdoor sunlight while at work between cases and control group from age 20's to 40's or even last 5 years. Regression models as shown in Table 9-14 page 9-191, upon full multivariate adjusted did not show any statistical significant finding.

The study results did not agree with most studies in the literature. Other studies reported sunlight as beneficial in reducing prostate cancer risk (Bodiwala *et al*, 2003a; Bodiwala *et al*, 2003b; John *et al*, 2004; Rukin *et al*, 2007). One point to be made is that our study cannot be compared with other studies because we look at specific amount of sunlight exposure during work while most studies combined both work and recreational sunlight exposure when reporting the results.

However, John et al whose study was based on cohort subjects in National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study in United States, managed to stratified small sample of 161 prostate cancer cases and 3367 control subjects among non-Hispanic white men for occupational self reported occupational sun exposure obtained non-statistical significant difference in prostate cancer risk between those had occasional or frequent sunlight exposure at work to those who had none or rare exposure (John *et al*, 2007).

The strength of our study although did not show any significant findings is to identify specific purpose of sunlight exposure i.e. work or recreational, that would have affect on prostate cancer risk. Our study also would be able to study at the types of occupation which requires greater outdoor exposure of sunlight compared to those who are more incline to stay indoor or office type of occupation, in association with prostate cancer risk, although in this case no association was seen between sunlight exposure while working and prostate cancer risk.

9.5.5 Outdoor sunlight exposure while not working

The results suggested that control group spent longer hours (3 hours or more categories) outdoor on non-working or recreational, compared to case group (refer to Table 9-17 page 9-193 and Table 9-18 page 9-194). P for trend also was significant at $p<0.001$ in all age decades at 20's, 30's, 40's and last 5 years.

History of sunlight exposure during non working time has shown to be associated with prostate cancer risk throughout age decades at 20's, 30's, 40's and last 5 years with exception for multivariate adjusted model at age 30's for exposure of '1-2 hours' (refer Table 9-19 page 9-195).

The multivariate adjusted odds ratios for prostate cancer were all of reduction risk at $OR<1.0$ across all age categories with highest reduction risk in category of exposure to sunlight at non-working of '5 hours or more' when compared with lowest category of 'less than 1 hour' as reference. The multivariate adjusted OR values for age 20's, 30's, 40's and last 5 years for '5 years or more' of sunlight exposure while not working are 0.534 (95%CI: 0.345-0.828), 0.469 (95%CI: 0.298-0.736), 0.469 (95%CI: 0.302-0.728), and 0.380 (95%CI: 0.256-0.565) respectively when compared to lowest amount of hours category.

The study findings are in keeping with several other studies that compared the highest and lowest category amount of ultraviolet radiation or sunlight exposure (Bodiwala *et al*, 2003a; Bodiwala *et al*, 2003b; John *et al*, 2004; John *et al*, 2007; Rukin *et al*, 2007). In Bodiwala case-control study with 453 cases and 312 control subjects using mean hours cumulative exposure, age-adjusted odds ratio was 0.999 (95%CI: 0.999-1.000), p=0.0001 (Bodiwala *et al*, 2003a). Another separate case-control study by Bodiwala on 212 cases and 135 controls showed

estimated risk of 0.998 (95%CI: 0.997-0.999) when mean weeks cumulative exposure was used (Bodiwala *et al*, 2003b).

Rukin performed a case-control study on 528 prostate cancer patients and 365 control subjects using the measurements of average of daily exposure, weekday exposure and weekend exposure to sunlight also obtained protective risk against prostate cancer at age and skin type adjusted odds ratios of 0.78 (95%CI: 0.72-0.85), 0.85 (95%CI: 0.80-0.91) and 0.79 (95%CI: 0.73-0.86) respectively (Rukin *et al*, 2007). John et al using a cohort subjects in United States of 161 prostate cancer cases and 3367 control subjects among non-Hispanic white men only obtained statistically significant protective age-adjusted relative risk of RR=0.47 (95%CI: 0.23-0.99) for fatal prostate cancer (John *et al*, 2007).

9.5.6 Protection habits while outdoor under the sun

There was no statistically significant difference in the protection habits while outdoor under the sun between cases and control group (refer Table 9-20 page 9-196, Table 9-21 page 9-197, Table 9-22 page 9-197 and Table 9-23 page 9-198). The trends of characteristics of both groups subjects' protection habits change gradually as they aged from less protection categories: 'always seek a sun tan' or 'wear very little'; to more of some amount of protection from the sun: 'wear normal summer clothing' or 'try to cover up from the sun'. The bulk of the subjects remained within the middle category of 'wear normal summer clothing'.

Our study finds this protection habit is of importance because it could be a potential confounder or could affect the relationship between the amounts of sunlight exposure on the skin for Vitamin D production in the human body. In most studies, the types of protection used against the sun especially outdoor exposure of hot summer sun, were not considered when trying to quantify the actual amount of sunshine that reach the skin. In true calculation, when wearing protective clothing, only face, neck, hands are exposed to direct sunlight or ultraviolet radiation to produce vitamin D for association studies to prostate cancer risk. Some studies uses habits of sunbathing in order to justify true measurement of higher sunlight or ultraviolet radiation to prostate cancer risk (Bodiwala *et al*, 2003a; Bodiwala *et al*, 2003b; John *et al*, 2007; Luscombe *et al*, 2001).

Since our analysis on the protection habits when outdoor did not find any statistical significant difference between cases and control group (refer Table 9-24

page 9-199, we assumed that this factor may have an overall same effect on both groups and may not be a strong confounder when trying to associate the relationship of sunlight exposure whether at work or non-working outdoor towards prostate cancer risk.

9.5.7 Frequency using suntan cream while outdoor

The frequency of suntan cream usage of 'always' or 'sometimes' at age 20's, 30's, 40's and last 5 years, seems higher proportion among control group, while case group has more proportion than control to likely use suntan cream 'rarely' or 'never'. Chi-square test however did not detect statistically significant difference in the proportion.

P for trend for odds ratio of prostate cancer risk was found to be only statistically significant at p=0.027 for age 20's.

The regression modelling for suntan cream usage to prostate cancer risk (refer Table 9-29 on page 9-203) revealed that subjects who 'always' use suntan cream when outdoor at 20's, 40's and during the last 5 years were at reduce prostate cancer risk in comparison with those who 'never' use suntan cream. Those in category of 'sometimes' used of suntan cream was found to have statistically significant reduction in prostate cancer risk in age-adjusted and multivariate adjusted regression models at all age decades.

The direction of the findings of this analysis seems to point out that higher frequency usage of suntan cream or lotion would result in lower risk of prostate cancer. Suntan cream lotion containing SPF (Sun-protection factor) is used to delay skin erythemal reaction induced by solar radiation. Habits of usage of suntan cream have been associated with increase duration in recreational sun exposure as shown in a double blind randomized trial (Autier *et al*, 1999). Therefore, suntan cream usage can be used as a proxy measurement or surrogate marker for sunlight exposure, to correlate the likelihood amount of sun exposure mainly for recreational activities such as sunbathing or just outdoor activities of non-working.

One limitation in our study is that we were not able to define the types of suntan cream that was use throughout the different age period, as by stratifying the groups, we would have a better picture whether suntan cream of higher SPF (sun-protection factor) i.e. SPF-30 versus SPF-15 would differ in its association

with prostate cancer risk. SPF-30 with higher UV block could resulted lower production of Vitamin D from sunlight and in our hypothesis cause a non-statistically significant association with lower risk of prostate cancer, when compared with those using lower SPF suntan cream.

In summary, in coherent with biological plausibility, the higher amount of suntan cream usage, resulting higher exposure to the outdoor sunlight or ultraviolet radiation to the skin, as discussed earlier would then resulted in higher vitamin D production and could explain the protective risk from prostate cancer found in this study.

9.5.8 Scoring Method for Total Vitamin D towards association with prostate cancer risk

The findings indicative of higher production of vitamin D from sunlight and skin and dietary intake (based on total scoring method), is associated with protective or reduced odds ratio and especially appears stronger at early stage in life (age 20's), followed by age 30's and 40's scoring (where only the two highest quartile obtained statistically significant protective odds ratios). For the last 5 years, the results were no longer significant. The findings suggested that vitamin D exposure earlier in life is protective against prostate cancer.

This study attempted to investigate all factors involving the source of vitamin D from ultraviolet light or sunlight exposure by exploring different aspects of factors that could affect the actual amount of Vitamin D produced by skin. The ideas were based on current knowledge and on literature review of available scientific articles and books, as well as current understanding of the factors that could account for production of Vitamin D by skin. The current evidence show sunlight provides protective against risk for prostate cancer when compared to those with lower exposure of sunlight (Bodiwala *et al*, 2003a; Bodiwala *et al*, 2003b; Freedman *et al*, 2002; John *et al*, 2004; John *et al*, 2007; Luscombe *et al*, 2001; Rukin *et al*, 2007; Schwartz & Hanchette, 2006). Meta-analysis by Gilbert et al concluded the limited support for the protective effect of sunlight to prostate cancer. The author mentioned in their article that heterogeneity between studies could not be tested due to small numbers of studies leading to weak association or null results (Gilbert *et al*, 2009).

Although the analysis of each isolated factor showed 'non-working sunlight exposure' and 'suntan cream usage' to be statistically significantly associated with prostate cancer risk, the other factors also involved in vitamin D production did not show any statistically significant. These factors have been described in detail on basis of biological plausibility existed in current knowledge therefore should be included to provide the bigger picture of potential vitamin D production.

The applied scoring method using the characteristics of skin complexion, color, reaction to prolonged sunlight, amount of sunlight exposure at work and while non-working, cloth protection from sun habits, frequency of using suntan cream and dietary vitamin D intake were able to provide coherent understanding of the relationship between productions of vitamin D in association with prostate cancer. The study, however, had a limitation of applying score from diet at various stages in life, other than the last 5 years.

The strength of scoring method includes firstly, the study places together all characteristics of skin and amount of sunlight exposure which are both important components in the production of vitamin D of non-diet origin, and maybe predictive of amount of production of vitamin D by human body. Although dietary intake vitamin D is vital, it only contributes 10% of Vitamin D (Gillie, 2006).

Secondly, measurement of circulating vitamin D in human may not be reliable (Ahn *et al*, 2008; Barnett *et al*, 2010; Park *et al*, 2010) when studying exposure of sunlight at different age period and the cumulative effect towards prostate cancer risk thus surrogate score can be used as alternative.

Thirdly, the proposed scoring model could provide prediction to an individual of prostate cancer risk, provided that the data is analyzed as a population sample and caution to be made when the model is applied to different region latitude, because location further from equator would provide lesser exposure from sunlight (John *et al*, 2004; John *et al*, 2007) and similarly climate or cloudy condition. However this is the first study proposed to use the scoring model and could be applied in geographical and climate area similar to the UK and its population.

9.6 Conclusions & Recommendations

In conclusion, this study showed that greater time of non-working outdoor exposure is associated with reduced prostate cancer risk. Higher frequency of usage of suntan cream is also associated with lower risk of prostate cancer compared to those who never applied cream when exposed to the sun. This may reflect amount of sunlight or ultraviolet radiation exposure.

To strengthen the study the association between vitamin D and prostate cancer risk, diet component of food containing dietary intake of vitamin D through various stages in life should be taken into account when calculating the risk.

There's a need to improve further on how to best to assess the actual hours of under the sun and not just outdoor per se and this should be addressed in the questionnaires, so as to get the closest amount of hours of actual sunlight exposure daily average. Further details of history of sunbathing and holidays in tropical country with details of duration accumulative should be collected.

Chapter 10 Diet Isoflavones (Phytoestrogens), Selenium, Vitamin D and Lycopene

10.1 Literature Review

10.1.1 Isoflavones (Phytoestrogens) and Prostate Cancer

Phytoestrogens defined by Ganry as estrogenic compounds found in plant food and broadly classified as isoflavones (e.g. genistein, diadzein, glycitein etc), lignans (e.g. enterolactone), flavonoids (e.g. quercetin, kaempferol) and coumenstans (sometimes classified under isoflavones). Isoflavonoids are found in soybean and soy products, while coumenstans in sprouts and beans. Lignans are found in seeds, whole grain cereals, berries etc, while flavonoids are high in fruits and vegetables such as apples, pears and onions (Ganry, 2005). Soy foods have been subject of considerable investigations since 1960s due to its potential health effects of soy isoflavones (Hsu *et al*, 2010).

Isoflavonoids phytoestrogens such as genistein, daidzein and glycitein, showed similarities structure with mammalian estrogens and have been most extensively studied. They have weak estrogenic activity and can interfere intracellular steroid metabolism (Adlercreutz, 2002). Phytoestrogens can therefore act as estrogen agonists and antagonists competing for estradiol at the receptor complex ERβ (Bingham *et al*, 1998).

In vitro study. it is suggested that genistein's mechanism of action reducing cell viability that induces apoptosis of prostate cancer cell lines indirectly inhibit cell growth, while control of tyrosine kinase phosphorylation has also been described (Kyle *et al*, 1997). However there is possibility that isoflavones have a biphasic effects, at low dose promote cell growth but at higher doses inhibit growth (Zhang *et al*, 2003).

In vivo studies involving mice also showed growth inhibition and increase apoptosis in LNCaP prostate cancer cell xenografts (Bylund *et al*, 2000; Rice *et al*, 2002). Genistein of isoflavones, also inhibits the activity of 5-alpha-reductase, an

enzyme required for androgen synthesis, such as testosterone which plays a role in prostate cancer cells growth (Evans *et al*, 1995). Similarly isoflavone rich soy protein isolate was found to suppress androgen receptor expression, which could benefit in preventing prostate cancer (Hamilton-Reeves *et al*, 2007).

Several case control studies have confirmed the beneficial protective effects of isoflavones dietary intake towards prostate cancer risk. Lee study in Chinese population of 133 cases and 265 controls found isoflavones genistein of highest versus lowest quartile intake, had Odds ratio of0.53(95%CI: 0.29-0.97) (Lee *et al*, 2003), while Nagata in Japanese population of 200 cases and 200 controls showed similar protective effect with Odds ratio of 0.42 (95%CI: 0.24-0.72)(Nagata *et al*, 2007). When soy food or soy products such as tofu was used to represent isoflavone intake, reduced odds ratios also were observed in Lee's study at OR 0.51 (95%CI: 0.28-0.95) and 0.58 (95%CI: 0.35-0.96) respectively (Lee *et al*, 2003). Another study in multiethnic population of USA and Canada, demonstrated reduced OR 0.62 (95%CI: 0.44-0.89) for groups with highest soy food intake compared to lowest quintile (Kolonel *et al*, 2000). Heald who used Scottish population, obtained protective odds ratio of 0.52 (95%CI: 0.30-0.91) when comparing those who consumed soy food and those who do not (Heald *et al*, 2007). One cohort study also described reduction in relative risk for prostate cancer among intake of soymilk more than once a day compared to never at RR= 0.3 (95%CI: 0.1-0.9) (Jacobsen *et al*, 1998).

However there is a study which showed increased risk of prostate risk such as case control study by Jian et al in southeast Chinese population of 130 cases and 274 controls, with OR=2.02 (95%CI: 1.08-3.78) when taking fermented soy products at highest compared to lowest tertile (Jian *et al*, 2004).

Other studies did not show any statistically significant association towards prostate cancer for isoflavones intake (Heald *et al*, 2007) or soy products (Nomura *et al*, 2004; Sonoda *et al*, 2004).

Several studies used serum phytoestrogens or isoflavones level instead of using diet FFQ when determining their association with prostate cancer. Ozasa who did validity study to compare the dietary habits and serum phytoestrogens found that

serum isoflavones genistein and daidzein was statistically significant correlation with the baseline dietary intake of soy tofu (Ozasa *et al*, 2005). Higher quintile serum isoflavone genistein was found to have lower relative risk at RR 0.71 (95%CI: 0.53-0.96) in the European population (Travis *et al*, 2009), but serum/plasma isoflavones was not statistically significantly associated with prostate cancer other studies (Kurahashi *et al*, 2008; Ward *et al*, 2008).

Similarly urinary isoflavones excretion has also been validated as a biomarker on its significant correlation with dietary intake of soy protein (Maskarinec *et al*, 1998). Park found higher level of urinary excretion level of isoflavones daidzein and genistein were associated with reduced odds ratio when compared with the lowest quintile (Park *et al*, 2009).

10.1.2 Selenium and Prostate cancer

Selenium is an essential micronutrient trace element for human and the amount in diet depends on the soil of the region where the plants and animals come from (Nadiminty & Gao, 2008). Selenium first entered the food chain from soil to the plants (Rayman, 2008). Large variations in content of selenium in food are determined by geological or environmental factors, supplementation of selenium in fertilizers or animal feed, as well as absorption (Fairweather-Tait *et al*, 2010; Rayman, 2008). Bioavailability issue has been brought up in much study due to complex metabolic transformation to biological active metabolites (Fairweather-Tait, 1997; Fairweather-Tait *et al*, 2010; Finley, 2006; Levander, 1987). Glutathione peroxidase (GPx) activity and tissue selenium has been used as criteria to study bioavailability. Absorption of selenium of all forms would vary according to selenium status of subject. Wheat and meats have high bioavailability, and fish have relatively high content of selenium but may have lower bioavailability (Finley, 2006). Selenized yeast has been the primary form of selenium available for use as a dietary supplement.

Greater awareness of the importance of selenium was partly due to publication by Clark *et al.* of a randomized clinical trial on studying effects of selenium supplementation for cancer prevention in patients with skin carcinoma in USA. Although selenium treatment did not reduce incidence of basal cell or squamos cell carcinoma, the secondary end point results showed reduction total cancer

deaths and incidence among those in the selenium group including prostate cancer.

Several mechanisms have been suggested to explain the function of selenium as anti-cancer. Nadiminty and Gao in their review stated specific mechanisms for prostate cancer are inhibition of AR (androgen receptor) signalling, reduction in the mRNA, and protein levels of androgen receptor, recruitment of corepressors to the AR elements in the promoters of androgen responsive genes, inhibition of signalling pathways like NF-kB, IL-6, Stat3 and induction of apoptosis. Selenoproteins has also been associated with prostate cancer cells expression and progression (Nadiminty & Gao, 2008).

Evidence on selenium and prostate cancer risk indicate mixed findings. Studies using nested case-control design and measurement of serum selenium are most common. Among these, some have shown inverse relationship of selenium and prostate cancer risk. Li et al obtain OR =0.52 (95%CI: 0.28-0.98) when comparing the highest quintile level of plasma selenium to the lowest of 586 cases and 577 control, of advanced prostate cancer risk in Physicians' Health Study population (Li *et al*, 2004). Nomura study of 249 cases and 249 matched controls revealed OR 0.5 (95%CI: 0.3-0.9) which compare with highest quartile and lowest serum selenium level, with more notable for advanced prostate cancer as well (Nomura *et al*, 2000). Pormand obtained reduced odds ratio of 0.16 (95%CI: 0.06-0.47) in Iran (Pourmand *et al*, 2008), while Gill study population of 467 cases and 936 controls obtained OR value 0.59 (95%CI: 0.38-0.93) when comparing serum selenium in the highest tertile to the lowest (Gill *et al*, 2009).

However there are also many studies which did not show any association between selenium and prostate cancer risk. These include case-control studies (Allen *et al*, 2008; Allen *et al*, 2004; Peters *et al*, 2007a; Peters *et al*, 2008; Zhang *et al*, 2009), cohort study (Hartman *et al*, 1998) or randomized control trials (Kristal *et al*, 2010; Lippman *et al*, 2009). Toenail selenium was also used as marker of selenium in the body (Allen *et al*, 2004; Brinkman *et al*, 2006), however not many studies used dietary questionnaire to assess selenium intake in association with prostate cancer.

None of the studies from the literature showed that selenium increases prostate cancer risk.

10.1.3 Vitamin D and Prostate cancer

Major source of Vitamin D comes from human's skin exposure to sunlight ultraviolet ray (Schwartz, 2005) with smaller contribution from dietary intake. Vitamin D content in food is rare. Due to concern of skin cancer, many have avoided direct sun exposure and they would depend on Vitamin D from dietary sources. Vitamin D in food mainly comes from oily fish such as salmon. However fortified dairy products with vitamin D are available in US and Canada, such as milk, while in Europe, margarine is normally fortified (Chen *et al*, 2007). Supplementary form of vitamin D i.e. Calciferol is also available (Giovannucci, 1998).

The active form of Vitamin D as 1,25 $(OH)_2D$ and 25(OH)D and their hypotheses mechanism of actions and its relationship to anti-cancer process has been explained earlier in the chapter on skin and sunlight of this thesis.

There are not many studies that studied the effects of vitamin D intake and prostate cancer risk. The case control study and cohort studies concluded non-statistically significance association (Park *et al*, 2007; Tavani *et al*, 2005a; Tseng *et al*, 2005). A meta-analysis done by Gilbert et al when conducting pooled random-effects odds ratio estimate per 1000 IU increase vitamin D intake was 0.83 (95%CI: 0.28-2.43) which is not statistically significant (Gilbert *et al*, 2011).

10.1.4 Lycopene and Prostate cancer

Lycopene is a type of carotenoid without provitamin A activity, present in fruits and vegetables. Tomato products including ketchup, tomato juice and pizza sauces are riches US diet at more than 80% for source of lycopene (Arab & Steck, 2000). However fruit such as watermelon, papaya and pink guava also contains lycopene. Lycopene from processed and cooked tomatoes was found to be more bioavailable than of fresh tomatoes (Gartner *et al*, 1997).

The hypothesis mechanism of action of lycopene on prostate cancer was through the mediation of endocrine factor of IGF-1 (Insulin-like Growth Factor-1) which

has been described by Wolk et al that elevated serum IGF-1 levels may be an important predictor of risk for prostate cancer (Wolk *et al*, 1998). Study by Mucci obtained result that consumption of cooked tomatoes was associated with inverse levels of IGF-1 with a mean reduction percentage of 31.5% (95%CI: 7.9% - 49.1%)(Mucci *et al*, 2001). Lycopene was also later found to inhibit IGF-1 signal transduction and growth in normal prostate epithelial cells by decreasing DHT (Dihydrotestosterone) modulated IGF-1 production in co-cultured reactive stromal cells (Liu *et al*, 2008).

The results on the association of serum, plasma or diet lycopene and tomato/tomato products intake towards prostate cancer risk have been of equivocal. Some case-control studies that used dietary intake reported reduction in prostate cancer risk (Jain *et al*, 1999; Jian *et al*, 2005; McCann *et al*, 2005; Norrish *et al*, 2000a). A cohort study was reported similar effect (Giovannucci *et al*, 2002). A number of studies that used plasma or serum level of lycopene as variable of interest towards prostate cancer risk also showed reduction odds ratios and relative risks when compared with lowest level category (Gann *et al*, 1999; Karppi *et al*, 2009; Key *et al*, 2007; Lu *et al*, 2001; Wu *et al*, 2004; Zhang *et al*, 2007).

However, there are articles that dshow non-statistically significant association between lycopenes, tomato/tomato products to prostate cancer (Beilby *et al*, 2010; Bosetti *et al*, 2004; Chang *et al*, 2005; Kirsh *et al*, 2006; Kristal *et al*, 2010; Kristal *et al*, 2011; Peters *et al*, 2007b).

10.2 Aim

The aim of this chapter is to investigate the relationship of specific components in diet and prostate cancer risk:

i. Isoflavones (Phytoestrogen)
ii. Selenium
iii. Vitamin D
iv. Lycopene

10.3 Method

Data on specific nutrient components were collected through the adaptation of the European Prospective Investigation into Cancer and Nutrition (EPIC) Food Frequency Questionnaire (FFQ). The validated FFQ was developed by Medical Research Council Dunn Nutritional Unit of Cambridge for UK, European Prospective Investigation of Cancer (EPIC) in Nutrition (Bingham, 1997b; Bingham *et al*, 1997a; Riboli, 1992). The EPIC FFQ was modified to be suitable for the retrospective case-control study. The questionnaire used in phase I of this study has been further expanded in Phase II. Additional items further to main Food Table include soy milk and spices, while in Vitamins & Supplements Table, saw palmetto, garlic, pomegranate, soy-based drink and tomato were added.

Subjects were asked to recall on their typical dietary in the last 5 years before prostate cancer diagnosis in the cases, or receiving questionnaire in the controls. The 130 food items were broadly categorized into:

i. Meat and fish
ii. Bread and savoury biscuits
iii. Cereals
iv. Potatoes, rice and pasta
v. Dairy products and fats
vi. Sweets and snacks
vii. Soups, sauces and spreads
viii. Fruits
ix. Vegetables
x. Drinks
xi. Milk
xii. Spices
xiii. Vitamins and supplements

The amount of food was indicated as medium serving size or in the units of slice or teaspoon. The average frequencies of intake for each food were measured by categorizing the answers (refer Table 10-1 page 10-221). Photographs examples of small, medium and large food portion were placed in the FFQ to aid the subjects in estimating portion size of medium as described by Ministry of Agriculture, Fisheries and Food (MAFF, 1993).

The FFQ questionnaire of this study has been used before in the UK population (Lophatananon *et al*, 2010; Muthuri, 2004; Muthuri, 2010).
Data included in all analyses here was obtained from both Phase I and phase II of the study.

10.4 Analysis

10.4.1 Calculation of nutrient daily intake

Daily intake of each specific nutrient was calculated by the nutritional software designed by the study teams. The calculation program was previously validated by comparing values of daily intake of all nutrients (from 10 randomly selected subjects from other study) derived from the program created by the study team to values derived from the EPIC calculation program by Cambridge group. The adjustments were made until the discrepancies of values between two calculations were less than 10%.

The calculation program includes sections for calculating nutrient intakes from EPIC FFQ, milk, cereal and Vitamins/supplement sections of the questionnaire. The algorithm was based on the equation below.

Total nutrient intakes (grams per day) =
*Portion size (amount consumed) x seasonality factor† x edible portion‡ x frequency of intake per day x nutrient** as percentage of all 130 food items*

*Where, † shows seasonal food availability and ‡ shows proportion of food edible

** The nutritional composition values for each food were derived from Ministry of Agriculture, Fisheries and Food composition tables (MAFF, 1993).

Frequency of each food was converted into daily value based on Table 10-1:

Table 10-1 Coding scheme for frequency of intake per day

Code	Frequency of intake (FFQ response)	Frequency of intake per day (value to replace)
1	Never or less than once/month	0.01
2	1 – 3 per month	0.07
3	Once a week	0.14
4	2 – 4 per week	0.43
5	5 – 6 per week	0.79
6	Once a day	1
7	2 – 3 per day	2.5
8	4 -5 per day	4.5
9	6+ per day	6.5

Total energy intake was calculated for each individual and was further used to adjust for the nutritional intake of the specific nutrient components such as Isoflavones, Selenium and Vitamin D (all measured in unit of μg) by the residual method as described and proposed by Willet (Willett, 1998). This residual method has also been applied in other studies (Bingham & Day, 1997c).

10.4.2 Data cleaning

Only subjects with total calorie intakes lay within two standard deviations were included in the analyses. This was done to exclude measurement bias due to extreme values or outlier.

Further data validation was done by comparing 'body shape of last 5 years' for individuals of low and high end total calorie. The lowest and highest individual total calorie intakes should be comparable of their body shape of severe thin or obese respectively. Any individual with incoherent between two variables were excluded from the analyses. The body shape variable has been described in detail in another chapter of this thesis.

From a total of 3,944 eligible subjects, 151 (3.83%) were excluded as outlier or not within the two standard deviation of the total calorie intake for individuals. From 3793 left, a further 21 subjects data were excluded from the analysis due to incomparable values of their total calorie intakes in the last 5 years diet history to their 'last 5 years body shape'. The final number of subjects' data eligible for diet analysis was 3772 (1815 cases and 1957 controls).

10.4.3 Nutrient analysis

SPSS version 17.0 was used to conduct statistical analysis and obtain odds ratios (OR) and confidence intervals through logistic regression. Each nutrient absolute intake was categorized into quartiles based on the distribution of energy-adjusted value of controls.

Since lycopene was not listed in the calculation program, Lycopene was analyzed separately by using frequency of intake of tomato (medium serving of 57g) and

tomato ketchup (medium serving of 30g). There were studies suggesting that tomato and tomato products such as tomato ketchup are good representatives as they are high in lycopene (Joanne M. Holden *et al*, 1999).

For selenium, estimated risks were calculated based on total daily intake from actual diet and vitamin supplement. The analyses were also conducted separately from these two selenium sources.

10.5 Results

10.5.1 Energy intake

The mean Total calorie intake for control subjects and cases were 2431.08 ± 2sd (18.17) and 2638.55± 2sd (21.57) respectively.

10.5.2 Isoflavone

The mean daily intake of total isoflavones in all study subjects is 1471.54 µg (standard deviation of 1.56 µg), or median 1471.55 µg (interquartile range 26.98 µg). Our study subjects' median value is higher than the median value obtained in an EPIC Norfolk arm in UK of average less than 1000 µg with interquartile range 390 to 820 µg which uses 7-day food diary method (Mulligan *et al*, 2007).

Table 10-2 Distribution of Isoflavone between cases and controls

Isoflavone Amount (µg)	Group		Total
	Control	Case	
	%	%	%
Q1 (<1470.84)	406	519	925
	25.0%	34.7%	29.7%
Q2 (1470.84-1471.70)	407	377	784
	25.1%	25.2%	25.1%
Q3 (1471.70-1472.45)	407	324	731
	25.1%	21.7%	23.4%
Q4 (≥1472.45)	403	275	678
	24.8%	18.4%	21.7%
Total	1623	1495	3118
	100.0%	100.0%	100.0%

Chi-square test p<0.001

The results showed higher proportion of cases as compared to controls in the first and the second quartile. The lowest proportion of cases was in the fourth or highest quartile. Chi-square test at p<0.001 suggested there is a statistically significant difference in the distribution of isoflavone intake between cases and controls.

The logistic regression results (Table 10-3 page 10-226) showed statistically significant odds ratio values in all models. In the fully adjusted model, the odds ratios value for 2nd, 3rd, and 4th quartile are 0.689 (95%CI: 0.563-0.843), 0.559 (95%CI: 0.455-0.688) and 0.464 (95%CI: 0.374-0.577) respectively. The P for

trend at $p<0.001$ also showed statistically significant trend of risk reduction across quartiles (as shown in Table 10-3).

Table 10-3 Odds Ratios and Confidence Intervals of Total Isoflavone Intake Amount Quartile and Prostate Cancer Risk

Isoflavone	Control	Case	Odds ratio[a] (95%CI)	P value[a]	Odds ratio[b] (95%CI)	P value[b]	Odds ratio[c] (95%CI)	P value[c]
Q1	406	519	Ref	-	Ref	-	Ref	-
Q2	407	377	**0.725 (0.599-0.877)**	**0.001**	**0.711 (0.587-0.861)**	**<0.001**	**0.689 (0.563-0.843)**	**<0.001**
Q3	407	324	**0.623 (0.512-0.757)**	**<0.001**	**0.597 (0.490-0.727)**	**<0.001**	**0.559 (0.455-0.688)**	**<0.001**
Q4	403	275	**0.534 (0.437-0.653)**	**<0.001**	**0.495 (0.404-0.607)**	**<0.001**	**0.464 (0.374-0.577)**	**<0.001**

[a]Calorie-adjusted regression model
[b]Age and calorie adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, family history of cancer and calorie
P for trend, p<0.001

10.5.3 Selenium

Total selenium mean daily intake in the study population is 52.12 μg (s.d. 8.38 μg). It is considered higher than the estimated selenium intake in the UK in 1997, although it has been suggested that the dietary selenium intakes in the UK has been falling over the last 20 years (Jackson *et al*, 2003). However it is still below the current UK reference nutrient intake (RNI- recommended amount of nutrient to prevent deficiency for different age group for UK population from Department of Health) for adult men at 75 μg per day (Department of Health, 1991; Jackson *et al*, 2004).

10.5.3.1 Total Selenium Intake

Table 10-4 Cross-tabulation of Total Selenium Intake and Case-Control Group based on Intake Amount Quartile

Total Selenium Amount (μg)	Group		Total
	Control	Case	
	%	%	%
Q1 (<44.76)	478	343	821
	24.6%	19.0%	21.9%
Q2 (44.76-50.48)	488	402	890
	25.1%	22.3%	23.8%
Q3 (50.48-56.63)	488	442	930
	25.1%	24.5%	24.8%
Q4 (≥56.63)	487	617	1104
	25.1%	34.2%	29.5%
Total	1941	1804	3745
	100.0%	100.0%	100.0%

Chi-square test, $p<0.001$

The results showed that in the 3rd and 4th quartiles, there were a greater proportion of cases as compared to controls. Chi-square of $p<0.001$ showed statistically significant difference in the total selenium intake between cases and control.

Results from analyses of logistic regression modelling (refer Table 10-15 page 10-239) showed consistent statistically significant odds ratios of all models for all 3rd and 4th quartiles when compared to lowest quartile. The fully multivariate-adjusted regression models showed increased odds ratios of 1.314 (95%CI:

1.072-1.610) and 1.997 (95%CI: 1.636-2.438) for 3rd and 4th quartiles as compared to reference (Q1) respectively. All P for trends was also statistically significant ($p<0.001$) suggesting increased selenium intake is associated with increased prostate cancer risk.

Table 10-5 Odds Ratios and Confidence Intervals of Total Selenium Intake Amount Quartile and Prostate Cancer Risk

Total Selenium	Control	Case	Odds ratio[a] (95%CI)	P value[a]	Odds ratio[b] (95%CI)	P value[b]	Odds ratio[c] (95%CI)	P value[c]
Q1	478	343	Ref	-	Ref	-	Ref	-
Q2	488	402	1.148 (0.948-1.390)	0.158	1.199 (0.988-1.454)	0.066	1.198 (0.977-1.468)	0.082
Q3	488	442	**1.262 (1.045-1.525)**	**0.016**	**1.343 (1.108-1.628)**	**0.003**	**1.314 (1.072-1.610)**	**0.009**
Q4	487	617	**1.766 (1.471-2.119)**	**<0.001**	**1.933 (1.601-2.333)**	**<0.001**	**1.997 (1.636-2.438)**	**<0.001**

[a]Calorie-adjusted regression model
[b]Age and calorie adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, family history of cancer and calorie
P for trend, p<0.001

10.5.3.2 Selenium intake from food source and from supplement

The mean selenium intake based on food source alone and on supplement alone is 44.89 µg (s.d. 9.37 µg) and 7.12 µg (s.d. 1.19 µg) respectively, and had a ratio of 6.3 to 1

a. Food Intake Selenium

Table 10-6 Cross-tabulation of Food origin Selenium Intake and Case-Control Group based on Intake Amount Quartile

Food origin Selenium Amount (µg)	Group		Total
	Control	Case	
	%	%	%
Q1 (<37.21)	489	349	838
	25.0%	19.2%	22.2%
Q2 (37.21-43.18)	490	400	890
	25.0%	22.0%	23.6%
Q3 (43.18-49.83)	489	472	961
	25.0%	26.0%	25.5%
Q4 (≥49.83)	489	594	1083
	25.0%	32.7%	28.7%
Total	1957	1815	3772
	100.0%	100.0%	100.0%

Chi-square test, $p<0.001$

When selenium intake was analysed based on values from diet alone, the higher proportion of cases are in quartiles 3rd and 4th at 26.0% and 32.7% respectively. Chi-square test was statistically significant (refer Table 10-6 page 10-230).

Results of logistic regression models (refer Table 10-7 page 10-231) showed increased risks for 3rd and 4th quartiles when compared to 1st quartile (OR 1.416, 95%CI: 1.158-1.731 and OR 1.933, 95%CI: 1.584-2.358 respectively). Test for trend was also statistically significant.

Table 10-7 Odds Ratios and Confidence Intervals of Food Origin Selenium Intake Amount Quartile and Prostate Cancer Risk

Food Origin Selenium	Control	Case	Odds ratio[a] (95%CI)	P value[a]	Odds ratio[b] (95%CI)	P value[b]	Odds ratio[c] (95%CI)	P value[c]
Q1	489	349	Ref	-	Ref	-	Ref	-
Q2	490	400	1.144 (0.945-1.384)	0.167	1.197 (0.987-1.450)	0.067	1.210 (0.988-1.481)	0.066
Q3	489	472	**1.352 (1.122-1.630)**	**0.002**	**1.437 (1.189-1.738)**	**<0.001**	**1.416 (1.158-1.731)**	**0.001**
Q4	489	594	**1.702 (1.419-2.042)**	**<0.001**	**1.858 (1.540-2.241)**	**<0.001**	**1.933 (1.584-2.358)**	**<0.001**

[a]Calorie-adjusted regression model
[b]Age and calorie adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, family history of cancer and calorie
P for trend <0.001

b. Selenium supplement

Table 10-8 Cross-tabulation of Tablet Supplement Selenium Intake and Case-Control Group based on Intake Amount Quartile

Tablet Supplement Selenium Amount (µg)	Group		Total
	Control	Case	
	%	%	%
Q1 (<6.55)	489	574	1063
	25.0%	31.6%	28.2%
Q2 (6.55-7.02)	489	421	910
	25.0%	23.2%	24.1%
Q3 (7.02-7.50)	490	377	867
	25.0%	20.8%	23.0%
Q4 (≥7.50)	489	443	932
	25.0%	24.4%	24.7%
Total	1957	1815	3772
	100.0%	100.0%	100.0%

Chi-square test p<0.001

A higher proportion of controls were in the 2nd, 3rd and 4th quartile when compared with controls. Chi-square test showed that there is statistically significant difference between the distribution of cases and controls among quartiles.

The logistic regression models in Table 10-9 page 10-233, showed statistically significant reduced odds ratios values for univariate, age-adjusted and multivariate adjusted regression models. Those who reported higher intake of selenium supplement were at reduced prostate cancer risks. The multivariate model gave odds ratio values of 2nd, 3rd and 4th quartiles at OR 0.685 (95%CI: 0.568-0.0.827), 0.611 (95%CI: 0.505-0.741) and 0.670 (95%CI: 0.555-0.810) respectively. Test for linear trend was also statistically significant at p-values of 0.001 suggesting a linear trend of risk reduction across quartiles.

Table 10-9 Odds Ratios and Confidence Intervals of Tablet Supplement Intake Selenium Amount Quartile and Prostate Cancer Risk

Tablet Supplement Selenium	Control	Case	Odds ratio[a] (95%CI)	P value[a]	Odds ratio[b] (95%CI)	P value[b]	Odds ratio[c] (95%CI)	P value[c]
Q1	489	574	Ref	-	Ref	-	Ref	-
Q2	489	421	**0.733 (0.614-0.876)**	**0.001**	**0.712 (0.596-0.852)**	**<0.001**	**0.685 (0.568-0.0.827)**	**<0.001**
Q3	490	377	**0.655 (0.547-0.785)**	**<0.001**	**0.627 (0.523-0.753)**	**<0.001**	**0.611 (0.505-0.741)**	**<0.001**
Q4	489	443	**0.772 (0.647-0.921)**	**0.004**	**0.738 (0.617-0.882)**	**0.001**	**0.670 (0.555-0.810)**	**<0.001**

[a]Calorie-adjusted regression model
[b]Age and calorie adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, family history of cancer and calorie
P for trend =0.001

10.5.4 Vitamin D

The mean dietary intake for Vitamin D in this study is 6.49 μg (s.d. 1.29 μg). The average dietary intake of vitamin D from food sources for men age 19 to 64 in the UK based on year 2000/2001 food and nutrient intake survey was 3.7 μg (s.d. 2.25 μg) and from all diet sources was 4.2 μg (3.06 μg), with those age 50 to 64 years old at 4.9 μg (s.d. 3.25 μg) (Henderson *et al*, 2003). The study figure is higher than the UK national average but still lower than national figure of US or Japan (Calvo *et al*, 2005).

Table 10-10 Distribution of Vitamin D Dietary Intake in cases and controls

Dietary Vitamin D Amount (μg)	Group		Total
	Control	Case	
	%	%	%
Q1 (<5.48)	478	353	831
	24.6%	19.6%	22.2%
Q2 (5.48-6.17)	488	402	890
	25.1%	22.3%	23.8%
Q3 (6.17-7.04)	488	478	966
	25.1%	26.5%	25.8%
Q4 (≥7.04)	487	571	1058
	25.1%	31.7%	28.3%
Total	1941	1804	3745
	100.0%	100.0%	100.0%

Chi-square test, $p<0.001$

The greater proportion of cases as compared to controls was observed at 3rd and 4th quartiles. Chi-square at $p<0.001$ showed statistically significant difference in the proportion of intake amount between cases and controls.

The logistic regression models showed statistically significant increased odds ratios for 3rd and 4th quartiles when compared with lowest (first) quartile (refer Table 10-11 page 10-235). The multivariate adjusted odds ratios for 3rd and 4th quartile is 1.401 (95%CI: 1.149-1.709) and 1.632 (95%CI: 1.342-1.985) respectively. P for trend was also found to be significant statistically at $p<0.001$

Table 10-11 Odds Ratios and Confidence Intervals of Dietary Vitamin D Intake Quartile and Prostate Cancer Risk

Dietary Vitamin D	Control	Case	Odds ratio[a] (95%CI)	P value[a]	Odds ratio[b] (95%CI)	P value[b]	Odds ratio[c] (95%CI)	P value[c]
Q1	478	353	Ref	-	Ref	-	Ref	-
Q2	488	402	1.115 (0.922-1.350)	0.261	1.126 (0.930-1.363)	0.224	1.168 (0.956-1.429)	0.129
Q3	488	478	**1.326 (1.101-1.598)**	**0.003**	**1.374 (1.138-1.658)**	**0.001**	**1.401 (1.149-1.709)**	**0.001**
Q4	487	571	**1.588 (1.322-1.907)**	**<0.001**	**1.649 (1.371-1.984)**	**<0.001**	**1.632 (1.342-1.985)**	**<0.001**

[a]Calorie-adjusted regression model
[b]Age and calorie adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, family history of cancer and calorie
P for trend, p<0.001

10.5.5 Lycopene

a. Lycopene from tomato

Table 10-12 Distribution of Tomato Intake in Case-Control Group

Tomato Intake Frequency	Group		Total
	Control	Case	
	%	%	%
Never or < 1 per month	176	148	324
	9.1%	8.2%	8.7%
1 - 4 per month	555	458	1013
	28.6%	25.5%	27.1%
2 - 6 per week	1060	1042	2102
	54.6%	58.0%	56.2%
Once or more per day	150	148	298
	7.7%	8.2%	8.0%
Total	1941	1796	3737
	100.0%	100.0%	100.0%

Chi-square test p=0.100

A slightly higher proportion of cases reported eating tomato 2-6 times per week and once or more per day. Chi-square test did not reveal any significant difference.

The logistic regression results were displayed in Table 10-13 page 10-237. The results suggested no association between tomato intake and prostate cancer risk. Test for linear trend however showed statistically significant at p values of 0.033, suggesting increased prostate cancer risk with increased tomato intake.

Table 10-13 Odds Ratios and Confidence Intervals of Tomato Lycopene Intake Frequency and Prostate Cancer Risk

Tomato Lycopene	Control	Case	Odds ratio[a] (95%CI)	P value[a]	Odds ratio[b] (95%CI)	P value[b]	Odds ratio[c] (95%CI)	P value[c]
Never or < 1 per month	176	148	Ref	-	Ref	-	Ref	-
1 - 4 per month	555	458	0.981 (0.763-1.262)	0.883	1.023 (0.796-1.322)	0.841	1.017 (0.781-1.325)	0.899
2 - 6 per week	1060	1042	1.169 (0.924-1.478)	0.192	1.210 (0.956-1.533)	0.113	1.187 (0.928-1.519)	0.173
Once or more per day	150	148	1.173 (0.856-1.608)	0.320	1.244 (0.905-1.711)	0.179	1.119 (0.801-1.563)	0.511

[a]Unadjusted regression model
[b]Age-adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, family history of cancer
P for trend, p=0.033

b. Ketchup Lycopene

Table 10-14 Distribution of Ketchup Intake in Case-Control Group

Ketchup Lycopene Intake Frequency	Group		Total
	Control	Case	
	%	%	%
Never or < 1 per month	896	772	1668
	46.3%	43.0%	44.7%
1 - 4 per month	743	645	1388
	38.4%	35.9%	37.2%
2 - 6 per week	272	350	622
	14.1%	19.5%	16.7%
Once or more per day	24	28	52
	1.2%	1.6%	1.4%
Total	1935	1795	3730
	100.0%	100.0%	100.0%

Chi-square test, $p<0.001$

Cases reported taking ketchup more frequent than control (refer Table 10-14 page 10-238).

The logistic regression models (refer Table 10-15 page 10-239) showed that subjects who reported ketchup intake 2-6 times per week were at increased prostate cancer risk (OR in the fully adjusted model 1.559, 95%CI: 1.283-1.894). P for trend was statistically significant.

Table 10-15 Odds Ratios and Confidence Intervals of Ketchup Lycopene Intake Frequency and Prostate Cancer Risk

Ketchup Lycopene	Control	Case	Odds ratio[a] (95%CI)	P value[a]	Odds ratio[b] (95%CI)	P value[b]	Odds ratio[c] (95%CI)	P value[c]
Never or < 1 per month	896	772	Ref	-	Ref	-	Ref	-
1 - 4 per month	743	645	1.008 (0.873-1.162)	0.918	1.007 (0.873-1.162)	0.923	1.035 (0.890-1.202)	0.656
2 - 6 per week	272	350	**1.493 (1.241-1.798)**	**<0.001**	**1.519 (1.261-1.829)**	**<0.001**	**1.559 (1.283-1.894)**	**<0.001**
Once or more per day	24	28	1.354 (0.778-2.355)	0.283	1.435 (0.823-2.501)	0.203	1.430 (0.796-2.569)	0.232

[a]Unadjusted regression model
[b]Age-adjusted regression model
[c]Multivariate adjusted regression model for age, education, ethnic, family history of cancer
P for trend, p<0.001

10.6 Discussion

10.6.1 Isoflavones

The results of the multivariate adjusted model showed that isoflavones at 2nd, 3rd and 4th quartile intake were all statistically significantly associated with reduction risk to prostate from 31.1% (range: 15.7% - 43.7%) in 2nd quartile to 53.6% (range: 42.3% - 62.6%) in the highest intake quartile (4th) (refer Table 10-3 page 10-226). The study findings are in agreement with most case-control studies involving measurement of dietary soy food or isoflavones (Heald *et al*, 2007; Kolonel *et al*, 2000; Lee *et al*, 2003; Nagata *et al*, 2007).

Test for trend of the odds ratio across all quartiles was also significant at $p<0.001$, suggesting higher intake of soy food or food containing rich isoflavones protect against prostate cancer. The odds ratios obtained in the present study are very much similar to those obtained from other case-control studies either the studies from the Far-east countries or from the western including the UK and Scotland.

The study findings add further evidence for the role of isoflavones in reducing risk of prostate cancer for western countries as previously evident on Far East Asian population studies such as Lee and Nagata (Lee *et al*, 2003; Nagata *et al*, 2007).

When considering time recalling typical diet history of last 5 years, one would anticipate some behavioural diet changes which would have taken place within this period particularly among those who were diagnosed with prostate cancer (cases subjects) due to awareness of current understanding of 'high anti-oxidant diet' strategy and to believe of its chemo preventive properties. This may affect the estimated risks in the reverse order due to cases take more isoflavones than controls. However, the reduced risk observed in this study did not support the above assumption.

10.6.2 Selenium

The regression models revealed statistically significant increased risk for prostate cancer for categories of 3rd and 4th quartiles (at higher intake of selenium) when compared with lowest intake (refer Table 10-5 page 10-229).

Selenium from dietary intake suggested increased prostate cancer risk with 3rd and 4th quartile as compared to reference with OR 1.416 (95%CI: 1.158-1.731) and OR 1.933 (95%CI: 1.584-2.358) (refer Table 10-7 page 10-231). Further results from analysis of supplement intake suggested an inverse relationship of selenium supplement and prostate cancer risk (quartiles of2nd, 3rd and 4th compared to the lowest quartile-1st quartile) with odds ratios of 0.685 (95%CI: 0.568-0.0.827), 0.611 (95%CI: 0.505-0.741) and 0.670 (95%CI: 0.555-0.810) respectively (refer Table 10-9 page 10-233)

The findings of total selenium intake which suggested increased prostate cancer risk when increased selenium intake could be due to the fact that cases were well aware of their prostate cancer conditions and were told of the possible risk factors. Among dietary recommendation for prostate cancer prevention, selenium has been one of the foremost nutrients. There is lots of bombardment of materials through the mass media on some of the preventive methods of lifestyle to prevent or lower risk of cancer, and among these dietary changes to a healthier. This is evident by higher mean intake of total selenium as compared to the average UK population.

Since diet history record of 5 years were obtained in this study, there could be a possibility that cases may not report the true account of the diet in the last 5 years to represent their diet of lifetime.

On the contrary, selenium supplement supported protection against prostate cancer. There is a possibility that this is a true account of the long healthy diet lifestyle since dietary selenium in the UK on average is getting lower in the last 20 years (Jackson *et al*, 2003). If selenium supplements are made of selenized yeast (Finley, 2006), it has been considered the best source of selenium compared to the selenium from other food, therefore there is biological plausibility to explain both effects of steady intake of selenium in supplement combined high bioavailability which would result in higher level of blood/serum selenium in circulation.

The author was not able to locate comparative articles that used case-control study design and investigate selenium of dietary intake in association with prostate cancer risk. One cohort study which uses FFQ to measure the dietary and supplement selenium intake in order to monitor their cohort subjects obtained non-statistical significant relative risks (Hartman *et al*, 1998). Other

studies used nested case-control study design but measuring only FFQ for selenium intakes obtained non-statistically significant findings (Kristal *et al*, 2010; Peters *et al*, 2008; Zhang *et al*, 2009). A randomized, placebo-controlled trial of 35,533 men from US, Canada and Puerto Rico aimed to study selenium supplements as preventive treatment also obtained non-statistically significant results (Lippman *et al*, 2009).

Based on the literature review, the studies that successfully obtained statistically significant inverse relationship with prostate cancer came from using plasma or serum level of selenium (Gill *et al*, 2009; Li *et al*, 2004; Nomura *et al*, 2000; Pourmand *et al*, 2008). Attempts to assess selenium amount through FFQ or dietary questionnaire proved to be a challenge and limitation due to complex metabolism of selenium compounds between individuals and issue of absorption, when bioavailability of selenium is used as an exposure (Fairweather-Tait, 1997; Fairweather-Tait *et al*, 2010; Finley, 2006; Levander, 1987).

Blood selenium levels are better representative of selenium status than plasma selenium, as the later reflects shorter term of selenium status (Levander, 1987). The first limitation in this present study is to use FFQ and not supplement with blood selenium specimen to support the correlation in the dietary data.

Secondly, even though this is a large case-control study, due to limited details of prostate cancer diagnosis in the database, we were not able to stratified cases into grades or aggressive of prostate cancer. Since previous studies have demonstrated selenium to be protective for aggressive or poor prognosis, and high grade prostate cancer (Li *et al*, 2004; Nomura *et al*, 2000). Further studies also indicate the role of genetics in this relationship (Penney *et al*, 2010; Platz, 2010) and as how to reconcile the contradictory findings of prostate cancer risk results in the two randomized control trial i.e. SELECT (Selenium and Vitamin E Cancer Prevention Trial) and NPC (Nutritional Prevention of Cancer).

Thirdly, the effect of selenium on prostate may not be a linear association. Bleys et al in their paper has made a hypothesis that dose responds of selenium to prostate cancer risk could be a 'U' shape. Using Restricted quadratic splines statistical analysis, he was able to demonstrate and identified a non-linear association of serum selenium with all cause and cancer mortality. Similar hazard ratios plot of 'U' shape was obtained for prostate cancer (Bleys *et al*, 2008).

Other researchers also support of this hypothesis (Fairweather-Tait & Hurst, 2009; Rayman *et al*, 2009).

10.6.3 Vitamin D

The dietary intake of Vitamin D obtained in this study 6.49 µg (s.d. 1.29 µg) is higher than the median daily intake of vitamin D from food sources in men aged 19-64 years old at 112 IU (s.d. 72) (the UK National Diet and Nutrition Survey) (Bates *et al*, 2010). It is possible that higher vitamin D intake in study subjects for both case and control groups are from men with mean age of 59 years which could have been taking vitamin D in response to bone health issues in older age.

The logistic regression models showed statistically significant increased risks in the 3rd and 4th quartiles (refer Table 10-11 page 10-235). The study findings suggested increase risk for prostate cancer among those with higher intake of vitamin D. The author is unable to confer to any studies of case-control design that obtained similar finding.

The study findings of higher risk among higher vitamin D intake may not be a true finding and cautious should be made when interpret the results.

Firstly, dietary vitamin D is normally obtained from fortified dairy food such as milk and margarine (Chen *et al*, 2007). However it is also showed that dairy products also contains calcium and phosphorus, and has been associated with increase prostate cancer risk. High intakes of calcium and phosphorus would lower circulating $1,25(OH)_2D$ level by suppressing its production, when actually $1,25(OH)_2D$ is doing the work of inhibiting prostate carcinogenesis (Giovannucci, 1998).

Secondly, the limitation of dietary intake of last 5 years as used in this study for vitamin D may not be able to capture of whether the subjects may have low vitamin D in earlier life, as process of prostate cancer carcinogenesis is likely to begin early in life (Giovannucci, 2007). In the study results on sun exposure to skin (as discussed in separate chapter in this thesis), we were able to capture the amount of sunlight (for vitamin D production) at different age periods i.e. 20's, 30's, 40's etc.

Thirdly, there's a high possibility that due to association of prostate cancer with the manifestation of losing weight and secondary metastasis to bones in higher

advanced stages of cancer, cases would have been prescribed with Vitamin D supplements as well as advised to consume more dairy products fortified with vitamin D for their bone health.

10.6.4 Lycopene

Lycopene from tomato is not associate with prostate cancer (refer Table 10-13 page 10-237). However test for linear trend still showed statistically significant value of 0.033 suggesting estimated risks are on increasing trend with increase consumption frequency of tomatoes.

By referring Table 10-14 page 10-238, most of the subjects in both groups fall into the category of consuming tomato ketchup 'never or less than once a month' between 43.0 to 46.3%, followed by 1-4 intakes per month (between 35.9-38.4%). The intake frequency of ketchup overall is less than tomato intake, although it was discussed earlier in the literature that processed tomato provides more lycopene nutrient compared to fresh tomatoes through better bioavailability (Gartner *et al*, 1997).

The logistic regression modelling for ketchup showed increased odds ratio in univariate, age-adjusted and multivariate adjusted models for those who consumed ketchup at '2-6 times per week' as compared to those who reported 'never or less than once per month' (OR 1.559, 95%CI: 1.283-1.894) (refer Table **10-15** page 10-239). The P for trend showed <0.001 of increasing trend of OR values with increasing intake of ketchup.

The results of lycopene nutrient in association with prostate cancer risk were based on intake frequency of tomatoes and ketchup. The findings are different from previously published articles. Most of these research results were of similar study design and showed reduction risk of prostate cancer (Jain *et al*, 1999; Jian *et al*, 2005; McCann *et al*, 2005; Norrish *et al*, 2000a) or at least a null association (Bosetti *et al*, 2004).

The limitation of the dietary intake of last 5 years history, would somewhat affect the findings. In terms of public health view point, one would definitely expect behavioural changes in terms of healthy eating or higher intake of anti-oxidant foods believed to be anti-cancer (Stahl *et al*, 1998), most abruptly among those who have been diagnosed of prostate cancer. Widely available access to material

reading for cancer patients on healthy lifestyle which constitute a lot on diet adjustment, would resulted in what appear as increased risk of prostate cancer among those taking ketchup more frequently.

Secondly, issue of lycopene bioavailability as absorption and metabolism differs in individuals; therefore it could affect the actual amount of lycopene in the circulation. Some limitation exists when compared dietary history to measurement of serum or plasma lycopene. Studies that have made comparison between dietary lycopene intake with the circulating lycopene, had shown weak correlation *r*, at approximately 0.25 (VandenLangenberg *et al*, 1996). Another study using Mediterranean diet which is rich in tomatoes and tomato products as seen in Greek EPIC cohort (Al-Delaimy *et al*, 2004), also shown weak correlation between diet score and plasma lycopene, therefore considered poor predictors of blood lycopenes (Jenab *et al*, 2005).

Thirdly, our limitation of using type of food intake was based on what is believed to be of highest amount of lycopene sources, as we do not have the actual lycopene nutrient value database in food of European region at this moment. Therefore surrogate foods as marker of lycopene intake was used instead.

Fourthly, even though tomatoes and ketchup intakes were recorded and probably contributed 85% of lycopene exposure, the exclusion of the types of tomato or how it was consumed was not recorded. Examples whether it was taken as raw or cooked, in juice form, or even in soup. The content of each of the types differed a lot in terms of the lycopene nutrient values (Campbell *et al*, 2004).

10.7 Conclusions and Recommendations

Higher dietary intake of isoflavones and tablet supplement of selenium has been shown to reduce risk to prostate cancer. Selenium supplement associates with reduced prostate cancer risk. This study also concludes no association between tomato frequency intake with prostate cancer risk, however ketchup intake of '2-6 times per week' when compared with those who reported frequency of intake as' Never or less than once per month' was statistically significant with increase odds ratio. Vitamin D dietary intake is associated with moderate increased prostate cancer risk.

For future studies, isoflavones could be strengthen further by measuring baseline blood sample for serum isoflavones or its' urinary excretion, in order to investigate the correlation with the dietary history among our subjects.

Vitamin D dietary intake should not be analysed alone but in combination with exposure to sunlight, as production of Vitamin D is more from skin exposure of sunlight. Comprehensive lycopene assessment of major resources in food should be explored, in order to capture better nutritional value of lycopene in all food and forms of tomatoes intake. Nutritional values of lycopene is to be used instead of surrogate types of food to ensure differences in types of preparation or tomato products form of lycopene content are taken into account. Longer period assessment of diet at younger age should be recorded in order to see the temporal effect of selenium, vitamin D and lycopene intake towards prostate cancer risk.

Chapter 11 Conclusions

This thesis aimed to investigate the epidemiological aspects of the association of six main areas that may contribute to prostate cancer risk namely (1) body shape & body fat distribution, (2) chronic diseases/conditions i.e. diabetes mellitus, hypertension, ischaemic heart diseases and hypercholesterolemia, (3) statin medications (4) painkillers (NSAIDs Aspirin & Ibuprofen and paracetamol), (5) skin type, suncream & sunlight exposures and (6) diet (isoflavones (Phytoeastrogens), selenium, vitamin D & lycopene). The exposures at different stages of life at age 20's, 30's, 40's and last 5 years, as well as cumulative risk for prostate cancer was carried out.

In view of the results of the quantitative analyses of data obtained through questionnaires for both cases and controls subjects, it was successful in view of the large samples obtained of 1963 cases and 2078 controls at ratio 1:1, as this study has one of the highest number of subjects for a study of prostate cancer alone in United Kingdom using the case-control study design.

Summary of Findings & Interpretation

Initial multivariate analysis of statistically significant univariate analyses of sociodemographic factors revealed that education category, ethnic group and family history of cancer showed consistent statistically significant associations with prostate cancer risk. These together with the a-priori variables of age, were included into the subsequent logistic regression modeling in all the analysis of the factors studied. The main findings were:

i. 'Apple' body fat distribution was associated with reduction of prostate cancer risk of 31% when compared to symmetrical shape.

ii. Body shape changes (increased or decreased) between age groups 20's to 40's was not associated with prostate cancer.

iii. Diabetes mellitus status of 5 years or more showed protection against prostate cancer risk (approximately 55% reduction) compared to non-diabetic.

iv. Hypertension, hypercholesterolemia and ischaemic diseases did not show any association with prostate cancer.

v. Statin usage was associated with protective risk against prostate cancer at almost 30% reduction compared to non-user.

vi. Longer use of statin showed a statistically significant cumulative risk towards reducing prostate cancer compared to non-user.

vii. Use of paracetamol duration of 20 to 30 years at regular interval showed a statistically significant risk reduction towards prostate cancer at almost 50% when compared non-user, while cumulative risk was a reduction risk of 30% if use paracetamol 20 years or more.

viii. Aspirin and Ibuprofen were not associated with prostate cancer.

ix. Skin type was not associated with prostate cancer.

x. Overall usage of suntan cream of 'always' and 'sometimes' frequency at age 20's, 30's, 40's and last 5 years was associated with reduction in prostate cancer risk (approximately between 24 - 39%) compared never use.

xi. Outdoor exposure of sunlight of categories more than 1 hour at age 20's, 30's, 40's and 50's when not working was associated with reduced prostate cancer (approximate protective risk between 33 - 62%) compared to those who are exposed less than 1 hour.

xii. Higher intake of isoflavones (phytoestrogens) and selenium tablets were associated with protective effect against prostate cancer at between 31-54% and 33-39% respectively.

xiii. However higher intake of total selenium (food & tablet form), vitamin D and Lycopene of tomato ketchup were associated with an increased of cancer.

xiv. Lycopene from tomatoes was not associated with prostate cancer.

The majority of the results obtained from our data supported our earlier hypotheses presented in chapter 2. Our results also indicated some similarity to the majority of the findings in other case-control and cohort design studies namely on family history of cancer, abdominal obesity, diabetes mellitus, statin, sunlight exposure, isoflavones and selenium supplement intake. The strength of the odds ratios of prostate cancer risk in our study are also similar to other studies.

In contrast, our study indicated that higher intake of aspirin, total selenium, vitamin D and lycopene was not associated with reduction in prostate cancer risk. We did not anticipate our findings which seem to suggest the positive relationship between total selenium, dietary vitamin D and lycopene (from tomatoes) towards prostate cancer risk. The absence of associations between aspirin and lycopene from tomato ketchup intake was also not expected, as the majority published

studies seem to show inverse associations. It should be noted at this point that one of the key differences in this study compared to others is in the age structure of the case and control population which was deliberately chosen to be of younger age.

A further possible explanation for these would be 'reverse causation' or dilution effect by other exposures. Reverse causation in this context, whereby higher dietary intake of selenium, vitamin D, and lycopene seems to indicate higher risk of prostate cancer could be due the fact that cases upon diagnosis would report changing the dietary behavior in their last 5 years of life to a healthy and full of anti-cancer or food containing high anti-oxidant in the believe that they will have reduced recurrence rate or could be as part of the treatment plan. Furthermore, they were bombarded during their visit to health check up facilities with posters or pamphlets of 'healthy and high anti-oxidant diet' information. Non cancer patients tend to maintain similar diet over time and may remain same in the last 10 years. Our food frequency questionnaire is only able to capture diet of last five years due to the strict ruling of validity in the information given. As for the aspirin intake, there is a limitation to the amount of dosage taken as the supply of aspirin is either in the tablet of 75mg or 320mg and these has not been indicated clearly in the questionnaire as the habits and dosage change overtime.

We also obtained a statistically significant inverse association of paracetamol with prostate cancer. This is the first time findings of long exposure use of paracetamol regularly of 20 years or more would reduce prostate cancer by almost 50% compared to non-regular user. Although it is biologically plausible as recent findings suggest that it is highly selective for COX2 (Hinz *et al*, 2008), there is still a need to study further on the dosage intake and the possibility of confounders' effect on the relationship.

Issues arising from the study

The results obtained from the analysis of this study although showing much agreement and at the same time some disagreement to the current knowledge literature could be due to a number of reasons:

Firstly, the comparison and extrapolation of this study's findings should only be specific for similar type of study designs, population, ethnic, skin colour and environment in a developed country. This would account some similarity in exposures such as the amount of sunlight and dietary habits.

Secondly, we do highlight that analyses combined both the data of younger onset cases (Phase I) of less than 60 years old and of all age group populations cases (Phase II). Since prostate cancer incidence is associated with increasing age, it is possible that those who are above 60 years and in the control group are not necessarily be free of prostate cancer. These controls have not been screened or diagnosed for prostate cancer because this disease is often asymptomatic for many people or they may be developing cancer at early stage or in the latent stage.

Even if simple screening methods such as prostatic specific antigen (PSA) testing are done (although not agreed to be used as wide screening method), it cannot be assumed that all those controls with higher than 4 ng/ml PSA level will have abnormal findings in their digital rectal examination (DRE), and therefore would decide not to proceed further for biopsy of prostate for histology due to believe that they are less likely to be suffering from prostate cancer or refused to be investigated further due to old age. This is a limitation in any control subject (in case-control study design or non-cases in cohort study) even if we do matching for age between cases and controls. However by taking only those with negative biopsy for prostate cancer or low PSA, as a control group would definitely reduce the possibility of bias.

However, with the inclusion of 'cases' in the control group would have the effect of attenuating the estimates of risk and as such, any significant risks seen would if anything be underestimated of the true values.

Thirdly, the possibility of bias introduced when selecting the controls from Nottinghamshire alone during phase II due to poor responses from some GPs and potential controls when matching the area with case population base which was done as the first phase and which remains the best design option. The second option of choosing controls from elsewhere was more feasible with the development of the computer software medical 'Read' code to help GPs identify potential controls for each case by age frequency and fulfilled other inclusion criteria. It is of interest that the center for data collection was in Nottingham at that time. The environmental exposure could well have been very different given the matching of case and control was just based up on age characteristics. They came from different area of the country with unknown population biases.

Fourthly, a case-control study design was used due to its convenience in obtaining the exposure histories from both cases and controls as well as cost and time savings. The advantage of case-control study is the exploration of many new areas of exposures that could be associated with a disease, either because the presence of the exposure or the length of exposure and even dose of exposure. This is necessary before further work of the findings be refined when conducting a cohort or clinical trial study design. Since the survival rate of prostate cancer patients in UK is more than 80% for 2-5 years, we were able to obtain history information on these cancer cases. A limitation is however to the amount of accuracy or reliability on the account of both cases and control in remembering remote information especially on body weight or dietary intake values. Therefore diet history of last 5 years were obtained, based on usage of valid food frequency questionnaire which has been described in earlier chapters. Food frequency questionnaire is the closest data on subjects dietary habits as most do have a sensible memory record of their diet in the last 5 years. Literature review will only reveal common food/diet associated with certain ethnics groups, culture or even their country of origin, and these habits do change when they moved to a new country due to change of lifestyle and adaptation to available food. Food frequency questionnaire is very cheap especially when applied to individuals in providing specific favoritism in cooking and taste.

Although we do not rule out the limitation of the possibility of intention bias or misclassification bias in the responses given in the questionnaire, we only include sections of valid and tested questionnaires of different areas of exposures and combined them into our prostate cancer questionnaire in order to study as many factors as possible.

Contribution of this Study and the way forward

During the past 13 years since this study's inception, progress has been made in the study of factors/risks associated with genetic or environmental exposures through epidemiological studies. This study also has further contributed to understanding of the interaction of risk factors for prostate cancer and the capacity needed to further enhance understanding of the risks in other populations/ethnic groups involved and exploring new areas of risk. The genetic component of these gene-environmental interaction studies has opened up better epidemiological evidence to the possibility of studying cause and effect. One interesting opportunity could occur if the case-control methodology was replicated

in Malaysia as the ethnic, environmental and genetic differences would permit further exploration.

In order to strengthen and or further justify the current findings in this thesis, we would proceed with trying to understand whether there are aspects of genetics which could link the statistically significant association environmental risk exposures; hence the study of genomic screening to identify some common predisposing genes or polymorphisms in repair genes would be appropriate. Furthermore, we hypothesize that certain environmental exposures could interact with such predisposing genes by creating a further increase or decrease to the risk to prostate cancer even if they are not acting as a direct causal agent.

The study from this thesis alone has identified new areas of exposure that need to be investigated further using other methodologies, refining the following criteria:

i. Prostate Cancer diagnosis through histology classification to be explored further according to the Gleason grade or scoring because some exposure such as obesity or body fat distribution could behave differently as risk to aggressive (fatal) or non-aggressive prostate cancer.

ii. Control subjects should be matched best with cases according to similar county/districts to reduce the bias due to effect of ecological reason such as food and water supply, industry or environmental non-working related factors.

iii. Control subjects should be those that have been screened for at least PSA (Prostatic specific antigen) and/or DRE (Digital rectal examination) for those above 50 years old and all suspicious cases, and investigate further when necessary for prostate biopsy histology in order not to miss out undiagnosed prostate cancer cases and to reduce bias.

iv. To focus on young onset (<60 years old) prostate cancer cases and controls with matched age, because of the potential outcome of the research will contribute more for the prevention/reducing risk exposure or at the same time promote good exposure to factors that reduced risk to prostate cancer such as diet or sunlight.

v. Since genetic factors which couple with interaction between types of exposures could contribute to the risk to prostate cancer, the

epidemiological findings should be combined in order to strengthen the predictive modeling.

vi. Cluster sampling of minority ethnic groups should be represented more in both cases and controls in order to better extrapolate the results of the samples to bigger population area and country or regions.

vii. Some possibility of verifying the data from questionnaire such as photos of subjects at age 20's to 40's and current for body shape, as well as medical records for other diseases/condition presence should be obtained as part of the validity checking process besides the validity of entering data to the database. List of medications received may help although subjects can always buy non-prescribed medication from the pharmacy OTC.

The exploration of new surrogate indicators obtained in this study such as body fat distribution and suntan cream usage, or scoring for vitamin D from sunlight exposure should be studied further through stronger methodology study design such as cohort studies. Besides exploring new proxy-markers, the use of cohort populations will improve the variable definitions, the measurement records obtained from follow ups in each visit, recorded by reliable methods and evaluator, new conditions or illness maybe reported every 5 years and subject's medical records for specific data may be obtained from relevant GPs upon consent from the patients and relevant hospitals. Under these circumstances, nested case-control study could also be done towards a time when prevalence/incidence of prostate cancer cases are ample for analysis.

Final Conclusions

The results of this study can be used to strengthen further the current findings of the association of certain exposures such as diabetes mellitus, usage of statins, obesity and exposure of sunlight to reduce prostate cancer. On one hand, some of the protective behaviours such as higher duration of sunlight exposure in daily life should be taken together with correct health understanding that vitamin D is important for our health and the sunlight is our main source of vitamin D.

However, the interpretation of how diabetes mellitus status, abdominal obesity or statins could reduce prostate cancer risk should not send a wrong message to the public, because these morbid conditions are risk themselves to the health of a person. The conclusion to be made as such would be to strengthen our understanding of the new knowledge in hypothetical or theoretical mechanisms

involved in preventing the initiation of carcinogenesis or how these actions stop the progress or recurrence of prostate cancer, which will be used towards public health preventive control measures of prostate cancer. Furthermore, through knowledge on genetic factors i.e. predisposing genes and their interaction with such environmental exposures, could help researchers to create better strategies towards the prevention of prostate cancer in public health as a whole.

As a clinician, the understanding of modifiable and non-modifiable risk factors to a disease such as prostate cancer is very useful when tackling queries or counseling patients and their relatives. The ability to provide some information using evidence based epidemiological findings could help them to understand what predisposed them to the condition. This is particularly true when dealing with those who have non-modifiable factors such as family cancer of cancer in 1st degree relatives, where the risk is higher towards prostate cancer. However this is only one part of the attributable risks. There are numerous environmental factors that are modifiable but could contribute to increase risk to prostate cancer. On the contrary some environmental factors could also attribute to lower risk of prostate cancer such as higher sunlight exposure or phytoestrogens intake.

My initial intention was to conduct similar research project on prostate cancer in Sabah, Malaysia, but in view of the problem of getting funding and time constraint, the study had to be postponed till later. This experience and knowledge that I've gained in the UK will strongly influence my approach to epidemiology work I will embark upon in Malaysia upon my return.

Chapter 12 References

Adami HO, Bergstrom R, Engholm G, Nyren O, Wolk A, Ekbom A, Englund A, Baron J (1996) A prospective study of smoking and risk of prostate cancer. *Int J Cancer* **67**(6): 764-8

Adlercreutz H (2002) Phyto-oestrogens and cancer. *Lancet Oncol* **3**(6): 364-73

Ahn J, Moore SC, Albanes D, Huang WY, Leitzmann MF, Hayes RB (2009) Height and risk of prostate cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. *Br J Cancer* **101**(3): 522-5

Ahn J, Peters U, Albanes D, Purdue MP, Abnet CC, Chatterjee N, Horst RL, Hollis BW, Huang WY, Shikany JM, Hayes RB (2008) Serum vitamin D concentration and prostate cancer risk: a nested case-control study. *J Natl Cancer Inst* **100**(11): 796-804

Alavanja MCR, Claudine Samanic, Mustafa Dosemeci, Jay Lubin, Robert Tarone, Charles F. Lynch, Charles Knott, Kent Thomas, Jane A. Hoppin, Joseph Barker, Joseph Coble, Dale P. Sandler, and Aaron Blair (2003) Use of Agricultural Pesticides and Prostate Cancer Risk in the Agricultural Health

Al-Delaimy WK, van Kappel AL, Ferrari P, Slimani N, Steghens JP, Bingham S, Johansson I, Wallstrom P, Overvad K, Tjonneland A, Key TJ, Welch AA, Bueno-de-Mesquita HB, Peeters PH, Boeing H, Linseisen J, Clavel-Chapelon F, Guibout C, Navarro C, Quiros JR, Palli D, Celentano E, Trichopoulou A, Benetou V, Kaaks R, Riboli E (2004) Plasma levels of six carotenoids in nine European countries: report from the European Prospective Investigation into Cancer and Nutrition (EPIC). *Public Health Nutr* **7**(6): 713-22

Alexander DD, Mink PJ, Cushing CA, Sceurman B (2010) A review and meta-analysis of prospective studies of red and processed meat intake and prostate cancer. *Nutr J* **9**: 50

Allen NE, Appleby PN, Roddam AW, Tjonneland A, Johnsen NF, Overvad K, Boeing H, Weikert S, Kaaks R, Linseisen J, Trichopoulou A, Misirli G, Trichopoulos D,

Sacerdote C, Grioni S, Palli D, Tumino R, Bueno-de-Mesquita HB, Kiemeney LA, Barricarte A, Larranaga N, Sanchez MJ, Agudo A, Tormo MJ, Rodriguez L, Stattin P, Hallmans G, Bingham S, Khaw KT, Slimani N, Rinaldi S, Boffetta P, Riboli E, Key TJ (2008) Plasma selenium concentration and prostate cancer risk: results from the European Prospective Investigation into Cancer and Nutrition (EPIC). *Am J Clin Nutr* **88**(6): 1567-75

Allen NE, Morris JS, Ngwenyama RA, Key TJ (2004) A case--control study of selenium in nails and prostate cancer risk in British men. *Br J Cancer* **90**(7): 1392-6

Altekruse S, Kosary C, Krapcho M, Neyman N, Aminou R, Waldron W, Ruhl J, Howlader N, Tatalovich Z, Cho H, Mariotto A, Eisner M, Lewis D, Cronin K, Chen H, Feuer E, Stinchcomb D, Edwards Be (2010) SEER Cancer Statistics Review, 1975-2007: National Cancer Institute. Bethesda, MD

Arab L, Steck S (2000) Lycopene and cardiovascular disease. *Am J Clin Nutr* **71**(6 Suppl): 1691S-5S; discussion 1696S-7S

Astner S, Anderson RR (2004) Skin Phototypes 2003. *J Investig Dermatol* **122**(2): xxx-xxxi

Autier P, DorÃ© J-Fo, NÃ©grier S, LiÃ©nard Dl, Panizzon R, Lejeune FJ, Guggisberg D, Eggermont AMM, Research FtEOf, Group ToCM (1999) Sunscreen Use and Duration of Sun Exposure: a Double-Blind, Randomized Trial. *Journal of the National Cancer Institute* **91**(15): 1304-1309

Bagnardi V, Blangiardo M, La Vecchia C, Corrao G (2001) A meta-analysis of alcohol drinking and cancer risk. *Br J Cancer* **85**(11): 1700-5

Baradaran N, Ahmadi H, Salem S, Lotfi M, Jahani Y, Mehrsai AR, Pourmand G (2009) The protective effect of diabetes mellitus against prostate cancer: role of sex hormones. *Prostate* **69**(16): 1744-50

Barnett C, Nielson C, Shannon J, Chan J, Shikany J, Bauer D, Hoffman A, Barrett-Connor E, Orwoll E, Beer T (2010) Serum 25-OH vitamin D levels and risk of developing prostate cancer in older men. *Cancer Causes and Control* **21**(8): 1297-1303

Bates B, Lennox A, Swan G (2010) National diet and nutrition survey: headlines results from year 1 of the rolling programme (2008/2009). Agency FS (ed). London: Department of Health

Beilby J, Ambrosini GL, Rossi E, de Klerk NH, Musk AW (2010) Serum levels of folate, lycopene, beta-carotene, retinol and vitamin E and prostate cancer risk. *Eur J Clin Nutr* **64**(10): 1235-8

Bianchini F, Kaaks R, Vainio H (2002) Overweight, obesity, and cancer risk. *Lancet Oncol* **3**(9): 565-74

Bingham SA (1997b) Dietary assessments in the European prospective study of diet and cancer (EPIC). *Eur J Cancer Prev* **6**(2): 118-24

Bingham SA, Atkinson C, Liggins J, Bluck L, Coward A (1998) Phyto-oestrogens: where are we now? *Br J Nutr* **79**(5): 393-406

Bingham SA, Day NE (1997c) Using biochemical markers to assess the validity of prospective dietary assessment methods and the effect of energy adjustment. *Am J Clin Nutr* **65**(4 Suppl): 1130S-1137S

Bingham SA, Gill C, Welch A, Cassidy A, Runswick SA, Oakes S, Lubin R, Thurnham DI, Key TJ, Roe L, Khaw KT, Day NE (1997a) Validation of dietary assessment methods in the UK arm of EPIC using weighed records, and 24-hour urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers. *Int J Epidemiol* **26** Suppl **1**: S137-51

Bleys J, Navas-Acien A, Guallar E (2008) Serum selenium levels and all-cause, cancer, and cardiovascular mortality among US adults. *Arch Intern Med* **168**(4): 404-10

Bodiwala D, Luscombe CJ, French ME, Liu S, Saxby MF, Jones PW, Ramachandran S, Fryer AA, Strange RC (2003a) Susceptibility to prostate cancer: studies on interactions between UVR exposure and skin type. *Carcinogenesis* **24**(4): 711-7

Bodiwala D, Luscombe CJ, Liu S, Saxby M, French M, Jones PW, Fryer AA, Strange RC (2003b) Prostate cancer risk and exposure to ultraviolet radiation: further support for the protective effect of sunlight. *Cancer Lett* **192**(2): 145-9

Bonovas S, Filioussi K, Sitaras NM (2006) Paracetamol use and risk of ovarian cancer: a meta-analysis. *Br J Clin Pharmacol* **62**(1): 113-21

Bonovas S, Filioussi K, Sitaras NM (2008) Statin use and the risk of prostate cancer: A metaanalysis of 6 randomized clinical trials and 13 observational studies. *Int J Cancer* **123**(4): 899-904

Bonovas S, Filioussi K, Tsantes A (2004) Diabetes mellitus and risk of prostate cancer: a meta-analysis. *Diabetologia* **47**(6): 1071-8

Bosetti C, Talamini R, Montella M, Negri E, Conti E, Franceschi S, La Vecchia C (2004) Retinol, carotenoids and the risk of prostate cancer: a case-control study from Italy. *Int J Cancer* **112**(4): 689-92

Bouchard C, Bray G, Hubbard V (1990) Basic and clinical aspects of regional fat distribution. *The American Journal of Clinical Nutrition* **52**(5): 946-950

Boudreau DM, Yu O, Buist DS, Miglioretti DL (2008) Statin use and prostate cancer risk in a large population-based setting. *Cancer Causes Control* **19**(7): 767-74

Boudreau DM, Yu O, Johnson J (2010) Statin use and cancer risk: a comprehensive review. *Expert Opin Drug Saf* **9**(4): 603-21

Bratt O (2002) Hereditary Prostate Cancer: Clinical Aspects. *The Journal of Urology* **168**(3): 906-913

Bravi F, Scotti L, Bosetti C, Talamini R, Negri E, Montella M, Franceschi S, La Vecchia C (2006) Self-reported history of hypercholesterolaemia and gallstones and the risk of prostate cancer. *Ann Oncol* **17**(6): 1014-7

Brinkman M, Reulen RC, Kellen E, Buntinx F, Zeegers MP (2006) Are men with low selenium levels at increased risk of prostate cancer? *Eur J Cancer* **42**(15): 2463-71

Browning DR, Martin RM (2007) Statins and risk of cancer: a systematic review and metaanalysis. *Int J Cancer* **120**(4): 833-43

Bylund A, Zhang JX, Bergh A, Damber JE, Widmark A, Johansson A, Adlercreutz H, Aman P, Shepherd MJ, Hallmans G (2000) Rye bran and soy protein delay growth and increase apoptosis of human LNCaP prostate adenocarcinoma in nude mice. *Prostate* **42**(4): 304-14

Calton BA, Chang SC, Wright ME, Kipnis V, Lawson K, Thompson FE, Subar AF, Mouw T, Campbell DS, Hurwitz P, Hollenbeck A, Schatzkin A, Leitzmann MF (2007) History of diabetes mellitus and subsequent prostate cancer risk in the NIH-AARP Diet and Health Study. *Cancer Causes Control* **18**(5): 493-503

Calvo MS, Whiting SJ, Barton CN (2005) Vitamin D Intake: A Global Perspective of Current Status. *The Journal of Nutrition* **135**(2): 310-316

Campbell JK, Canene-Adams K, Lindshield BL, Boileau TW, Clinton SK, Erdman JW, Jr. (2004) Tomato phytochemicals and prostate cancer risk. *J Nutr* **134**(12 Suppl): 3486S-3492S

CDC CfDCaP (2010) Cholesterol among persons 20 years of age and over, by selected characteristics: United States, selected years 1988-1994 through 2005-2008 In *Health United States 2010*

Chamie K, DeVere White RW, Lee D, Ok JH, Ellison LM (2008) Agent Orange exposure, Vietnam War veterans, and the risk of prostate cancer. *Cancer* **113**(9): 2464-70

Chan JL, Ehrlich A, Lawrence RC, Moshell AN, Turner ML, Kimball AB (2005) Assessing the role of race in quantitative measures of skin pigmentation and clinical assessments of photosensitivity. *J Am Acad Dermatol* **52**(4): 609-15

Chan JM, Latini DM, Cowan J, Duchane J, Carroll PR (2005) History of diabetes, clinical features of prostate cancer, and prostate cancer recurrence-data from CaPSURE (United States). *Cancer Causes Control* **16**(7): 789-97

Chan KK, Oza AM, Siu LL (2003) The statins as anticancer agents. *Clin Cancer Res* **9**(1): 10-9

Chang S, Erdman JW, Jr., Clinton SK, Vadiveloo M, Strom SS, Yamamura Y, Duphorne CM, Spitz MR, Amos CI, Contois JH, Gu X, Babaian RJ, Scardino PT, Hursting SD (2005) Relationship between plasma carotenoids and prostate cancer. *Nutr Cancer* **53**(2): 127-34

Chang S, Hursting SD, Contois JH, Strom SS, Yamamura Y, Babaian RJ, Troncoso P, Scardino PS, Wheeler TM, Amos CI, Spitz MR (2001) Leptin and prostate cancer. *Prostate* **46**(1): 62-7

Chen TC, Chimeh F, Lu Z, Mathieu J, Person KS, Zhang A, Kohn N, Martinello S, Berkowitz R, Holick MF (2007) Factors that influence the cutaneous synthesis and dietary sources of vitamin D. *Arch Biochem Biophys* **460**(2): 213-7

Chen Y-C, Page JH, Chen R, Giovannucci E (2008) Family history of prostate and breast cancer and the risk of prostate cancer in the PSA era. *The Prostate* **68**(14): 1582-1591

Cheng I, Liu X, Plummer SJ, Krumroy LM, Casey G, Witte JS (2007) COX2 genetic variation, NSAIDs, and advanced prostate cancer risk. *Br J Cancer* **97**(4): 557-61

Cheng I, Witte JS, McClure LA, Shema SJ, Cockburn MG, John EM, Clarke CA (2009) Socioeconomic status and prostate cancer incidence and mortality rates among the diverse population of California. *Cancer Causes Control* **20**(8): 1431-40

Coker AL, Sanderson M, Zheng W, Fadden MK (2004) Diabetes mellitus and prostate cancer risk among older men: population-based case-control study. *Br J Cancer* **90**(11): 2171-5

Colli JL, Amling CL (2009) High cholesterol levels are associated with reduced prostate cancer mortality rates during periods of high but not low statin use in the United States. *Urologic Oncology: Seminars and Original Investigations* **27**(2): 170-173

Coogan PF, Rosenberg L, Palmer JR, Strom BL, Zauber AG, Shapiro S (2002) Statin use and the risk of breast and prostate cancer. *Epidemiology* **13**(3): 262-7

Cox B, Sneyd MJ, Paul C, Delahunt B, Skegg DC (2002) Vasectomy and risk of prostate cancer. *JAMA* **287**(23): 3110-5

CRUK (2010) Prostate cancer statistics, UK CR (ed) Vol. 2010. London

Curado. M. P., Edwards B, Shin. H.R., Storm. H., Ferlay. J., M. H, Boyle. P. e (eds) (2007) *Cancer Incidence in Five Continents, Vol. IX* Lyon: IARC

Dal Maso L, Zucchetto A, La Vecchia C, Montella M, Conti E, Canzonieri V, Talamini R, Tavani A, Negri E, Garbeglio A, Franceschi S (2004) Prostate cancer and body size at different ages: an Italian multicentre case-control study. *Br J Cancer* **90**(11): 2176-80

Daniels NA, Chen YH, Bent S (2009) Antibiotic and anti-inflammatory use and the risk of prostate cancer. *BMC Res Notes* **2**: 57

Darbinian JA, Ferrara AM, Van Den Eeden SK, Quesenberry CP, Jr., Fireman B, Habel LA (2008) Glycemic status and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* **17**(3): 628-35

Dasgupta K, Di Cesar D, Ghosn J, Rajan R, Mahmud S, Rahme E (2006) Association between nonsteroidal anti-inflammatory drugs and prostate cancer occurrence. *Cancer J* **12**(2): 130-5

Davey Smith G, Ebrahim S (2003) 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol* **32**(1): 1-22

Davey Smith G, Pekkanen J (1992) Should there be a moratorium on the use of cholesterol lowering drugs? *BMJ* **304**(6824): 431-4

De Marzo AM, Platz EA, Sutcliffe S, Xu J, Gronberg H, Drake CG, Nakai Y, Isaacs WB, Nelson WG (2007) Inflammation in prostate carcinogenesis. *Nat Rev Cancer* **7**(4): 256-269

Dennis LK, Coughlin JA, McKinnon BC, Wells TS, Gaydos CA, Hamsikova E, Gray GC (2009) Sexually Transmitted Infections and Prostate Cancer among Men in the U.S. Military. *Cancer Epidemiology Biomarkers & Prevention* **18**(10): 2665-2671

Dennis LK, Hayes RB (2001) Alcohol and prostate cancer. *Epidemiol Rev* **23**(1): 110-4

Dennis LK, Lynch CF, Torner JC (2002b) Epidemiologic association between prostatitis and prostate cancer. *Urology* **60**(1): 78-83

Dennis LKaD, Deborah V. (2002a) Meta-Analysis of Measures of Sexual Activity and Prostate Cancer. *Epidemiology* Volume **13(1):** pp 72-79

Department of Health (1991) *Dietary Reference Values for Fodd, Energy and Nutrients for the UK.* Report on Health and Social Subjects no. 41. London: HMSO

Derby CA, Zilber S, Brambilla D, Morales KH, McKinlay JB (2006) Body mass index, waist circumference and waist to hip ratio and change in sex steroid hormones: the Massachusetts Male Ageing Study. *Clin Endocrinol (Oxf)* **65**(1): 125-31

Dimitropoulou P, Lophatananon A, Easton D, Pocock R, Dearnaley DP, Guy M, Edwards S, O'Brien L, Hall A, Wilkinson R, The Uk Genetic Prostate Cancer Study Collaborators BAoUSSoO, Eeles R, Muir KR (2009) Sexual activity and prostate cancer risk in men diagnosed at a younger age. *BJU International* **103**(2): 178-185

Dimitropoulou P, Martin RM, Turner EL, Lane JA, Gilbert R, Davis M, Donovan JL, Hamdy FC, Neal DE (2011) Association of obesity with prostate cancer: a case-control study within the population-based PSA testing phase of the ProtecT study. *Br J Cancer* **104**(5): 875-81

Dimitroulakos J, Nohynek D, Backway KL, Hedley DW, Yeger H, Freedman MH, Minden MD, Penn LZ (1999) Increased Sensitivity of Acute Myeloid Leukemias to Lovastatin-Induced Apoptosis: A Potential Therapeutic Approach. *Blood* **93**(4): 1308-1318

Doll R, Peto R, Boreham J, Sutherland I (2005) Mortality from cancer in relation to smoking: 50 years observations on British doctors. *Br J Cancer* **92**(3): 426-429

Driver JA, Yung R, Gaziano JM, Kurth T (2010) Chronic disease in men with newly diagnosed cancer: a nested case-control study. *Am J Epidemiol* **172**(3): 299-308

Edwards P, Roberts I, Clarke M, DiGuiseppi C, Pratap S, Wentz R, Kwan I (2002) Increasing response rates to postal questionnaires: systematic review. *BMJ* **324**(7347): 1183

Eeles RA, Kote-Jarai Z, Giles GG, Olama AAA, Guy M, Jugurnauth SK, Mulholland S, Leongamornlert DA, Edwards SM, Morrison J, Field HI, Southey MC, Severi G, Donovan JL, Hamdy FC, Dearnaley DP, Muir KR, Smith C, Bagnato M, Ardern-Jones AT, Hall AL, O'Brien LT, Gehr-Swain BN, Wilkinson RA, Cox A, Lewis S, Brown PM, Jhavar SG, Tymrakiewicz M, Lophatananon A, Bryant SL, Horwich A, Huddart RA, Khoo VS, Parker CC, Woodhouse CJ, Thompson A, Christmas T, Ogden C, Fisher C, Jamieson C, Cooper CS, English DR, Hopper JL, Neal DE, Easton DF (2008) Multiple newly identified loci associated with prostate cancer susceptibility. *Nat Genet* **40**(3): 316-321

Epstein JI, Allsbrook WC, Jr., Amin MB, Egevad LL (2005) The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *Am J Surg Pathol* **29**(9): 1228-42

Evans BA, Griffiths K, Morton MS (1995) Inhibition of 5 alpha-reductase in genital skin fibroblasts and prostate tissue by dietary lignans and isoflavonoids. *J Endocrinol* **147**(2): 295-302

Fairweather-Tait S, Hurst R (2009) Plasma selenium concentration and prostate cancer risk: effects are dependent on the level of exposure. *Am J Clin Nutr* **89**(3): 927-8

Fairweather-Tait SJ (1997) Bioavailability of selenium. *Eur J Clin Nutr* **51 Suppl 1**: S20-3

Fairweather-Tait SJ, Collings R, Hurst R (2010) Selenium bioavailability: current knowledge and future research requirements. *The American Journal of Clinical Nutrition* **91**(5): 1484S-1491S

Ferlay J, Shin H, Bray F, Forman D, Mathers C, Parkin D (2008) GLOBOCAN 2008. Cancer Incidence and Mortality Worldwide: IARC Cancer Base no.10. Lyon, France: International Agency for Research on Cancer

Fernandez L, Galan Y, Jimenez R, Gutierrez A, Guerra M, Pereda C, Alonso C, Riboli E, Agudo A, Gonzalez C (2005) Sexual behaviour, history of sexually transmitted diseases, and the risk of prostate cancer: a case-control study in Cuba. *Int J Epidemiol* **34**(1): 193-7

Field AE, Coakley EH, Must A, Spadano JL, Laird N, Dietz WH, Rimm E, Colditz GA (2001) Impact of overweight on the risk of developing common chronic diseases during a 10-year period. *Arch Intern Med* **161**(13): 1581-6

Finley JW (2006) Bioavailability of selenium from foods. *Nutr Rev* **64**(3): 146-51

Fitzgerald LM, Kwon EM, Koopmeiners JS, Salinas CA, Stanford JL, Ostrander EA (2009) Analysis of recently identified prostate cancer susceptibility loci in a population-based study: associations with family history and clinical features. *Clin Cancer Res* **15**(9): 3231-7

Fitzpatrick AL, Daling JR, Furberg CD, Kronmal RA, Weissfeld JL (2001) Hypertension, heart rate, use of antihypertensives, and incident prostate cancer. *Ann Epidemiol* **11**(8): 534-42

Fitzpatrick TB, Wolff K (2008) *Fitzpatrick's dermatology in general medicine*: McGraw-Hill

Flick ED, Habel LA, Chan KA, Van Den Eeden SK, Quinn VP, Haque R, Orav EJ, Seeger JD, Sadler MC, Quesenberry CP, Jr., Sternfeld B, Jacobsen SJ, Whitmer RA, Caan BJ (2007) Statin use and risk of prostate cancer in the California Men's Health Study cohort. *Cancer Epidemiol Biomarkers Prev* **16**(11): 2218-25

Freedland SJ, Platz EA (2007) Obesity and prostate cancer: making sense out of apparently conflicting data. *Epidemiol Rev* **29**: 88-97

Freedland SJ, Wen J, Wuerstle M, Shah A, Lai D, Moalej B, Atala C, Aronson WJ (2008) Obesity is a significant risk factor for prostate cancer at the time of biopsy. *Urology* **72**(5): 1102-5

Freedman DM, Dosemeci M, McGlynn K (2002) Sunlight and mortality from breast, ovarian, colon, prostate, and non-melanoma skin cancer: a composite death certificate based case-control study. *Occup Environ Med* **59**(4): 257-62

Friis S, Nielsen GL, Mellemkjaer L, McLaughlin JK, Thulstrup AM, Blot WJ, Lipworth L, Vilstrup H, Olsen JH (2002) Cancer risk in persons receiving prescriptions for paracetamol: a Danish cohort study. *Int J Cancer* **97**(1): 96-101

Funkhouser AB, Laferrere B, Wang J, Thornton J, Pi-Sunyer FX (2000) Measurement of percent body fat during weight loss in obese women. Comparison of four methods. *Ann N Y Acad Sci* **904**: 539-41

Gallus S, Foschi R, Talamini R, Altieri A, Negri E, Franceschi S, Montella M, Dal Maso L, Ramazzotti V, La Vecchia C (2007) Risk factors for prostate cancer in men aged less than 60 years: a case-control study from Italy. *Urology* **70**(6): 1121-6

Gann PH, Daviglus ML, Dyer AR, Stamler J (1995) Heart rate and prostate cancer mortality: results of a prospective analysis. *Cancer Epidemiol Biomarkers Prev* **4**(6): 611-6

Gann PH, Ma J, Giovannucci E, Willett W, Sacks FM, Hennekens CH, Stampfer MJ (1999) Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis. *Cancer Res* **59**(6): 1225-30

Ganry O (2005) Phytoestrogens and prostate cancer risk. *Prev Med* **41**(1): 1-6

Garcia Rodriguez LAG-P, Antonio (2004) Inverse Association between Nonsteroidal Anti-inflammatory Drugs and Prostate Cancer. *Cancer Epidemiology Biomarkers & Prevention* **13**(4): 649-653

Gartner C, Stahl W, Sies H (1997) Lycopene is more bioavailable from tomato paste than from fresh tomatoes. *Am J Clin Nutr* **66**(1): 116-22

Gilbert R, Martin RM, Beynon R, Harris R, Savovic J, Zuccolo L, Bekkering GE, Fraser WD, Sterne JA, Metcalfe C (2011) Associations of circulating and dietary vitamin D with prostate cancer risk: a systematic review and dose-response meta-analysis. *Cancer Causes Control* **22**(3): 319-40

Gilbert R, Metcalfe C, Oliver SE, Whiteman DC, Bain C, Ness A, Donovan J, Hamdy F, Neal DE, Lane JA, Martin RM (2009) Life course sun exposure and risk of prostate cancer: population-based nested case-control study and meta-analysis. *Int J Cancer* **125**(6): 1414-23

Giles GG, Severi G, English DR, McCredie MR, MacInnis R, Boyle P, Hopper JL (2003a) Early growth, adult body size and prostate cancer risk. *Int J Cancer* **103**(2): 241-5

Giles GG, Severi G, English DR, McCredie MRE, Borland R, Boyle P, Hopper JL (2003b) Sexual factors and prostate cancer. *BJU International* **92**(3): 211-216

Giles GG, Severi G, McCredie MR, English DR, Johnson W, Hopper JL, Boyle P (2001) Smoking and prostate cancer: findings from an Australian case-control study. *Ann Oncol* **12**(6): 761-5

Gill JK, Franke AA, Steven Morris J, Cooney RV, Wilkens LR, Le Marchand L, Goodman MT, Henderson BE, Kolonel LN (2009) Association of selenium, tocopherols, carotenoids, retinol, and 15-isoprostane F(2t) in serum or urine with prostate cancer risk: the multiethnic cohort. *Cancer Causes Control* **20**(7): 1161-71

Gillie O (ed) (2006) *Sunlight, Vitamin D & Health*. London: Health Research Forum Publishing

Giovannucci E (1998) Dietary influences of 1,25(OH)2 vitamin D in relation to prostate cancer: a hypothesis. *Cancer Causes Control* **9**(6): 567-82

Giovannucci E (2005) The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). *Cancer Causes Control* **16**(2): 83-95

Giovannucci E (2007) Strengths and limitations of current epidemiologic studies: vitamin D as a modifier of colon and prostate cancer risk. *Nutr Rev* **65**(8 Pt 2): S77-9

Giovannucci E, Michaud D (2007) The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. *Gastroenterology* **132**(6): 2208-25

Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC (2002) A prospective study of tomato products, lycopene, and prostate cancer risk. *J Natl Cancer Inst* **94**(5): 391-8

Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Willett WC (1997) Height, body weight, and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* **6**(8): 557-63

Gong Z, Kristal AR, Schenk JM, Tangen CM, Goodman PJ, Thompson IM (2009) Alcohol consumption, finasteride, and prostate cancer risk: results from the Prostate Cancer Prevention Trial. *Cancer* **115**(16): 3661-9

Gong Z, Neuhouser ML, Goodman PJ, Albanes D, Chi C, Hsing AW, Lippman SM, Platz EA, Pollak MN, Thompson IM, Kristal AR (2006) Obesity, Diabetes, and Risk of Prostate Cancer: Results from the Prostate Cancer Prevention Trial. *Cancer Epidemiology Biomarkers & Prevention* **15**(10): 1977-1983

Gonzalgo MLI, W. B. (2003) Molecular pathways to prostate cancer. *J Urol* **170**(6 Pt 1): 2444-52

Grandin L, Orsi L, Troussard X, Monnereau A, Berthou C, Fenaux P, Marit G, Soubeyran P, Huguet F, Milpied N, Leporrier M, Hemon D, Clavel J (2008) UV radiation exposure, skin type and lymphoid malignancies: results of a French case-control study. *Cancer Causes Control* **19**(3): 305-15

Grundy SM, Vega GL (1990) Causes of high blood cholesterol. *Circulation* **81**(2): 412-27

Habel LA, Van Den Eeden SK, Friedman GD (2000) Body size, age at shaving initiation, and prostate cancer in a large, multiracial cohort. *Prostate* **43**(2): 136-43

Hack EE, Siemens DR, Groome PA (2010) The relationship between adiposity and gleason score in men with localized prostate cancer. *Prostate* **70**(15): 1683-91

Hamilton-Reeves JM, Rebello SA, Thomas W, Slaton JW, Kurzer MS (2007) Isoflavone-Rich Soy Protein Isolate Suppresses Androgen Receptor Expression without Altering Estrogen Receptor-ÃŸ Expression or Serum Hormonal Profiles in Men at High Risk of Prostate Cancer. *The Journal of Nutrition* **137**(7): 1769-1775

Hartman TJ, Albanes D, Pietinen P, Hartman AM, Rautalahti M, Tangrea JA, Taylor PR (1998) The association between baseline vitamin E, selenium, and prostate cancer in the alpha-tocopherol, beta-carotene cancer prevention study. *Cancer Epidemiol Biomarkers Prev* **7**(4): 335-40

Harvei S, Kravdal O (1997) The importance of marital and socioeconomic status in incidence and survival of prostate cancer. An analysis of complete Norwegian birth cohorts. *Prev Med* **26**(5 Pt 1): 623-32

Hayes RB, Pottern LM, Strickler H, Rabkin C, Pope V, Swanson GM, Greenberg RS, Schoenberg JB, Liff J, Schwartz AG, Hoover RN, Fraumeni JF, Jr. (2000) Sexual behaviour, STDs and risks for prostate cancer. *Br J Cancer* **82**(3): 718-25

Heald CL, Ritchie MR, Bolton-Smith C, Morton MS, Alexander FE (2007) Phyto-oestrogens and risk of prostate cancer in Scottish men. *Br J Nutr* **98**(2): 388-96

Hemminki K, Chen B (2005) Familial association of prostate cancer with other cancers in the Swedish Family-Cancer Database. *The Prostate* **65**(2): 188-194

Hemminki K, Sundquist J, Bermejo JL (2008) How common is familial cancer? *Annals of Oncology* **19**(1): 163-167

Henderson L, Irving K, Gregory J, Bates CJ, Prentice A, Perks J, Swan G, Farron M (eds) (2003) *The National Diet & Nutrition Survey: adults aged 19 to 64 years. Vitamin and mineral intake and urinary analytes*. London: HMSO

Hernandez BY, Park SY, Wilkens LR, Henderson BE, Kolonel LN (2009) Relationship of body mass, height, and weight gain to prostate cancer risk in the multiethnic cohort. *Cancer Epidemiology Biomarkers and Prevention* **18**(9): 2413-2421

Hinz B, Cheremina O, Brune K (2008) Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. *The FASEB Journal* **22**(2): 383-390

Holt SK, Salinas CA, Stanford JL (2008) Vasectomy and the risk of prostate cancer. *J Urol* **180**(6): 2565-7; discussion 2567-8

Hsing AW, Chen C, Chokkalingam AP, Gao YT, Dightman DA, Nguyen HT, Deng J, Cheng J, Sesterhenn IA, Mostofi FK, Stanczyk FZ, Reichardt JK (2001) Polymorphic markers in the SRD5A2 gene and prostate cancer risk: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev* **10**(10): 1077-82

Hsing AW, Deng J, Sesterhenn IA, Mostofi FK, Stanczyk FZ, Benichou J, Xie T, Gao YT (2000a) Body size and prostate cancer: a population-based case-control study in China. *Cancer Epidemiol Biomarkers Prev* **9**(12): 1335-41

Hsing AW, Tsao L, Devesa SS (2000b) International trends and patterns of prostate cancer incidence and mortality. *Int J Cancer* **85**(1): 60-7

Hsu A, Bray TM, Ho E (2010) Anti-inflammatory activity of soy and tea in prostate cancer prevention. *Exp Biol Med (Maywood)* **235**(6): 659-67

IDF (2006) The IDF consensus worldwide definition of the Metabolic Syndrome, George Alberti PZ, Jonathan Shaw, Scott M. Grundy, (ed): International Diabetes Federation,

Jackson MD, Walker SP, Simpson CM, McFarlane-Anderson N, Bennett FI, Coard KCM, Aiken WD, Tulloch T, Paul TJ, Wan RL (2010) Body size and risk of prostate cancer in Jamaican men. *Cancer Causes and Control* **21**(6): 909-917

Jackson MJ, Broome CS, McArdle F (2003) Marginal dietary selenium intakes in the UK: are there functional consequences? *J Nutr* **133**(5 Suppl 1): 1557S-9S

Jackson MJ, Dillon SA, Broome CS, McArdle A, Hart CA, McArdle F (2004) Are there functional consequences of a reduction in selenium intake in UK subjects? *Proc Nutr Soc* **63**(4): 513-7

Jacobs EJ, Rodriguez C, Bain EB, Wang Y, Thun MJ, Calle EE (2007a) Cholesterol-lowering drugs and advanced prostate cancer incidence in a large U.S. cohort. *Cancer Epidemiol Biomarkers Prev* **16**(11): 2213-7

Jacobs EJ, Rodriguez C, Mondul AM, Connell CJ, Henley SJ, Calle EE, Thun MJ (2005) A large cohort study of aspirin and other nonsteroidal anti-inflammatory drugs and prostate cancer incidence. *J Natl Cancer Inst* **97**(13): 975-80

Jacobs EJ, Thun MJ, Bain EB, Rodriguez C, Henley SJ, Calle EE (2007b) A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence. *J Natl Cancer Inst* **99**(8): 608-15

Jacobsen BK, Knutsen SF, Fraser GE (1998) Does high soy milk intake reduce prostate cancer incidence? The Adventist Health Study (United States). *Cancer Causes Control* **9**(6): 553-7

Jain MG, Hislop GT, Howe GR, Ghadirian P (1999) Plant foods, antioxidants, and prostate cancer risk: findings from case-control studies in Canada. *Nutr Cancer* **34**(2): 173-84

Jenab M, Ferrari P, Mazuir M, Tjonneland A, Clavel-Chapelon F, Linseisen J, Trichopoulou A, Tumino R, Bueno-de-Mesquita HB, Lund E, Gonzalez CA, Johansson G, Key TJ, Riboli E (2005) Variations in lycopene blood levels and tomato consumption across European countries based on the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *J Nutr* **135**(8): 2032S-6S

Jian L, Du C-J, Lee AH, Binns CW (2005) Do dietary lycopene and other carotenoids protect against prostate cancer? *International Journal of Cancer* **113**(6): 1010-1014

Jian L, Zhang DH, Lee AH, Binns CW (2004) Do preserved foods increase prostate cancer risk? *Br J Cancer* **90**(9): 1792-5

Joanne M. Holden, Alison L. Eldridge, Gary R. Beecher I, Marilyn Buzzard, Seema Bhagwat, Carol S. Davis LW, Douglass SG, David Haytowitz, Schakel S (1999) Carotenoid Content of U.S. Foods: An Update of the Database. *Journal of Food Composition and Analysis* **Vol.12**(Issue3): Pages 169-196

John EM, Dreon DM, Koo J, Schwartz GG (2004) Residential sunlight exposure is associated with a decreased risk of prostate cancer. *J Steroid Biochem Mol Biol* **89-90**(1-5): 549-52

John EM, Koo J, Schwartz GG (2007) Sun exposure and prostate cancer risk: evidence for a protective effect of early-life exposure. *Cancer Epidemiol Biomarkers Prev* **16**(6): 1283-6

Johns LE, Houlston RS (2003) A systematic review and meta-analysis of familial prostate cancer risk. *BJU International* **91**(9): 789-794

Jung H, Kim KH, Yoon SJ, Kim TB (2010) Second to fourth digit ratio: a predictor of prostate-specific antigen level and the presence of prostate cancer. *BJU Int*

Karppi J, Kurl S, Nurmi T, Rissanen TH, Pukkala E, Nyyssonen K (2009) Serum lycopene and the risk of cancer: the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) study. *Ann Epidemiol* **19**(7): 512-8

Kasper JS, Giovannucci E (2006) A meta-analysis of diabetes mellitus and the risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* **15**(11): 2056-62

Kasper JS, Liu Y, Giovannucci E (2009) Diabetes mellitus and risk of prostate cancer in the health professionals follow-up study. *Int J Cancer* **124**(6): 1398-403

Kasper JS, Liu Y, Pollak MN, Rifai N, Giovannucci E (2008) Hormonal profile of diabetic men and the potential link to prostate cancer. *Cancer Causes Control* **19**(7): 703-10

Kaye JA, Jick H (2004) Statin use and cancer risk in the General Practice Research Database. *Br J Cancer* **90**(3): 635-7

Kerber RA, O'Brien E (2005) A cohort study of cancer risk in relation to family histories of cancer in the Utah population database. *Cancer* **103**(9): 1906-1915

Key TJ, Appleby PN, Allen NE, Travis RC, Roddam AW, Jenab M, Egevad L, Tjonneland A, Johnsen NF, Overvad K, Linseisen J, Rohrmann S, Boeing H, Pischon T, Psaltopoulou T, Trichopoulou A, Trichopoulos D, Palli D, Vineis P, Tumino R, Berrino F, Kiemeney L, Bueno-de-Mesquita HB, Quiros JR, Gonzalez CA, Martinez C, Larranaga N, Chirlaque MD, Ardanaz E, Stattin P, Hallmans G, Khaw KT, Bingham S, Slimani N, Ferrari P, Rinaldi S, Riboli E (2007) Plasma carotenoids, retinol, and tocopherols and the risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition study. *Am J Clin Nutr* **86**(3): 672-81

Key TJA, Silcocks PB, Davey GK, Appleby PN, Bishop DT (1997) A case-control study of diet and prostate cancer. *Br J Cancer* **76**(5): 678-687

Kirby RSMIP (ed) (2009) *Fast facts : prostate cancer* Oxford: Health Press

Kirsh VA, Mayne ST, Peters U, Chatterjee N, Leitzmann MF, Dixon LB, Urban DA, Crawford ED, Hayes RB (2006) A prospective study of lycopene and tomato product intake and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* **15**(1): 92-8

Kolonel LN, Hankin JH, Whittemore AS, Wu AH, Gallagher RP, Wilkens LR, John EM, Howe GR, Dreon DM, West DW, Paffenbarger RS, Jr. (2000) Vegetables, fruits, legumes and prostate cancer: a multiethnic case-control study. *Cancer Epidemiol Biomarkers Prev* **9**(8): 795-804

Krishnadasan A, Kennedy N, Zhao Y, Morgenstern H, Ritz B (2007) Nested case-control study of occupational chemical exposures and prostate cancer in aerospace and radiation workers. *Am J Ind Med* **50**(5): 383-90

Kristal AR, Arnold KB, Neuhouser ML, Goodman P, Platz EA, Albanes D, Thompson IM (2010) Diet, supplement use, and prostate cancer risk: results from the prostate cancer prevention trial. *Am J Epidemiol* **172**(5): 566-77

Kristal AR, Till C, Platz EA, Song X, King IB, Neuhouser ML, Ambrosone CB, Thompson IM (2011) Serum lycopene concentration and prostate cancer risk: results from the Prostate Cancer Prevention Trial. *Cancer Epidemiol Biomarkers Prev* **20**(4): 638-46

Kritchevsky SB, Kritchevsky D (1992) Serum cholesterol and cancer risk: an epidemiologic perspective. *Annu Rev Nutr* **12:** 391-416

Kuoppala J, Lamminpaa A, Pukkala E (2008) Statins and cancer: A systematic review and meta-analysis. *Eur J Cancer* **44**(15): 2122-32

Kurahashi N, Iwasaki M, Inoue M, Sasazuki S, Tsugane S (2008) Plasma isoflavones and subsequent risk of prostate cancer in a nested case-control study: the Japan Public Health Center. *J Clin Oncol* **26**(36): 5923-9

Kyle E, Neckers L, Takimoto C, Curt G, Bergan R (1997) Genistein-induced apoptosis of prostate cancer cells is preceded by a specific decrease in focal adhesion kinase activity. *Mol Pharmacol* **51**(2): 193-200

La Vecchia C, Franceschi S, Talamini R, Negri E, Boyle P, D'Avanzo B (1993) Marital status, indicators of sexual activity and prostatic cancer. *J Epidemiol Community Health* **47**(6): 450-3

Langman MJ, Cheng KK, Gilman EA, Lancashire RJ (2000) Effect of anti-inflammatory drugs on overall risk of common cancer: case-control study in general practice research database. *BMJ* **320**(7250): 1642-6

Lee IM, Sesso HD, Paffenbarger RS, Jr. (2001) A prospective cohort study of physical activity and body size in relation to prostate cancer risk (United States). *Cancer Causes Control* **12**(2): 187-93

Lee MM, Gomez SL, Chang JS, Wey M, Wang RT, Hsing AW (2003) Soy and isoflavone consumption in relation to prostate cancer risk in China. *Cancer Epidemiol Biomarkers Prev* **12**(7): 665-8

Leitzmann MF, Ahn J, Albanes D, Hsing AW, Schatzkin A, Chang SC, Huang WY, Weiss JM, Danforth KN, Grubb RL, 3rd, Andriole GL (2008) Diabetes mellitus and prostate cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Cancer Causes Control* **19**(10): 1267-76

Levander OA (1987) A global view of human selenium nutrition. *Annu Rev Nutr* **7:** 227-50

Lewis SJ, Murad A, Chen L, Davey Smith G, Donovan J, Palmer T, Hamdy F, Neal D, Lane JA, Davis M, Cox A, Martin RM (2010) Associations between an obesity related genetic variant (FTO rs9939609) and prostate cancer risk. *PLoS One* **5**(10): e13485

Li H, Stampfer MJ, Giovannucci EL, Morris JS, Willett WC, Gaziano JM, Ma J (2004) A prospective study of plasma selenium levels and prostate cancer risk. *J Natl Cancer Inst* **96**(9): 696-703

Li Q, Kuriyama S, Kakizaki M, Yan H, Sone T, Nagai M, Sugawara Y, Ohmori-Matsuda K, Hozawa A, Nishino Y, Tsuji I (2010) History of diabetes mellitus and the risk of prostate cancer: the Ohsaki Cohort Study. *Cancer Causes Control* **21**(7): 1025-32

Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, Parnes HL, Minasian LM, Gaziano JM, Hartline JA, Parsons JK, Bearden JD, 3rd, Crawford ED, Goodman GE, Claudio J, Winquist E, Cook ED, Karp DD, Walther P, Lieber MM, Kristal AR, Darke AK, Arnold KB, Ganz PA, Santella RM, Albanes D, Taylor PR, Probstfield JL, Jagpal TJ, Crowley JJ, Meyskens FL, Jr., Baker LH, Coltman CA, Jr. (2009) Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* **301**(1): 39-51

Littman AJ, White E, Kristal AR (2007) Anthropometrics and prostate cancer risk. *Am J Epidemiol* **165**(11): 1271-9

Liu L, Cozen W, Bernstein L, Ross RK, Deapen D (2001) Changing Relationship Between Socioeconomic Status and Prostate Cancer Incidence. *Journal of the National Cancer Institute* **93**(9): 705-709

Liu X, Allen JD, Arnold JT, Blackman MR (2008) Lycopene inhibits IGF-I signal transduction and growth in normal prostate epithelial cells by decreasing DHT-modulated IGF-I production in co-cultured reactive stromal cells. *Carcinogenesis* **29**(4): 816-23

Liu X, Plummer SJ, Nock NL, Casey G, Witte JS (2006) Nonsteroidal antiinflammatory drugs and decreased risk of advanced prostate cancer: modification by lymphotoxin alpha. *Am J Epidemiol* **164**(10): 984-9

Liu X, Rybicki BA, Casey G, Witte JS (2005) Relationship between body size and prostate cancer in a sibling based case-control study. *J Urol* **174**(6): 2169-73

Lophatananon A, Archer J, Easton D, Pocock R, Dearnaley D, Guy M, Kote-Jarai Z, O'Brien L, Wilkinson RA, Hall AL, Sawyer E, Page E, Liu JF, Barratt S, Rahman AA, Eeles R, Muir K (2010) Dietary fat and early-onset prostate cancer risk. *Br J Nutr* **103**(9): 1375-80

Lu QY, Hung JC, Heber D, Go VL, Reuter VE, Cordon-Cardo C, Scher HI, Marshall JR, Zhang ZF (2001) Inverse associations between plasma lycopene and other carotenoids and prostate cancer. *Cancer Epidemiol Biomarkers Prev* **10**(7): 749-56

Lund Nilsen TI, Johnsen R, Vatten LJ (2000) Socio-economic and lifestyle factors associated with the risk of prostate cancer. *Br J Cancer* **82**(7): 1358-63

Luscombe CJ, Fryer AA, French ME, Liu S, Saxby MF, Jones PW, Strange RC (2001) Exposure to ultraviolet radiation: association with susceptibility and age at presentation with prostate cancer. *The Lancet* **358**(9282): 641-642

Ma J, Sehgal NL, Ayanian JZ, Stafford RS (2005) National trends in statin use by coronary heart disease risk category. *PLoS Med* **2**(5): e123

MacInnis RJ, English DR, Gertig DM, Hopper JL, Giles GG (2003) Body size and composition and prostate cancer risk. *Cancer Epidemiol Biomarkers Prev* **12**(12): 1417-21

MAFF (1993) Ministry of Agriculture Fisheries and Foods. In *Annual Reports of National Food Survey Committee*. London: HMSO

Magura L, Blanchard R, Hope B, Beal JR, Schwartz GG, Sahmoun AE (2008) Hypercholesterolemia and prostate cancer: a hospital-based case-control study. *Cancer Causes Control* **19**(10): 1259-66

Mahajan R, Blair A, Lynch CF, Schroeder P, Hoppin JA, Sandler DP, Alavanja MC (2006) Fonofos exposure and cancer incidence in the agricultural health study. *Environ Health Perspect* **114**(12): 1838-42

Mahmud S, Franco E, Aprikian A (2004) Prostate cancer and use of nonsteroidal anti-inflammatory drugs: systematic review and meta-analysis. *Br J Cancer* **90**(1): 93-9

Mahmud SM, Franco EL, Aprikian AG (2010) Use of nonsteroidal anti-inflammatory drugs and prostate cancer risk: a meta-analysis. *Int J Cancer* **127**(7): 1680-91

Manning JT, Bundred PE, Flanagan BF (2002) The ratio of 2nd to 4th digit length: a proxy for transactivation activity of the androgen receptor gene? *Med Hypotheses* **59**(3): 334-6

Mantzoros CS (1999) The role of leptin in human obesity and disease: a review of current evidence. *Ann Intern Med* **130**(8): 671-80

Martin RM, Vatten L, Gunnell D, Romundstad P (2010) Blood pressure and risk of prostate cancer: Cohort Norway (CONOR). *Cancer Causes Control* **21**(3): 463-72

Maskarinec G, Singh S, Meng L, Franke AA (1998) Dietary soy intake and urinary isoflavone excretion among women from a multiethnic population. *Cancer Epidemiol Biomarkers Prev* **7**(7): 613-9

McCann SE, Ambrosone CB, Moysich KB, Brasure J, Marshall JR, Freudenheim JL, Wilkinson GS, Graham S (2005) Intakes of selected nutrients, foods, and phytochemicals and prostate cancer risk in western New York. *Nutr Cancer* **53**(1): 33-41

McCarty MF (1997) Up-regulation of IGF binding protein-1 as an anticarcinogenic strategy: relevance to caloric restriction, exercise, and insulin sensitivity. *Med Hypotheses* **48**(4): 297-308

Menezes RJ, Swede H, Niles R, Moysich KB (2006) Regular use of aspirin and prostate cancer risk (United States). *Cancer Causes Control* **17**(3): 251-6

Montironi R, Mazzucchelli R, Algaba F, Lopez-Beltran A (2000) Morphological identification of the patterns of prostatic intraepithelial neoplasia and their importance. *Journal of Clinical Pathology* **53**(9): 655-665

Morton LM, Cahill J, Hartge P (2006) Reporting participation in epidemiologic studies: a survey of practice. *Am J Epidemiol* **163**(3): 197-203

Moser M From JNC I to JNC 7--What Have We Learned? *Progress in Cardiovascular Diseases* **48**(5): 303-315

Mouw T, Koster A, Wright ME, Blank MM, Moore SC, Hollenbeck A, Schatzkin A (2008) Education and risk of cancer in a large cohort of men and women in the United States. *PLoS One* **3**(11): e3639

Mucci LA, Tamimi R, Lagiou P, Trichopoulou A, Benetou V, Spanos E, Trichopoulos D (2001) Are dietary influences on the risk of prostate cancer mediated through the insulin-like growth factor system? *BJU Int* **87**(9): 814-20

Mulligan AA, Welch AA, McTaggart AA, Bhaniani A, Bingham SA (2007) Intakes and sources of soya foods and isoflavones in a UK population cohort study (EPIC-Norfolk). *Eur J Clin Nutr* **61**(2): 248-54

Murad AS, Down L, Davey Smith G, Donovan JL, Athene Lane J, Hamdy FC, Neal DE, Martin RM (2011) Associations of aspirin, nonsteroidal anti-inflammatory drug and paracetamol use with PSA-detected prostate cancer: findings from a large, population-based, case-control study (the ProtecT study). *Int J Cancer* **128**(6): 1442-8

Murtola TJ, Tammela TL, Lahtela J, Auvinen A (2007) Cholesterol-lowering drugs and prostate cancer risk: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev* **16**(11): 2226-32

Murtola TJ, Tammela TL, Lahtela J, Auvinen A (2008) Antidiabetic medication and prostate cancer risk: a population-based case-control study. *Am J Epidemiol* **168**(8): 925-31

Murtola TJ, Tammela TL, Maattanen L, Huhtala H, Platz EA, Ala-Opas M, Stenman UH, Auvinen A (2010) Prostate cancer and PSA among statin users in the Finnish prostate cancer screening trial. *Int J Cancer* **127**(7): 1650-9

Must A, Willett WC, Dietz WH (1993) Remote Recall of Childhood Height, Weight, and Body Build by Elderly Subjects. *American Journal of Epidemiology* **138**(1): 56-64

Muthuri SG. A case-control study of dietary factors and gene-environment = interactions in large joint osteoarthritis / Stella Gakii Muthuri. PhD, University of, Nottingham, 2010

Muthuri SG. An Investigation of selenium in protection of prostate cancer. MPH, University of Nottingham, 2004

Myles P, Evans S, Lophatananon A, Dimitropoulou P, Easton D, Key T, Pocock R, Dearnaley D, Guy M, Edwards S, O'Brien L, Gehr-Swain B, Hall A, Wilkinson R, Eeles R, Muir K (2008) Diagnostic radiation procedures and risk of prostate cancer. *Br J Cancer* **98**(11): 1852-6

Nadiminty N, Gao AC (2008) Mechanisms of selenium chemoprevention and therapy in prostate cancer. *Mol Nutr Food Res* **52**(11): 1247-60
Nagata Y, Sonoda T, Mori M, Miyanaga N, Okumura K, Goto K, Naito S, Fujimoto K, Hirao Y, Takahashi A, Tsukamoto T, Akaza H (2007) Dietary isoflavones may protect against prostate cancer in Japanese men. *J Nutr* **137**(8): 1974-9

Neugut AI, Rosenberg DJ, Ahsan H, Jacobson JS, Wahid N, Hagan M, Rahman MI, Khan ZR, Chen L, Pablos-Mendez A, Shea S (1998) Association between coronary heart disease and cancers of the breast, prostate, and colon. *Cancer Epidemiology Biomarkers & Prevention* **7**(10): 869-873

Nilsen TIL, Johnsen R, Vatten LJ (2000) Socio-economic and lifestyle factors associated with the risk of prostate cancer. *Br J Cancer* **82**(7): 1358-1363

Nomura AM, Hankin JH, Lee J, Stemmermann GN (2004) Cohort study of tofu intake and prostate cancer: no apparent association. *Cancer Epidemiol Biomarkers Prev* **13**(12): 2277-9

Nomura AMY, Lee J, Stemmermann GN, Combs GF (2000) Serum Selenium and Subsequent Risk of Prostate Cancer. *Cancer Epidemiology Biomarkers & Prevention* **9**(9): 883-887

Norrish AE, Jackson RT, Sharpe SJ, Skeaff CM (2000a) Prostate cancer and dietary carotenoids. *Am J Epidemiol* **151**(2): 119-23

Norrish AE, McRae CU, Holdaway IM, Jackson RT (2000b) Height-related risk factors for prostate cancer. *Br J Cancer* **82**(1): 241-5

Olsen JH, Johansen C, Sorensen HT, McLaughlin JK, Mellemkjaer L, Steffensen FH, Fraumeni JF, Jr. (1999) Lipid-lowering medication and risk of cancer. *J Clin Epidemiol* **52**(2): 167-9

ONS OfNS (1998a) Prevalence of non-insulin treated diabetes per 1000 patients, by age, sex and ONS area classification 1994-1998. Key Health Statistics from General Practice 1998

ONS OfNS (1998b) Prevalence of raised blood pressure per 1000 patients, by age, sex and calendar year 1994-1998. Key Health Statistics from General Practice 1998

ONS OfNS (1998c) Prevalence of treated coronary heart disease and stroke by age and gender 1998 England & Wales, Agency MC (ed)

ONS OfNS (2001) High Blood Pressure by sex and age 2001, Health Do (ed). Health Survey for England

ONS OfNS (2009) Health Survey of England 2009 Adult Trend Tables:

ONS OfNS (ed) (2000) *Standard Occupational Classification 2000 (SOC2000)*: London: The Stationery Office

Ozasa K, Nakao M, Watanabe Y, Hayashi K, Miki T, Mikami K, Mori M, Sakauchi F, Washio M, Ito Y, Suzuki K, Kubo T, Wakai K, Tamakoshi A (2005) Association of serum phytoestrogen concentration and dietary habits in a sample set of the JACC Study. *J Epidemiol* **15** Suppl **2**: S196-202

Padayatty SJ, Marcelli M, Shao TC, Cunningham GR (1997) Lovastatin-induced apoptosis in prostate stromal cells. *J Clin Endocrinol Metab* **82**(5): 1434-9

Pareek G, Shevchuk M, Armenakas NA, Vasjovic L, Hochberg DA, Basillote JB, Fracchia JA (2003) The effect of finasteride on the expression of vascular endothelial growth factor and microvessel density: a possible mechanism for decreased prostatic bleeding in treated patients. *J Urol* **169**(1): 20-3

Parent ME, Desy M, Siemiatycki J (2009) Does exposure to agricultural chemicals increase the risk of prostate cancer among farmers? *Mcgill J Med* **12**(1): 70-7

Parent ME, Rousseau MC, El-Zein M, Latreille B, Desy M, Siemiatycki J (2010) Occupational and recreational physical activity during adult life and the risk of cancer among men. *Cancer Epidemiol*

Park SY, Cooney RV, Wilkens LR, Murphy SP, Henderson BE, Kolonel LN (2010) Plasma 25-hydroxyvitamin D and prostate cancer risk: the multiethnic cohort. *Eur J Cancer* **46**(5): 932-6

Park SY, Murphy SP, Wilkens LR, Stram DO, Henderson BE, Kolonel LN (2007) Calcium, vitamin D, and dairy product intake and prostate cancer risk: the Multiethnic Cohort Study. *Am J Epidemiol* **166**(11): 1259-69

Park SY, Wilkens LR, Franke AA, Le Marchand L, Kakazu KK, Goodman MT, Murphy SP, Henderson BE, Kolonel LN (2009) Urinary phytoestrogen excretion and prostate cancer risk: a nested case-control study in the Multiethnic Cohort. *Br J Cancer* **101**(1): 185-191

Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB, eds (eds) (2002) *Cancer Incidence in Five Continents, Vol. VIII* Lyon: IARC

Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB, eds (eds) (2002) *Cancer Incidence in Five Continents, Vol. VIII* Lyon: IARC

Penney KL, Schumacher FR, Li H, Kraft P, Morris JS, Kurth T, Mucci LA, Hunter DJ, Kantoff PW, Stampfer MJ, Ma J (2010) A large prospective study of SEP15 genetic variation, interaction with plasma selenium levels, and prostate cancer risk and survival. *Cancer Prev Res (Phila)* **3**(5): 604-10

Perron L, Bairati I, Moore L, Meyer F (2003) Dosage, duration and timing of nonsteroidal antiinflammatory drug use and risk of prostate cancer. *Int J Cancer* **106**(3): 409-15

Peters U, Foster CB, Chatterjee N, Schatzkin A, Reding D, Andriole GL, Crawford ED, Sturup S, Chanock SJ, Hayes RB (2007a) Serum selenium and risk of prostate cancer-a nested case-control study. *Am J Clin Nutr* **85**(1): 209-17

Peters U, Leitzmann MF, Chatterjee N, Wang Y, Albanes D, Gelmann EP, Friesen MD, Riboli E, Hayes RB (2007b) Serum lycopene, other carotenoids, and prostate cancer risk: a nested case-control study in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol Biomarkers Prev* **16**(5): 962-8

Peters U, Littman AJ, Kristal AR, Patterson RE, Potter JD, White E (2008) Vitamin E and selenium supplementation and risk of prostate cancer in the Vitamins and lifestyle (VITAL) study cohort. *Cancer Causes Control* **19**(1): 75-87

Pierce BL, Plymate S, Ostrander EA, Stanford JL (2008) Diabetes mellitus and prostate cancer risk. *Prostate* **68**(10): 1126-32

Pischon T, Boeing H, Weikert S, Allen N, Key T, Johnsen NF, Tjonneland A, Severinsen MT, Overvad K, Rohrmann S, Kaaks R, Trichopoulou A, Zoi G, Trichopoulos D, Pala V, Palli D, Tumino R, Sacerdote C, Bueno-de-Mesquita HB, May A, Manjer J, Wallstrom P, Stattin P, Hallmans G, Buckland G, Larranaga N, Chirlaque MD, Martinez C, Redondo Cornejo ML, Ardanaz E, Bingham S, Khaw KT, Rinaldi S, Slimani N, Jenab M, Riboli E (2008) Body size and risk of prostate cancer in the European prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomarkers Prev* **17**(11): 3252-61

Platz EA (2010) Is prostate cancer prevention with selenium all in the genes? *Cancer Prev Res (Phila)* **3**(5): 576-8

Platz EA, Leitzmann MF, Michaud DS, Willett WC, Giovannucci E (2003) Interrelation of energy intake, body size, and physical activity with prostate cancer in a large prospective cohort study. *Cancer Res* **63**(23): 8542-8

Platz EA, Leitzmann MF, Rimm EB, Willett WC, Giovannucci E (2004) Alcohol intake, drinking patterns, and risk of prostate cancer in a large prospective cohort study. *Am J Epidemiol* **159**(5): 444-53

Platz EA, Leitzmann MF, Visvanathan K, Rimm EB, Stampfer MJ, Willett WC, Giovannucci E (2006) Statin drugs and risk of advanced prostate cancer. *J Natl Cancer Inst* **98**(24): 1819-25

Platz EA, Rohrmann S, Pearson JD, Corrada MM, Watson DJ, De Marzo AM, Landis PK, Metter EJ, Carter HB (2005) Nonsteroidal Anti-inflammatory Drugs and Risk of Prostate Cancer in the Baltimore Longitudinal Study of Aging. *Cancer Epidemiology Biomarkers & Prevention* **14**(2): 390-396

Platz EA, Till C, Goodman PJ, Parnes HL, Figg WD, Albanes D, Neuhouser ML, Klein EA, Thompson IM, Kristal AR (2009) Men with Low Serum Cholesterol Have a Lower Risk of High-Grade Prostate Cancer in the Placebo Arm of the Prostate Cancer Prevention Trial. *Cancer Epidemiology Biomarkers & Prevention* **18**(11): 2807-2813

Pourmand G, Salem S, Mehrsai A, Lotfi M, Amirzargar MA, Mazdak H, Roshani A, Kheirollahi A, Kalantar E, Baradaran N, Saboury B, Allameh F, Karami A, Ahmadi H, Jahani Y (2007) The risk factors of prostate cancer: a multicentric case-control study in Iran. *Asian Pac J Cancer Prev* **8**(3): 422-8

Pourmand G, Salem S, Moradi K, Nikoobakht MR, Tajik P, Mehrsai A (2008) Serum selenium level and prostate cancer: a case-control study. *Nutr Cancer* **60**(2): 171-6

PSC PSC (2007) Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55[punctuation space]000 vascular deaths. *The Lancet* **370**(9602): 1829-1839

Rahman A. Risk factors for Prostate cancer: A Case-control study investigating selected key exposures and their interactions with predisposition genes. PhD Thesis, University of Nottingham, 2010

Rahman AA, Lophatananon A, Brown SS, Harriss D, Anderson J, Parker T, Easton D, Kote-Jarai Z, Pocock R, Dearnaley D, Guy M, O'Brien L, Wilkinson RA, Hall AL,

Sawyer E, Page E, Liu JF, Eeles RA, Muir K (2010) Hand pattern indicates prostate cancer risk. *Br J Cancer*

Raju N, Sobieraj-Teague M, Hirsh J, O'Donnell M, Eikelboom J (2011) Effect of aspirin on Mortality in the Primary Prevention of Cardiovascular Disease. *The American Journal of Medicine* **124**(7): 621-629

Ramon JD, L.J. (ed) (2007) *Prostate Cancer*. Berlin ; London Springer

Rapp K, Klenk J, Ulmer H, Concin H, Diem G, Oberaigner W, Schroeder J (2008) Weight change and cancer risk in a cohort of more than 65,000 adults in Austria. *Ann Oncol* **19**(4): 641-8

Rayman MP (2008) Food-chain selenium and human health: emphasis on intake. *The British journal of nutrition* **100**(2): 254-68

Rayman MP, Combs GF, Jr., Waters DJ (2009) Selenium and vitamin E supplementation for cancer prevention. *JAMA* **301**(18): 1876; author reply 1877

Riboli E (1992) Nutrition and cancer: background and rationale of the European Prospective Investigation into Cancer and Nutrition (EPIC). *Ann Oncol* **3**(10): 783-91

Rice L, Samedi VG, Medrano TA, Sweeney CA, Baker HV, Stenstrom A, Furman J, Shiverick KT (2002) Mechanisms of the growth inhibitory effects of the isoflavonoid biochanin A on LNCaP cells and xenografts. *Prostate* **52**(3): 201-12

Robinson WR, Stevens J, Gammon MD, John EM (2005) Obesity before age 30 years and risk of advanced prostate cancer. *Am J Epidemiol* **161**(12): 1107-14

Rodnguez C, Tatham LM, Thun MJ, Calle EE, Heath CW (1997) Smoking and Fatal Prostate Cancer in a Large Cohort of Adult Men. *American Journal of Epidemiology* **145**(5): 466-475

Rodriguez C, Freedland SJ, Deka A, Jacobs EJ, McCullough ML, Patel AV, Thun MJ, Calle EE (2007) Body Mass Index, Weight Change, and Risk of Prostate Cancer in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiology Biomarkers & Prevention* **16**(1): 63-69

Rodriguez C, Patel AV, Mondul AM, Jacobs EJ, Thun MJ, Calle EE (2005) Diabetes and risk of prostate cancer in a prospective cohort of US men. *Am J Epidemiol* **161**(2): 147-52

Rohrmann S, Genkinger JM, Burke A, Helzlsouer KJ, Comstock GW, Alberg AJ, Platz EA (2007) Smoking and Risk of Fatal Prostate Cancer in a Prospective U.S. Study. *Urology* **69**(4): 721-725

Rohrmann S, Linseisen J, Key TJ, Jensen MK, Overvad K, Johnsen NF, Tjonneland A, Kaaks R, Bergmann MM, Weikert C, Naska A, Trichopoulou A, Trichopoulos D, Pala V, Sacerdote C, Palli D, Tumino R, Bueno-de-Mesquita HB, Vrieling A, Gonzalez CA, Larranaga N, Navarro C, Barricarte A, Quiros JR, Martinez-Garcia C, Hallmans G, Stattin P, Manjer J, Wirfalt E, Bingham S, Khaw KT, Egevad L, Ferrari P, Jenab M, Riboli E (2008) Alcohol consumption and the risk for prostate cancer in the European Prospective Investigation into Cancer and Nutrition. *Cancer Epidemiol Biomarkers Prev* **17**(5): 1282-7

Rosenblatt KA, Wicklund KG, Stanford JL (2001) Sexual factors and the risk of prostate cancer. *Am J Epidemiol* **153**(12): 1152-8

Rowlands MA, Gunnell D, Harris R, Vatten LJ, Holly JM, Martin RM (2009) Circulating insulin-like growth factor peptides and prostate cancer risk: a systematic review and meta-analysis. *Int J Cancer* **124**(10): 2416-29

Rukin NJ, Zeegers MP, Ramachandran S, Luscombe CJ, Liu S, Saxby M, Lear J, Strange RC (2007) A comparison of sunlight exposure in men with prostate cancer and basal cell carcinoma. *Br J Cancer* **96**(3): 523-528

Salinas CA, Kwon EM, FitzGerald LM, Feng Z, Nelson PS, Ostrander EA, Peters U, Stanford JL (2010) Use of aspirin and other nonsteroidal antiinflammatory medications in relation to prostate cancer risk. *Am J Epidemiol* **172**(5): 578-90

Schoenborn CA (2004) Marital status and health: United States, 1999-2002. *Adv Data*(351): 1-32

Schroder FH, Hermanek P, Denis L, Fair WR, Gospodarowicz MK, Pavone-Macaluso M (1992) The TNM classification of prostate cancer. *Prostate Suppl* **4:** 129-38

Schwartz GG (2005) Vitamin D and the epidemiology of prostate cancer. *Semin Dial* **18**(4): 276-89

Schwartz GG, Hanchette CL (2006) UV, latitude, and spatial trends in prostate cancer mortality: all sunlight is not the same (United States). *Cancer Causes Control* **17**(8): 1091-101

Shannon J, Tewoderos S, Garzotto M, Beer TM, Derenick R, Palma A, Farris PE (2005) Statins and prostate cancer risk: a case-control study. *Am J Epidemiol* **162**(4): 318-25

Sharpe CR, Siemiatycki J, Parent ME (2001) Activities and exposures during leisure and prostate cancer risk. *Cancer Epidemiol Biomarkers Prev* **10**(8): 855-60

Sinha R, Park Y, Graubard BI, Leitzmann MF, Hollenbeck A, Schatzkin A, Cross AJ (2009) Meat and meat-related compounds and risk of prostate cancer in a large prospective cohort study in the United States. *Am J Epidemiol* **170**(9): 1165-77

Sivaprasad U, Abbas T, Dutta A (2006) Differential efficacy of 3-hydroxy-3-methylglutaryl CoA reductase inhibitors on the cell cycle of prostate cancer cells. *Mol Cancer Ther* **5**(9): 2310-6

Solomon KR, Freeman MR (2008) Do the cholesterol-lowering properties of statins affect cancer risk? *Trends Endocrinol Metab* **19**(4): 113-21

Sonoda T, Nagata Y, Mori M, Miyanaga N, Takashima N, Okumura K, Goto K, Naito S, Fujimoto K, Hirao Y, Takahashi A, Tsukamoto T, Fujioka T, Akaza H (2004) A case-control study of diet and prostate cancer in Japan: possible protective effect of traditional Japanese diet. *Cancer Sci* **95**(3): 238-42

Stahl W, Junghans A, de Boer B, Driomina ES, Briviba K, Sies H (1998) Carotenoid mixtures protect multilamellar liposomes against oxidative damage: synergistic effects of lycopene and lutein. *FEBS Lett* **427**(2): 305-8

Stamatiou KN, Alevizos AG, Mihas K, Mariolis AD, Michalodimitrakis E, Sofras F (2007) Associations between coronary heart disease, obesity and histological prostate cancer. *Int Urol Nephrol* **39**(1): 197-201

Stanford JL, FitzGerald LM, McDonnell SK, Carlson EE, McIntosh LM, Deutsch K, Hood L, Ostrander EA, Schaid DJ (2009) Dense genome-wide SNP linkage scan in 301 hereditary prostate cancer families identifies multiple regions with suggestive evidence for linkage. *Hum Mol Genet* **18**(10): 1839-48

Stang A, Ahrens W, Jockel KH (1999) Control response proportions in population-based case-control studies in Germany. *Epidemiology* **10**(2): 181-3

Stark J, Judson G, Alderete J, Mundodi V, Kucknoor A, Giovannucci E, Platz E, Sutcliffe S, Fall K, Kurth T, Ma J, Stampfer M, Mucci L (2009) Prospective study of Trichomonas vaginalis infection and prostate cancer incidence and mortality: Physicians' Health Study. *Journal of the National Cancer Institute* **101(20):** 1406-11

Stattin P, Bylund A, Rinaldi S, Biessy C, Dechaud H, Stenman UH, Egevad L, Riboli E, Hallmans G, Kaaks R (2000) Plasma insulin-like growth factor-I, insulin-like growth factor-binding proteins, and prostate cancer risk: a prospective study. *J Natl Cancer Inst* **92**(23): 1910-7

Stevens VL, Ahn J, Sun J, Jacobs EJ, Moore SC, Patel AV, Berndt SI, Albanes D, Hayes RB (2010) HNF1B and JAZF1 genes, diabetes, and prostate cancer risk. *Prostate* **70**(6): 601-7

Stock DC, Groome PA, Siemens DR, Rohland SL, Song Z (2008) Effects of non-selective non-steroidal anti-inflammatory drugs on the aggressiveness of prostate cancer. *Prostate* **68**(15): 1655-65

Stocks T, Hergens MP, Englund A, Ye W, Stattin P (2010) Blood pressure, body size and prostate cancer risk in the Swedish Construction Workers cohort. *Int J Cancer* **127**(7): 1660-8

Study Cohort. *American Journal of Epidemiology* **157**(9): 800-814

Sung J, Song YM, Lawlor DA, Smith GD, Ebrahim S (2009) Height and site-specific cancer risk: A cohort study of a korean adult population. *Am J Epidemiol* **170**(1): 53-64

Suzuki T, Matsuo K, Wakai K, Hiraki A, Hirose K, Sato S, Ueda R, Tajima K (2007) Effect of familial history and smoking on common cancer risks in Japan. *Cancer* **109**(10): 2116-2123

Syrigos KN (ed) (2001) *Prostate cancer : biology, diagnosis and management* Oxford: Oxford University Press

Tavani A, Bertuccio P, Bosetti C, Talamini R, Negri E, Franceschi S, Montella M, La Vecchia C (2005a) Dietary intake of calcium, vitamin D, phosphorus and the risk of prostate cancer. *Eur Urol* **48**(1): 27-33

Tavani A, Gallus S, Bertuzzi M, Dal Maso L, Zucchetto A, Negri E, Franceschi S, Ramazzotti V, Montella M, La Vecchia C (2005b) Diabetes mellitus and the risk of prostate cancer in Italy. *Eur Urol* **47**(3): 313-7; discussion 317

Tavani A, Gallus S, Bosetti C, Tzonou A, Lagiou P, Negri E, Trichopoulos D, La Vecchia C (2002) Diabetes and the risk of prostate cancer. *Eur J Cancer Prev* **11**(2): 125-8

Thomas G, Jacobs KB, Yeager M, Kraft P, Wacholder S, Orr N, Yu K, Chatterjee N, Welch R, Hutchinson A, Crenshaw A, Cancel-Tassin G, Staats BJ, Wang Z, Gonzalez-Bosquet J, Fang J, Deng X, Berndt SI, Calle EE, Feigelson HS, Thun MJ, Rodriguez C, Albanes D, Virtamo J, Weinstein S, Schumacher FR, Giovannucci E, Willett WC, Cussenot O, Valeri A, Andriole GL, Crawford ED, Tucker M, Gerhard DS, Fraumeni JF, Hoover R, Hayes RB, Hunter DJ, Chanock SJ (2008) Multiple loci identified in a genome-wide association study of prostate cancer. *Nat Genet* **40**(3): 310-315

Thompson IM, Tangen CM, Goodman PJ, Lucia MS, Klein EA (2009) Chemoprevention of prostate cancer. *J Urol* **182**(2): 499-507; discussion 508

Travis RC, Spencer EA, Allen NE, Appleby PN, Roddam AW, Overvad K, Johnsen NF, Olsen A, Kaaks R, Linseisen J, Boeing H, Nothlings U, Bueno-de-Mesquita HB, Ros MM, Sacerdote C, Palli D, Tumino R, Berrino F, Trichopoulou A, Dilis V,

Trichopoulos D, Chirlaque MD, Ardanaz E, Larranaga N, Gonzalez C, Suarez LR, Sanchez MJ, Bingham S, Khaw KT, Hallmans G, Stattin P, Rinaldi S, Slimani N, Jenab M, Riboli E, Key TJ (2009) Plasma phyto-oestrogens and prostate cancer in the European Prospective Investigation into Cancer and Nutrition. *Br J Cancer* **100**(11): 1817-23

Tseng CH (2011) Prostate cancer mortality in Taiwanese men: increasing age-standardized trend in general population and increased risk in diabetic men. *Ann Med* **43**(2): 142-50

Tseng M, Breslow RA, Graubard BI, Ziegler RG (2005) Dairy, calcium, and vitamin D intakes and prostate cancer risk in the National Health and Nutrition Examination Epidemiologic Follow-up Study cohort. *Am J Clin Nutr* **81**(5): 1147-54

Van Maele-Fabry G, Libotte V, Willems J, Lison D (2006) Review and meta-analysis of risk estimates for prostate cancer in pesticide manufacturing workers. *Cancer Causes Control* **17**(4): 353-73

VandenLangenberg GM, Brady WE, Nebeling LC, Block G, Forman M, Bowen PE, Stacewicz-Sapuntzakis M, Mares-Perlman JA (1996) Influence of using different sources of carotenoid data in epidemiologic studies. *J Am Diet Assoc* **96**(12): 1271-5

Vidarsdottir H, Gunnarsdottir HK, Olafsdottir EJ, Olafsdottir GH, Pukkala E, Tryggvadottir L (2008) Cancer risk by education in Iceland; a census-based cohort study. *Acta Oncol* **47**(3): 385-90 **Volume 13(1):** pp 72-79

Walley T, Folino-Gallo P, Schwabe U, van Ganse E (2004) Variations and increase in use of statins across Europe: data from administrative databases. *BMJ* **328**(7436): 385-6

Wallstrom P, Bjartell A, Gullberg B, Olsson H, Wirfalt E (2009) A prospective Swedish study on body size, body composition, diabetes, and prostate cancer risk. *Br J Cancer* **100**(11): 1799-805

Walter RB, Milano F, Brasky TM, White E (2011) Long-Term Use of Acetaminophen, Aspirin, and Other Nonsteroidal Anti-Inflammatory Drugs and

Risk of Hematologic Malignancies: Results From the Prospective Vitamins and Lifestyle (VITAL) Study. *Journal of Clinical Oncology*

Ward H, Chapelais G, Kuhnle GG, Luben R, Khaw KT, Bingham S (2008) Lack of prospective associations between plasma and urinary phytoestrogens and risk of prostate or colorectal cancer in the European Prospective into Cancer-Norfolk study. *Cancer Epidemiol Biomarkers Prev* **17**(10): 2891-4

Waters KM, Henderson BE, Stram DO, Wan P, Kolonel LN, Haiman CA (2009) Association of diabetes with prostate cancer risk in the multiethnic cohort. *Am J Epidemiol* **169**(8): 937-45

Watters JL, Park Y, Hollenbeck A, Schatzkin A, Albanes D (2009) Cigarette smoking and prostate cancer in a prospective US cohort study. *Cancer Epidemiol Biomarkers Prev* **18**(9): 2427-35

Waxman J (ed) (2002) *The prostate cancer book* London

Weiderpass E, Ye W, Vainio H, Kaaks R, Adami HO (2002) Reduced risk of prostate cancer among patients with diabetes mellitus. *Int J Cancer* **102**(3): 258-61

Weinmann S, Shapiro JA, Rybicki BA, Enger SM, Van Den Eeden SK, Richert-Boe KE, Weiss NS (2010) Medical history, body size, and cigarette smoking in relation to fatal prostate cancer. *Cancer Causes Control* **21**(1): 117-25

Wellman NS, Friedberg B (2002) Causes and consequences of adult obesity: health, social and economic impacts in the United States. *Asia Pac J Clin Nutr* **11 Suppl 8:** S705-9

Wells JC, Treleaven P, Cole TJ (2007) BMI compared with 3-dimensional body shape: the UK National Sizing Survey. *Am J Clin Nutr* **85**(2): 419-25

Wells TS, Bukowinski AT, Smith TC, Smith B, Dennis LK, Chu LK, Gray GC, Ryan MA (2010) Racial differences in prostate cancer risk remain among US servicemen with equal access to care. *Prostate* **70**(7): 727-34

White C (2002) A review of the pharmacologic and pharmacokinetic aspects of rosuvastatin. *The Journal of Clinical Pharmacology* **42**(9): 963-970

Wild SH, Fischbacher CM, Brock A, Griffiths C, Bhopal R (2006) Mortality from all cancers and lung, colorectal, breast and prostate cancer by country of birth in England and Wales, 2001-2003. *Br J Cancer* **94**(7): 1079-85

Will JC, Vinicor F, Calle EE (1999) Is diabetes mellitus associated with prostate cancer incidence and survival? *Epidemiology* **10**(3): 313-8

Willett W (1998) *Nutritional epidemiology*: Oxford University Press

Wolk A, Mantzoros CS, Andersson SO, Bergstrom R, Signorello LB, Lagiou P, Adami HO, Trichopoulos D (1998) Insulin-like growth factor 1 and prostate cancer risk: a population-based, case-control study. *J Natl Cancer Inst* **90**(12): 911-5

Wright JL, Stanford JL (2009) Metformin use and prostate cancer in Caucasian men: results from a population-based case-control study. *Cancer Causes Control* **20**(9): 1617-22

Wright ME, Chang SC, Schatzkin A, Albanes D, Kipnis V, Mouw T, Hurwitz P, Hollenbeck A, Leitzmann MF (2007) Prospective study of adiposity and weight change in relation to prostate cancer incidence and mortality. *Cancer* **109**(4): 675-84

Wu K, Erdman JW, Jr., Schwartz SJ, Platz EA, Leitzmann M, Clinton SK, DeGroff V, Willett WC, Giovannucci E (2004) Plasma and dietary carotenoids, and the risk of prostate cancer: a nested case-control study. *Cancer Epidemiol Biomarkers Prev* **13**(2): 260-9

Xu J, Sun J, Kader AK, Lindstrom S, Wiklund F, Hsu FC, Johansson JE, Zheng SL, Thomas G, Hayes RB, Kraft P, Hunter DJ, Chanock SJ, Isaacs WB, Gronberg H (2009) Estimation of absolute risk for prostate cancer using genetic markers and family history. *Prostate* **69**(14): 1565-72

Zeegers MPA, Jellema A, Ostrer H (2003) Empiric risk of prostate carcinoma for relatives of patients with prostate carcinoma. *Cancer* **97**(8): 1894-1903

Zhang J, Dhakal I, Stone A, Ning B, Greene G, Lang NP, Kadlubar FF (2007) Plasma carotenoids and prostate cancer: a population-based case-control study in Arkansas. *Nutr Cancer* **59**(1): 46-53

Zhang W, Hu R (2010) Why does diabetes offer protective effects against prostate cancer? The possible role of its microvascular complications. *Med Hypotheses* **74**(2): 242-3

Zhang Y, Coogan P, Palmer JR, Strom BL, Rosenberg L (2009) Vitamin and mineral use and risk of prostate cancer: the case-control surveillance study. *Cancer Causes Control* **20**(5): 691-8

Zhang YC, Albrecht D, Bomser J, Schwartz SJ, Vodovotz Y (2003) Isoflavone profile and biological activity of soy bread. *J Agric Food Chem* **51**(26): 7611-6

Zheng SL, Liu W, Wiklund F, Dimitrov L, Balter K, Sun J, Adami HO, Johansson JE, Chang B, Loza M, Turner AR, Bleecker ER, Meyers DA, Carpten JD, Duggan D, Isaacs WB, Xu J, Gronberg H (2006) A comprehensive association study for genes in inflammation pathway provides support for their roles in prostate cancer risk in the CAPS study. *Prostate* **66**(14): 1556-64

Zhu K, Lee IM, Sesso HD, Buring JE, Levine RS, Gaziano JM (2004) History of diabetes mellitus and risk of prostate cancer in physicians. *Am J Epidemiol* **159**(10): 978-82

Appendices

Cancer Registry and Report of Prostate Cancer Prevalence & Incidence in Asia and Malaysia

Progress of Gene-Environment Interactions in Prostate Cancer Research (United Kingdom)

Prostate Cancer Questionnaire

Cancer Registry and Report of Prostate Cancer Prevalence & Incidence in Asia and Malaysia

Prostate cancer reporting in Asia is mainly through reported cases in hospitals with confirmation through histology. The highest level of evidence is through the International Agency for research on Cancer (IARC) and International Association of Cancer Registries: *Cancer Incidence in Five Continents* which is produced every 5 years through collaborations of clinicians, preclinical staffs, epidemiologists, and statisticians contributing to accurate diagnosis and correct coding of cancer. This population based cancer registry is a recognised reference source covers incidence of cancer in population around the world. In Asia, the countries in the report include China, India, Japan, South Korea, Thailand, Malaysia, Philippines, Singapore, Pakistan, Oman, Bahrain, Kuwait, Israel, Cyprus and Turkey.

In terms of prostate cancer (ICD-10 code C61), the age-standardized (world) incidence rate (per 100,000) in specific cancer registry in Asian countries are as shown in Table 1, based on latest report of *Cancer Incidence in Five Continents: 2007 (Year 2002-2006).*

Table 1 Prostate Cancer Age-standardized (world) Incidence rate (per 100,000)

Country	Region	Age-standardized (world) incidence rate (per 100,000)	
		Vol. VIII 2002 (Year 1997-2001)	Vo. IX 2007 (Year 2002-2006)
Bahrain	Bahraini	NA	14.3
China	Beijing	2.9	NA
	Guangzhou City	NA	6.7
	Hong Kong	8.6	15.0
	Jiashan	1.9	1.4
	Nangang district, Harbin	NA	2.1
	Qidong County	1.1	NA
	Shanghai	3.0	6.9
	Taiwan	11.9	NA
	Tianjin	2.0	NA
	Wuhan	2.0	NA
	Zhongshan	NA	2.3
Cyprus	Cyprus	NA	40.8
India	Ahmedabad	3.6	NA
	Bangalore	3.8	NA
	Chennai (Madras)	4.9	3.9
	New Delhi	6.8	8.4
	Karunagappally	2.3	4.4
	Mumbai (Bombay)	7.4	6.9
	Nagpur	3.4	3.0
	Poona	6.6	6.4
	Trivandrum	4.0	5.6
Israel	Israel	43.2	50.2
	Jews	43.4	49.2
	Jews born in Israel	47.5	NA
	Jews born in Europe or	43.4	NA

Country	Region	Age-standardized (world) incidence rate (per 100,000)	
		Vol. VIII 2002 (Year 1997-2001)	Vo. IX 2007 (Year 2002-2006)
	America		
	Jews born in Africa or Asia	41.3	NA
	Non-Jews	14.8	20.0
Japan	Aichi Prefecture	NA	14.2
	Fukui Prefecture	NA	13.6
	Hiroshima	14.1	21.5
	Miyagi Prefecture	12.7	22.0
	Nagasaki Prefecture	12.6	20.0
	Osaka Prefecture	9.0	11.3
	Saga Prefecture	10.5	NA
	Yamagata Prefecture	9.3	13.4
Korea	Korea	NA	8.5
	Busan	7.1	7.3
	Daegu	6.6	7.7
	Daejeon	NA	5.8
	Gwangju	NA	9.0
	Incheon	NA	7.8
	Jejudo	NA	11.8
	Kangwa County	5.4	NA
	Seoul	8.5	12.7
	Ulsan	NA	8.6
Kuwait	Kuwaitis	11.4	10.5
	Non-Kuwaitis	10.9	9.4
Malaysia	Penang	NA	11.3
	Sarawak	NA	5.8
Oman	Omani	8.9	10.5
Pakistan	South Karachi	5.3	10.1
Philippines	Manila	22.3	25.3

Country	Region	Age-standardized (world) incidence rate (per 100,000)	
		Vol. VIII 2002 (Year 1997-2001)	Vo. IX 2007 (Year 2002-2006)
	Rizal	16.6	NA
Singapore	Singapore	NA	17.3
	Chinese	14.4	18.6
	Indian	9.9	11.1
	Malay	13.3	16.1
Thailand	Bangkok	6.8	NA
	Chiang Mai	4.2	5.3
	Khon Kaen	2.4	NA
	Lampang	3.9	4.9
	Songkhla	4.0	4.6
Turkey	Antalya	NA	19.1
	Izmir	NA	13.7
Vietnam	Hanoi	1.5	NA
	Ho Chi Minh City	3.8	NA

(Data excerpted from Cancer Incidence in Five Continents Volume VIII & IX. Parkin et al. 2002 & Curado et al. 2007)

*NA- not available

The Cancer Incidence in Five Continents report showed an overall increase in the age standardized incidence rate of prostate cancer between 2002 to 2007. A higher incidence rate in countries (middle-east and west Asia) close to Europe like Turkey, Israel, Cyprus; in countries of Eastern part of Asia, more developed countries like Japan, Singapore but not South Korea also have higher incidence compared to neighbouring countries. The increased incidence rates between the two reports could be due to better reporting and active detection of cases on all countries, but could also be due to a true increase in the number of new cases every year, due to environmental risk factors. The higher incidence rate observed in developing countries could in part be caused by lifestyle or environmental factors. Even if the incidence rate of prostate cancer is higher in the developed countries situated on

eastern part of Asia the rates were still lower compared to countries of middle-east or West Asia. Attempts to find the risk factors for this difference in rates between these two regions in Asia (West and East Asia) could lie in the genetic and environmental interaction.

Globocan reference data incidence and mortality rates are based on calculations from population based cancer registries as in Cancer Incidence in Five Continents report which is produced once every five years. The rates for Asia have been calculated as the population-weighted average of Eastern, South-Eastern, South-Central and Western Asia. The calculation based on country e.g. Malaysia, was by utilising on the Malaysia National Cancer Registry Report 2001 & 2002, and Regional Cancer Registry of Penang & Sarawak. Prior to 2003, calculation of rates was based on the closest neighbouring country with a similar population ethnic structure i.e. Singapore, population based cancer registry.

Prostate cancer in 2008 was ranked 6th in Asia overall but 9th in China, 4th in Japan and 3rd in Singapore. In Malaysia, prostate is ranked 5th among male cancers. In World data, Prostate cancer was ranked 2nd after lung cancer in terms of incidence rate, while developed country like Great Britain in Europe, it was ranked first, similarly the USA in North America.

Progress of Gene-Environment Interactions in Prostate Cancer Research (United Kingdom)

The Study of Gene-Environment Interactions in Prostate Cancer is a large scale case-control study and ongoing. The study is in collaboration between the University of Nottingham, Warwick and the Institute of Cancer Research UK, and began in 1999, aims to investigate environmental exposures risk to prostate cancer and explore genetic components involved in disease aetiology. The data collection was divided in to two phases, the first phase focusing on young onset cases (<60 years of age) began in March 1999 and was frozen in December 2004 for the purpose of interim analysis, to review/modify questionnaire and simplify/improve data collection process. The second phase was extended to also cover subjects of 60 years and above was started in December 2007 and data collection was also frozen in September 2009 to assess new leads of both genetics and environmental exposures. The third phase is proposed to start in 2010.

During the past 11 years since the study inception, progress has been made in the study of factors/risks associated through genetic or environmental exposures through evidence based epidemiological studies. The study also has contributed to the further understanding on the interaction of gene-environment towards prostate cancer, the capacity for further refining the risks involved and to explore other new risk factors. Genetic component of these gene-environmental interaction studies has opened up better epidemiological evidence to the possibility of studying to the cause and effect.

The number of original article publications has also increased over the years from this case control study. Below is a summary of the areas or factors studied, as well as their main finding(s) (Refer to Table 2).

Table 2. Summary of Published Research Findings from Gene-Environment Interaction Prostate Cancer Research (UK)

Aims	Subjects	Results/ Conclusions	Author	Publication
Hand pattern and prostate cancer risk	1524 cases and 3044 controls information on right hand 2^{nd} and 4^{th} fingers' length were obtained.	Those with index finger longer than ring finger (or low 2D:4D) has protective risk against prostate cancer compared to those with index ginger longer than the ring finger (or high 2D:4D) at OR 0.67 (95% CI: 0.57-0.80). Those less than 60 years old have even lower risk at OR 0.13 (95% CI: 0.09-0.21). Finger length through 2^{nd} to 4^{th} digit ratio can be suggested as a marker for prostate cancer risk.	Rahman et al.	2010. British Journal of Cancer
Dietary fat and early onset prostate cancer risk	512 cases and 838 controls were administered with FFQ	Increased risk with statistical significant trend ($p<0.001$) for higher intake of total fat, SFA, MUFA and PUFA. Adjusted OR between highest quintile to lowest quintile intake of total fat SFA, MUFA and PUFA were 2.53 (95% CI: 1.72-3.74), 2.49 (95% CI: 1.69-3.66), 2.69 (95% CI: 1.82-3.96) and 2.34 (95% CI: 1.59-3.46) respectively.	Lophatananon et al.	2010. British Journal of Nutrition
Sexual activity and early onset prostate cancer risk	431 cases and 409 controls information on sexual activity in particular frequencies of intercourse and masturbation were obtained.	Higher frequency activity of masturbation at age 20's and 30's was statistically significant associated with increased risk of early onset prostate cancer. While frequent overall sexual activity in 20's increase disease risk, at age 50's appeared to be protective, although both were not statistically significant.	Dimitropoulou et al.	2008. British Journal of Urology
Diagnostic radiation procedures to early onset prostate cancer risk	Matched 431 cases and 409 controls below 60 years were asked on their exposure to their past diagnostic imaging experiences.	Increased risk were observed for barium enema OR 2.06 (95% CI: 1.01-4.20), hip x-rays at least 5 years before diagnosis, OR 2.23 (95% CI: 1.43-3.49). For those with family history of cancer, earlier exposure to hip x-rays dated 10 years and 20 years before diagnosis showed higher risk at OR 5.01 (95% CI: 1.64-15.31) and 14.23 (95% CI: 1.83-110.74). All are adjusted ratios.	Myles et al.	2008. British Journal of Cancer

Aims	Subjects	Results/ Conclusions	Author	Publication
		Findings suggested genetic factor interaction with diagnostic radiation exposure towards early onset prostate cancer risk.		
Association of Omega 3 and Omega 6 PUFAs to risk of early onset prostate cancer	805 cases and 1283 controls of below 60 years were given FFQ	Dietary intake of Omega 3 PUFAs showed protective trends to risk of early onset Prostate cancer while Omega 6 showed increase risk, although both were not statistically significant.	Undergraduates of medical school	2009. Research project.

*PUFA – Polyunsaturated Fatty Acids

*SFA – Saturated Fatty Acid

*MUFA – Monounsaturated Fatty Acid

*FFQ – Food Frequency Questionnaire

As the case control data gathering is still on-going, this bigger mass of data will inevitably increase the strength of the case-control database.

ID number

Official use only

Gene-Environment Interactions in Prostate Cancer

This study is being conducted by the Division of Epidemiology and Public Health, University of Nottingham, Institute of Cancer Research and the Royal Marsden Hospital NHS Trust. We are investigating factors that may be involved in the occurrence of prostate disease.

We would be very grateful if you could complete this questionnaire. This should only take about 30-45 minutes and we hope you will find it interesting. Your information will be *treated in the strictest confidence*.

Please *DO NOT* write your name anywhere on the questionnaire. You will be identified only by the unique ID number at the top of this page.
Please *return* the completed questionnaire at your earliest convenience in the enclosed prepaid envelope - *no stamp is required*.

Thank you for your help.

Dr Aneela Rahman (Researcher) Tel: 0115-8230495

Study Team from The University of Nottingham

Prof. Ken Muir	(Principal Investigator)
Dr Artitaya Lophatananon	(Research Officer)
Dr Aneela Rahman	(Researcher)
Ms Jo-Fen Liu	(Research Officer)

Study Team from The Institute of Cancer Research/The Royal Marsden Hospital NHS Trust

Dr Rosalind Eeles	(Principal Investigator)
Prof. Douglas Easton	(Co- Investigator)
Prof. David Dearnaley	(Consultant Oncologist)

ID Number

Official use only

Section 1: About you

We would like to ask about your personal details.

1) Date of birth

☐☐/☐☐/☐☐

Date Month Year

2) Your marital status *(please tick the appropriate box)*

☐ Married ☐ Widowed ☐ Single

☐ Divorced ☐ Separated ☐ Other, please specify.....

3) Please indicate which group you belong to *(please tick the appropriate box)*

☐ White ☐ Black- Caribbean

☐ Black- African ☐ Black- other

☐ Indian ☐ Pakistani

☐ Jewish ☐ Sephardic

☐ Ashkenazi ☐ Chinese

☐ Other, please specify.....

4) In which country were you born? *(Please tick the appropriate box)*

☐ UK ☐ Other, please specify.....

5) Have you always lived in the UK? *(Please tick the appropriate box)*

☐ Yes *(go on to question 7)* ☐ No *(go on to question 6)*

6) How long have you been living in the UK? *(Please specify number of years)*

.....years

7) What is the highest educational qualification you have obtained?
(Please tick the appropriate box)

☐ None

☐ GCSEs, "O" levels or equivalent

☐ "A" Levels, higher or equivalent

☐ Higher or professional qualifications e.g. degree, HND

☐ Other, please specify.....

Section 2: Employment

This section is about the jobs you have had since you left school.

8) Can you briefly describe all the jobs you have had for ***more than 1 year***.
(Please start with your current job or your latest job).

Job title and description of duties	Full time (FT) or Part time (PT)	Started (year)	Finished (year)	Self-Employed (SE) or Employed (E)	Did you supervise any others? (Y or N)
1					
2					
3					
4					
5					
6					
7					
8					
9					

Job title and description of duties	Full time (FT) or Part time (PT)	Started (year)	Finished (year)	Self-Employed (SE) or Employed (E)	Did you supervise any others? (Y or N)
10					
11					
12					
13					
14					

9) Have you ever been exposed to chemical substances in any of your jobs?

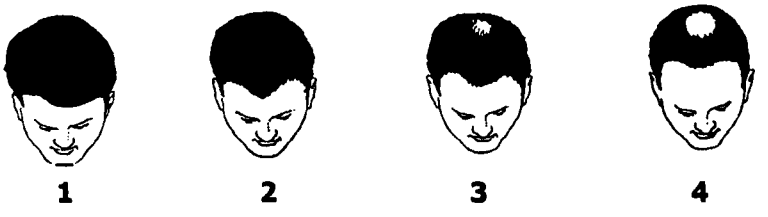
☐ Yes (*please complete the table below*) ☐ No (*go on to Section3*)

Chemical substances	(Y/N)	Degree of exposure i.e. *high, intermediate or background*	Regularity i.e. *daily, weekly*	Total number of years exposed	From which job? – *please give the job number from the list above*
Paints/varnishes/lacquers					
Solvents/degreasing agents					
Petrol/diesel/hydrocarbons					
Weed killers/herbicides					
Radiation					

Section 3: Your hormones

Evidence has suggested a possible relationship between male hormones and prostate disease. The effect of hormones can be seen physically, for example, pattern of hair loss, frequency of shaving, acne or hand pattern. In this section we would like to ask you about these factors at various ages.

Please choose the **NUMBER** corresponding to the hair pattern nearest to your own at the ages below. Please select one answer to each question. If you can't remember precisely, please make your best estimate.

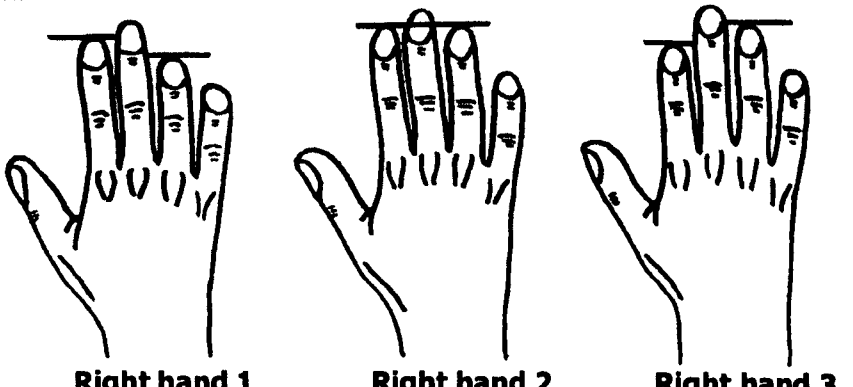


1 **2** **3** **4**

5 **6** **7**

10) In your 20s ☐ 11) In your 30s ☐ 12) In your 40s ☐

13) From the picture below, could you please look at the ***index*** and the ***ring*** fingers on your ***right hand*** by putting your hand on the table and compare these to the patterns below. Please tick the appropriate box for the pattern that is nearest to your own.



Right hand 1 ☐ **Right hand 2** ☐ **Right hand 3** ☐

14) In your 20s, how often, on average, did you need to shave in order to keep clean shaven?

☐ Once a day ☐ Twice a day ☐ Every other day
☐ Less than every other day ☐ Do not shave

15) Did you have acne when you were young?

☐ Yes *(if yes go on to question 16)* ☐ No *(go on to Section 4)*

16) Did you still have acne when you were:

	Yes	No
In your 20s	☐	☐
In your 30s	☐	☐

Section 4: Smoking

We would like to know a bit more about your smoking habit in this section.

17) How would you describe yourself? *(Please tick one box only)*

- ☐ Current smoker, smoke daily *(go on to question 18)*
- ☐ Current smoker, smoke occasionally *(go on to question 18)*
- ☐ Ex-smoker, don't smoke at all now *(go on to question 21)*
- ☐ Never smoked *(go on to Section 5)*

Smokers only

18) In a day, I usually smoke (*please tick the box – you can tick more than one box and write down the number of cigarettes/ cigars or amount of pipe tobacco you smoke per day or per week)*

- ☐ Cigarettes number.....per day or number.....per week *(go on to questions 19,20)*
- ☐ Cigar number.....per day or number.....per week *(go on to questions 19)*
- ☐ Pipe amount .....per day or amount.....per week *(go on to questions 19)*

19) The cigarettes I normally smoke are: *(Please tick appropriate box)*

☐ High tar level ☐ Middle tar level ☐ Low tar level

20) I have been a smoker for.....years (*please write down a number and go to next section)*

Ex-smokers only

21) I have been an ex-smoker for: (*please tick appropriate box)*

☐ Less than a year ☐ 1-3 years
☐ 4-10 years ☐ over 10 years

22) When I was smoking, I used to smoke (*please tick the box – you can tick more than one box and write down the number of cigarettes/ cigars or amount of pipe tobacco you smoke per day or per week)*

- ☐ Cigarettes number.....per day or number.....per week
- ☐ Cigar number.....per day or number.....per week
- ☐ Pipe amount .....per day or amount.....per week

Section 5: About sex

The prostate gland is responsible for producing fluid that helps sperm to survive when they enter the female reproductive tract following ejaculation. Changes in the prostate gland may occur depending on how often you have sexual intercourse or masturbate. Some sexual activities may also be related to hormone levels or may lead to an increased risk of infection. To help us find out if there is an association between prostate changes and sexual activities we need to know about past and present sexual practices.

We realise that this is a very sensitive subject but we would be very grateful if you could complete this section. ***Please answer these questions only if you feel able to do so***.

All your answers will be treated as STRICTLY CONFIDENTIAL AND NO INFORMATION WILL BE PASSED ON TO ANYONE OUTSIDE THE STUDY INCLUDING YOUR FAMILY DOCTOR.

23) At what age did you first have sexual intercourse? *(Please tick appropriate box)*

- ☐ Never
- ☐ Under 15 years old
- ☐ 15-19 years old
- ☐ 20-24 years old
- ☐ 25-29 years old
- ☐ 30 years or older

24) How often on average did you have sexual intercourse? *(Please tick one box and indicate yes or no, as appropriate)*

In your	Never	Less than once a month	Once to three times a month	Once a week	Two to three times a week	Four to six times a week	Daily	Condom normally used	
								Yes	No
20s								☐	☐
30s								☐	☐
40s								☐	☐
50s								☐	☐

25) In your lifetime, how many women ***in total*** have you had sexual intercourse with? *(Please tick appropriate box)*

☐ None ☐ One ☐ Two
☐ Three to five ☐ Six to ten ☐ Eleven to twenty
☐ More than twenty

26) From your answer to question 25, how many of them would you have classified as your "partner" *(i.e. someone you have/had sexual intercourse with once a week or more for a period of 3 months or longer).*

☐ None ☐ One ☐ Two
☐ Three to five ☐ Six to ten ☐ Eleven to twenty
☐ More than twenty

27) In your lifetime, have you ever paid money to women for sexual intercourse? *(Please tick appropriate box)*

☐ Yes *(go on to question 28)* ☐ No *(go on to question 29)*

28) Did you normally use condoms on those occasions?

☐ Yes ☐ No

29) At what age did you first masturbate? *(Please tick appropriate box)*

☐ Never ☐ Under 15 years old
☐ 15-19 years old ☐ 20-24 years old
☐ 25-29 years old ☐ 30 years or older

30) How often on average did you masturbate?

In your	Never	Less than once a month	1-3 times a month	Once a week	2-3 times a week	4-6 times a week	Daily
20s							
30s							
40s							
50s							

31) Overall, did you regard yourself has having a problem with sexual activity at different ages? *(please tick appropriate box)*

In your 20s ☐ Yes ☐ No
30s ☐ Yes ☐ No
40s ☐ Yes ☐ No
50s ☐ Yes ☐ No

32) In your 20s, 30s, 40s and 50s, did you encounter any of the following statement(s) that might have restricted you from sexual activity? ***(you can tick √ more than 1 statement)***

Statements	**In your**			
	20s	**30s**	**40s**	**50s**
1. Were not in any relationships	☐	☐	☐	☐
2. Your partner had physical/ emotional difficulties	☐	☐	☐	☐
3. You suffered from the following conditions which restricted your sexual activity. (*You can tick more than 1 box.*)	☐	☐	☐	☐
- depression	☐	☐	☐	☐
- diabetes (high blood sugar)	☐	☐	☐	☐
- high blood pressure	☐	☐	☐	☐
- arthritis or rheumatism	☐	☐	☐	☐
- prostate cancer	☐	☐	☐	☐
- enlarged or swollen prostate	☐	☐	☐	☐
- back problem	☐	☐	☐	☐
- impotence / erectile dysfunction	☐	☐	☐	☐
- lack of desire/ too tired	☐	☐	☐	☐
- other, please specify	☐	☐	☐	☐

33) In your lifetime, have you ever attended a sexually transmitted disease (STD) or special (VD) clinic? (*Please tick appropriate box)*

☐ Yes ☐ No

34) Have you ever been told by a doctor that you had any of the following conditions, even if it was a long time ago? (*Please tick appropriate box)*

Gonorrhoea	☐ Yes	☐ No
Syphilis	☐ Yes	☐ No
Genital herpes	☐ Yes	☐ No
Genital warts *(ie.warts on your penis/anal area)*	☐ Yes	☐ No
Non-specific urethritis (NSU)	☐ Yes	☐ No
Any other type of venereal disease	☐ Yes	☐ No

35) Have you ever had sores or ulcers on your penis?

☐ Yes (*go on to question 36)* ☐ No (*go on to Section 6)*

36) Have you ever had sexual intercourse while you had sores or ulcers on your penis? (*Please tick appropriate box)*

☐ Yes ☐ No

Section 6: About your skin and sun exposure

There is growing evidence on the relationship between UV radiation exposure from sunlight and prostate diseases. Thus we would like to ask you questions about your skin colour and also lifetime sun exposure.

Please tick appropriate box for each question:

37) What type of complexion do you have?

☐ Oily ☐ Dry ☐ Combination ☐ Normal

38) What is your skin colour when you are not sun tanned?

☐ Very fair ☐ Fair ☐ Medium
☐ Olive ☐ Very dark

39) What happens when you stay in the sun too long?

☐ Painful, bad blistering and peeling ☐ Blistering followed by peeling
☐ Burns sometimes ☐ Rarely burns
☐ Never had burns

40) On average looking back at the various stages of your life, in the daytime, how long were you out of doors during your working and non working hours? (*If during the last 5, 10 or 20 years you did not work please answer only non working time.)*

In your		**Less than 1 hour**	**1-2 hours**	**3-4 hours**	**More than 5 hours**
20s	Working				
	Non- working				
30s	Working				
	Non- working				
40s	Working				
	Non- working				
During the last 5 years	Working				
	Non- working				

41) On average looking back at the various stages of your life in the day time when outdoors, did you generally try one of the following? *Please put √ under the activity. You can answer more than one activity. If you did not spend time outdoors at all, please put √ under the far right column*

In your	When outdoors, you.....				Did not spend time outdoors at all
	Always seek a sun tan	Wear very little	Wear normal summer clothing	Try to cover yourself up from the sun	
20s					
30s					
40s					
During the last 5 years					

42) Did you use suntan oil, lotion or cream to protect your skin when you were out in the sun? *Please tick √*

In your	Always	Sometimes	Rarely	Never
20s				
30s				
40s				
During the last 5 years				

Section 7: About the health of your family

Some prostate diseases may be hereditary. We would like to ask if any of your family have ever been diagnosed with prostate problems or any type of cancer.

43) Have any male members of your family been told by a doctor that he has/had any of the following? (*If there is no one, please go on to question 44)*

☐ Yes *(Please answer the following)*

Identify relationship to you

☐ A swollen or enlarged prostate (benign prostatic hyperplasia) .....

.....

☐ Prostatitis (infection of the prostate) .....

.....

☐ No (*please go on to question 44)*

Certain cancers are known to have a genetic or familial component. Please record below any cancers that you are aware of and that have occurred in your **first degree relatives (parents, siblings or your children).**

44) Have any of your first degree relatives have cancer of any type?

☐ Yes *(go on to question 45)* ☐ No *(go on to Section 8)*

45) If yes, please specify their relationship to you and type of cancer that they have (including ***prostate cancer***).

Relationship to you	Type of cancer	Age at diagnosis (if known)	Date of birth
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

Section 8: Physical activity

In this section we would like you to think about the physical activity you have undertaken in a typical day at various stages of your life.

On average have you undertaken *at least 30 minutes of **moderate** physical activity per day – **either** at home or at work.* (These activities can be made up of many components, for example, moving a table, pushing a vacuum cleaner, bowling or playing golf).

46) In your 20s	☐ Yes	☐ No	☐ Not applicable
47) In your 30s	☐ Yes	☐ No	☐ Not applicable
48) In your 40s	☐ Yes	☐ No	☐ Not applicable
49) During the last 5 years	☐ Yes	☐ No	☐ Not applicable

On average have you undertaken *20 minutes or more of **energetic** activity at least 3 times per week whilst NOT at work.* (These include, for example, keep fit, dancing or exercises, swimming or other brisk sport, long walks, jogging or running, hard work in a job at home or in the garden, cycling).

50) In your 20s	☐ Yes	☐ No	☐ Not applicable
51) In your 30s	☐ Yes	☐ No	☐ Not applicable
52) In your 40s	☐ Yes	☐ No	☐ Not applicable
53) During the last 5 years	☐ Yes	☐ No	☐ Not applicable

Section 9: Your general health and medication

In this section we would like to know more about your general health, medication (use of steroids, hormone treatments, or pain killers etc), as well as any X-ray procedures you have ever had at various stage of your life time.

54) Have you had a vasectomy?

☐ Yes (*go on to question 55)* ☐ No *(go on to question 56)*

55) How old were you? ☐☐

56) Have you ever taken any of the following? *(If no please go on to question 57)*

	Yes/ No	At age	Treatment for	Duration of use (mm/yy)
Androgens or testosterone				
Anabolic steroids				
Oestrogen				
Cortisone not as a skin cream				
Cortisone or corticosteroids as a skin cream				
Thyroid drugs				

One of the questions researchers want to know is whether the exposure of medical diagnostic procedures such as X-ray, is associated with prostate disease. In order to answer this question, we will need to collect detailed information about any X-ray or radiological procedures you have ever had.

57) Have you ever had any of the following x-ray procedures? (if yes, please give details with your best estimates)

Procedure	Yes/ No	Number of times	Details of procedure		
				At age / date	Purpose of x-ray and site (if applicable)
Barium meal i.e. x-rays of your **stomach** taken after swallowing a glass of chalky liquid			1		
			2		
			3		
			4		
			5		
Cholecystogram *i.e.* x-ray of your **gall bladder** taken after swallowing a glass of thick liquid			1		
			2		
			3		
			4		
			5		
IVP Kidney X-ray following an injection			1		
			2		
			3		
			4		
			5		
X-ray of hand, shoulder or arms			1		
			2		
			3		
			4		
			5		

Procedure	Yes/ No	Number of times	Details of procedure		
			At age / date		Purpose of x-ray and site (if applicable)
X-ray of upper leg or thigh			1		
			2		
			3		
			4		
			5		
X-ray of hips/pelvic region			1		
			2		
			3		
			4		
			5		
Lymphangiogram *i.e.* x-ray taken of different parts of the body after dye has been injected			1		
			2		
			3		
			4		
			5		
CAT scan *i.e.* x-ray of your body taken inside a machine where the equipment rotates around you			1		
			2		
			3		
			4		
			5		
NMR or MRI (magnetic resonance imaging) Scan *i.e.* where you are put inside a large magnet			1		
			2		
			3		
			4		
			5		

Procedure	Yes/ No	Number of times	Details of procedure	
			At age / date	Purpose of x-ray and site (if applicable)
Radioactive or isotope injections with pictures or x-ray taken afterwards			1	
			2	
			3	
			4	
			5	
Venogram *i.e.* x-rays of vein after dye has been injected			1	
			2	
			3	
			4	
			5	
Angiogram or arteriogram *i.e.* an x-ray to view your heart or body blood vessels taken after a tube has been passed into your arm or groin			1	
			2	
			3	
			4	
			5	

58) Have you ever been told by doctor that you have/had any of the following conditions?

Conditions	Yes/No	Age at diagnosis
Diabetes		
Heart disease		
Hypercholesterolaemia (high blood cholesterol)		
High blood pressure		
Other please specify		

Some medications may be associated with prostate diseases. In order to study this question in detail, we would like to ask you some questions about your use of prescription or non-prescription painkillers in the past.

59) Have you ever regularly taken statin (e.g, Atorvastatin, Cerivastatin, Simvastatin) in the past 10 years?

☐ Yes *(go on to question 60)* ☐ No *(go on to question 61)*

60) If Yes, could you please let us know

(a) Which type of statin (or brand name) you have taken?

.....

(b) The dosage of pills or capsule? ..... mg or ..... µg

(c) Roughly how often do you take the medicine? .....

(d) For how many years have you been taking the medicine? ..... years

(e) Reason for taking statin? .....

61) Have you ever regularly taken any non-prescription painkillers bought over the counter from a chemist or a supermarket in the last 10 YEARS?
(*By regularly, we mean at least one tablet per week for more than three months.*)

☐ Yes *(go on to question 62)* ☐ No *(go on to question 63)*

62) We would like to know more details about the painkiller(s) you have regularly taken. Could you please let us know:

a) Which type of painkiller(s) you have taken?
b) Do you recall the dose?
c) Roughly how often do you take the tablets or medicine?
d) For how many years have you been taking the tablets or medicine?
e) For what reason do you take them?

Please provide the information in the table on next page.

a) Name of Painkiller	b) Dose Dosage of pills/capsules or teaspoons each time	c) Average frequency Tick one box per line Never or less than once a month	At least once a month but not every day	At least once a day	d) Duration Number of years of taking painkillers	e) Reason for taking painkillers
1 Aspirin or preparation containing aspirin eg Alka-Seltzer, Disprin						
2 Ibuprofen – e.g. Nurofen, Ibufen, Advil, Migrafen						
3 Paracetamol or preparation containing Paracetamol – eg Panadol, Co-proxamol, Co-codamol						
4 Other pain medication (please specify)						

63) Do you have any side-effects if you take aspirin?

☐ Yes *(go on to question 64)* ☐ Don't know/ I don't use aspirin *(go on to question 65)*

☐ No (*go on to question 65)*

64) Do the side effects make you stop taking aspirin?

☐ Yes (*go on to question 65)*

☐ No, I still take aspirin because .....

.....

In this section, we would like you to think about the three most commonly used painkillers in various stages in your adult life. This includes painkillers available in pharmacy or supermarket (i.e., over the counter; OTC), as well as those prescribed by doctor.

65) Have you been taken any painkilling medication on a regular basis (at least once a week for more than three months) during your adult life, either prescribed by your GP or bought over the counter (OTC).

☐ Yes *(go on to question 66)* ☐ No *(go on to section 10)*

66) If Yes, please can you give us more details

In your	**A** Painkiller 1			**B** Painkiller 2			**C** Painkiller 3		
	Name	From	No of years used	Name	From	No of years used	Name	From	No of years used
20s		GP ☐ OTC ☐			GP ☐ OTC ☐			GP ☐ OTC ☐	
30s		GP ☐ OTC ☐			GP ☐ OTC ☐			GP ☐ OTC ☐	
40s		GP ☐ OTC ☐			GP ☐ OTC ☐			GP ☐ OTC ☐	
50s		GP ☐ OTC ☐			GP ☐ OTC ☐			GP ☐ OTC ☐	

Section 10: Further details about you

In this section we would like to know more about your body size and body shape. This includes the changes of your weight or trouser size in the past years. Please give as approximate estimates if you can and

67) Please can you tell me your current weight and height?

My weight is..... Stones.....Pounds or ..... Kilograms

My height is..... Feet.....Inches or..... Centimetres

68) Has your weight changed over the last 5 years?

☐ Yes my weight was ..... Stones.....Pounds or .....Kilograms
☐ No

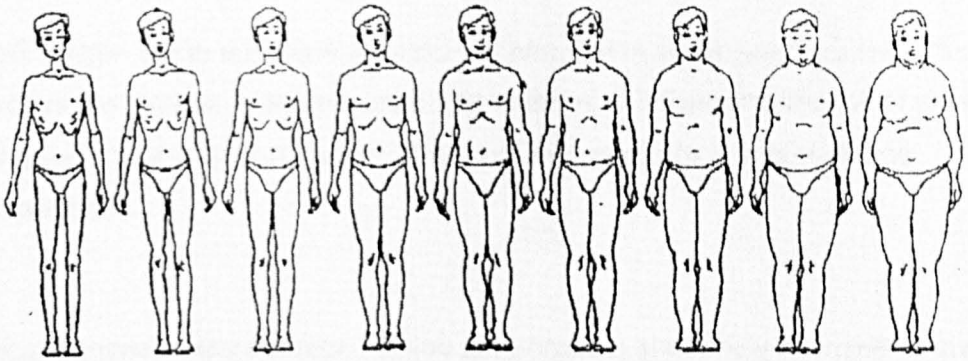
69) What is your collar-size?

	inches

70) Please can you tell me your waist and your approximate hip circumference, either in inches or in centimetres? If you cannot remember your waist circumference, can you recall your trouser size (for example size 30)?

	Waist/ Trouser Size		**Hip**	
	inch	**cm**	**inch**	**cm**
In your 20s				
In your 30s				
In your 40s				
During the last 5 years				

Please select the shape you think you were at different ages. *(Please write down the number you think you were).*



71) In your 20s ☐
72) In your 30s ☐
73) In your 40s ☐
74) During the last 5 years ☐

Overall please select one of the descriptions below that suit you the most.

(please write down number in the box)

1. ***Apple shape-*** where your body fat is distributed mainly around your tummy area.

2. ***Pear shape-*** where your body fat is distributed mainly on your hip and thigh.

3. ***Oval shape-*** where your body fat is distributed around your neck, your chest, your tummy area and also your thigh.

4. ***Symmetric shape-*** where you are lean with no fat distribution around your body.

75) My body shape is ☐

Food Frequency Questionnaire

This section of the questionnaire asks for information about what you eat. Dietary factors are thought to be very important in terms of influencing the risk of prostate disease. Your help in completing this section is particularly important and appreciated.

Please answer every question. If you are uncertain about how to answer a question then do the best you can, but please **do not leave a question blank**. If you have any problems with the questions please phone the number at the end of the questionnaire.

Your answers will be treated as strictly confidential and will be used only for medical research.

About Your Diet

We would like to ask about your typical diet in the past 5 years.
Please start by thinking and identify any major events that may have marked this time period. This should help you to recall this particular time.

For each food the amount shown is, either a "medium serving" or a common household unit such as a slice or teaspoon. Please put a tick (√) in the box to indicate how often, on average, you have eaten the specified amount of each food.

Please complete each line as shown in the **following examples**.

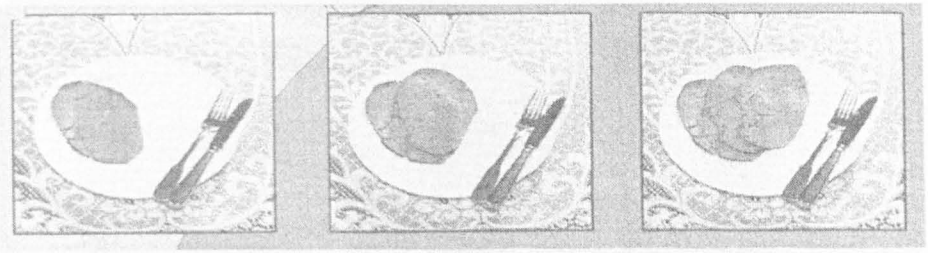
Foods and Amounts	**AVERAGE USE OVER THE LAST 5 YEARS**								
BREAD AND SAVOURY BISCUITS (one slice or biscuit)	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
White bread and rolls								√	

For chips, the amount is a "medium serving", so if you had a helping of chips twice a week you should put a tick in the column headed "2-4 per week".

POTATOES, RICE AND PASTA (medium serving)	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
Chips				√					

For very seasonal fruits such as strawberries and raspberries you should estimate your average use when the fruits are in season, so if you ate strawberries or raspberries about once a week when they were in season you should put a tick in the column headed "once a week".

Please estimate your average food use as best you can based on a "***medium portion***". For example, for ***beef,*** a medium serving is as shown in the ***middle***. Please answer every question - **do not leave ANY lines blank**.



Medium serving

PLEASE PUT ONLY ONE TICK ON EVERY LINE

Foods and Amounts	**AVERAGE USE OVER THE LAST 5 YEARS**								
MEAT AND FISH (Medium serving)	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
Beef: roast, steak, mince, stew or casserole									
Beefburgers									
Pork: roast, chops, stew or slices									
Lamb: roast, chops or stew									
Chicken or other poultry e.g. turkey									
Bacon									
Ham									
Corned beef, spam, luncheon meats									
Sausages									
Savoury pies, e.g. meat pie, pork pie, pasties, steak & kidney pie, sausage rolls									
Live, liver pate, liver sausage									
Fried fish in batter, as in fish and chips									
Fish fingers, fish cakes									
Other white fish, fresh or frozen, e.g. cod, haddock, plaice, sole, halibut									
Oily fish, fresh or canned e.g. mackerel, kippers, tuna, salmon, sardines, herring									
Shellfish, e.g. crab, prawns, mussels									
Fish roe, taramasalata									

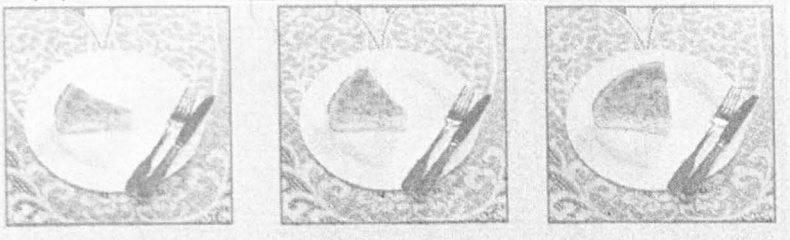
Please estimate your average food use as best you can based on a "***medium portion***". For example, for ***cereal***, a medium serving is as shown in the ***middle***. Please answer every question - **do not leave ANY lines blank**.

Medium serving

PLEASE PUT ONLY ONE TICK ON EVERY LINE

Foods and Amounts	**AVERAGE USE OVER THE LAST 5 YEARS**								
BREAD AND SAVOURY BISCUITS (one slice or biscuit)	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
White bread and rolls									
Brown bread and rolls									
Wholemeal bread and rolls									
Cream crackers, cheese biscuits									
Crispbread e.g. Ryvita									
CEREALS (one bowl)									
Porridge, Readybrek									
Breakfast cereal such as Cornflakes, muesli etc.									
POTATOES, RICE AND PASTA(medium serving)									
Boiled, mashed, instant or jacket potatoes									
Chips									
Roast potatoes									
Potato salad									
White rice									
Brown rice									
White or green pasta, e.g. spaghetti, macaroni, noodles									
Wholemeal pasta									
Lasagne, moussaka									
Pizza									

Please estimate your average food use as best you can based on a "***medium portion***".
For example, for ***Quiche***, a medium serving is as shown in the ***middle***.
Please answer every question - **do not leave ANY lines blank**.

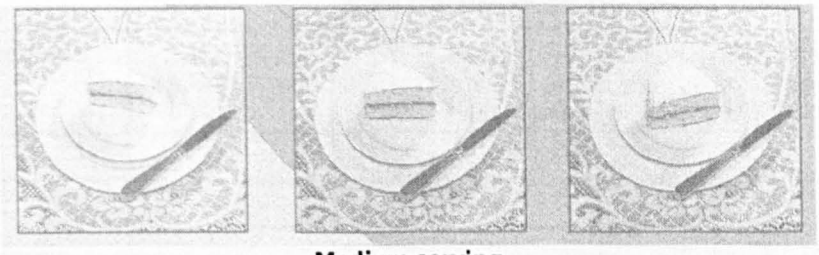


Medium serving

PLEASE PUT ONLY ONE TICK ON EVERY LINE

Foods and amounts	**AVERAGE USE OVER THE LAST 5 YEARS**								
DAIRY PRODUCTS AND FATS	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
Single or sour cream (tablespoon)									
Double or clotted cream (tablespoon)									
Low fat yoghurt, fromage frais (125g carton)									
Full fat or Greek yoghurt (125g carton)									
Dairy desserts (125g carton)									
Cheese e.g. Cheddar, Brie, Edam (medium serving)									
Cottage cheese, low fat soft cheese (medium serving)									
Eggs as boiled, fried, scrambled etc.(one)									
Quiche (medium serving)									
Low calorie, low fat salad cream (tablespoon)									
Salad cream, mayonnaise (tablespoon)									
French dressing									
Other salad dressing (tablespoon)									
... AND A TEASPOON OF THE FOLLOWING ON BREAD OR VEGETABLES									
Butter									
Block margarine, e.g. Stork, Krona									
Polyunsaturated margarine (tub) e.g. Flora sunflower									
Other soft margarine, dairy spreads (tub) e.g. Blue Band, Clover									
Low fat spread (tub) e.g. Outline, Gold									
Very low fat spread (tub)									

Please estimate your average food use as best you can based on a "***medium portion***".
For example, for ***SPONGE CAKE***, a medium serving is as shown in the ***middle***.
Please answer every question - **do not leave ANY lines blank.**



Medium serving

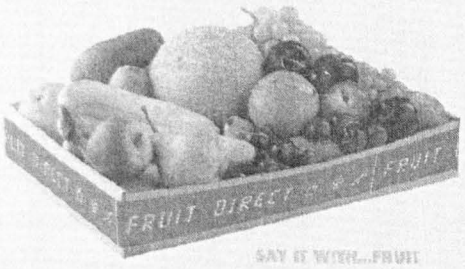
PLEASE PUT ONLY ONE TICK ON EVERY LINE

Food and Amounts	**AVERAGE USE OVER THE LAST 5 YEARS**								
SWEETS AND SNACKS (medium serving)	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
Sweet biscuits, chocolate e.g. digestive (one)									
Sweet biscuits, plain e.g. Nice, ginger (one)									
Cakes e.g. fruit, sponge, home baked									
Cakes e.g. fruit, sponge, ready made									
Buns, pastries e.g. scones, flapjacks, home baked									
Buns, pastries e.g. croissants, doughnuts, ready made									
Fruit pies, tarts, crumbles, home baked									
Fruit pies, tarts, crumbles ready made									
Sponge puddings, home baked									
Sponge puddings, ready made									
Milk puddings e.g. rice, custard trifle									
Ice cream, choc ices									
Chocolates, single or squares									
Chocolate snack bars e.g. Mars, Crunchie									
Sweets, toffees, mints									
Sugar added to tea, coffee, cereal (teaspoon)									
Crisps or other packet snacks, e.g. Wotsits									
Peanuts or other nuts									

Please estimate your average food use as best you can based on a "***medium portion***".
Please answer every question - **do not leave ANY lines blank**.

PLEASE PUT ONLY ONE TICK ON EVERY LINE

Food and Amounts	**AVERAGE USE OVER THE LAST 5 YEARS**								
SOUPS, SAUCES AND SPREADS	never or less than once/month	1-3 per month	once a week	2-4 per week	5-6 per week	once a day	2-3 per day	4-5 per day	6+ per day
Vegetable soups (bowl)									
Meat soups (bowl)									
Sauces e.g. white sauce, cheese sauce, gravy (tablespoon)									
Tomato ketchup (tablespoon)									
Pickles, chutney (tablespoon)									
Marmite, Bovril (teaspoon)									
Jam, Marmalade, honey (teaspoon)									
Peanut butter (teaspoon)									



FRUIT (1 fruit or medium serving). For very seasonal fruits such as strawberries, please estimate your average use when the fruit is in season for example if you ate strawberries about **once a week** when they were in **season** you should put a tick in the column headed **"once a week"**

Apples									
Pears									
Oranges, satsumas, mandarins									
Grapefruit									
Bananas									
Grapes									
Melon									
Peaches, plums, apricots									
Strawberries, raspberries, kiwi fruit									
Tinned fruit									
Dried fruit, e.g. raisins, prunes									

Please estimate your average food use as best you can based on a "***medium portion***".
For example, for ***BAKED BEANS***, a medium serving is as shown in the ***middle***.
Please answer every question - **do not leave ANY lines blank**.

Medium serving

PLEASE PUT ONLY ONE TICK ON EVERY LINE

Food and Amounts	**AVERAGE USE OVER THE LAST 5 YEARS**								
Vegetables Fresh, frozen or tinned (medium serving)	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
Carrot									
Spinach									
Broccoli, spring greens, kale									
Brussels sprouts									
Cabbage									
Peas									
Baked beans									
Marrow, courgettes									
Cauliflower									
Parsnips, turnips, Swedes									
Leeks									
Onions									
Garlic									
Mushrooms									
Sweet peppers									
Bean sprouts									
Green salad, lettuce, cucumber, celery									
Watercress									
Tomatoes									
Sweet corn									
Beetroot									
Coleslaw									
Green beans, broad beans, runner beans									
Avocado									
Dried lentils, beans, peas									
Tofu, Soya meat, TVP, Vegeburger									

Please estimate your average food use as best you can based on a "***medium portion***".
Please answer every question - **do not leave ANY lines blank.**

PLEASE PUT ONLY ONE TICK ON EVERY LINE

Food and Amounts	**AVERAGE USE OVER THE LAST 5 YEARS**								
Drinks	never or less than once/month	1-3 per month	once a week	2-4 per week	5-6 per week	once a day	2-3 per day	4-5 per day	6+ per day
Tea (cup)									
Coffee, instant or ground (cup)									
Coffee, decaffeinated (cup)									
Coffee whitener e.g. Coffee-mate (teaspoon)									
Cocoa, hot chocolate (cup)									
Horlicks, Ovaltine (cup)									
Wine (glass)									
Beer, lager or cider (half pint)									
Port, sherry, vermouth, liqueurs (glass)									
Spirits, e.g. gin, brandy, whisky, vodka (single)									
Low calorie or diet fizzy soft drinks (glass)									
Fizzy soft drinks, e.g. Coca cola, lemonade (glass)									
Pure fruit juice - 100% e.g. orange, apple juice (glass)									
Fruit squash or cordial (glass)									
Soya Milk (glass)									

76) Did you have curry more than once a week, either home-cooked, tinned sauce, take-away or from supermarket?

☐ Yes ☐ No

If yes, please list below

Type of curry (e.g., Korma, Thai green curry)	Usual serving size (small, medium or large)	Number of times eaten each week

77) Are there any **other** foods, which you ate more than once a week?

☐ Yes ☐ No

If yes, please list below

Food	Usual serving size	Number of times eaten each week

78) What type of milk did you most often use? **Select one only**

☐ Full cream
☐ Skimmed
☐ Dried milk
☐ None
☐ Semi-skimmed
☐ Channel Islands
☐ Soya
☐ Other, specify.....

79) How much milk did you drink each day, including milk with tea, coffee, cereals etc?

☐ None
☐ Quarter of a pint
☐ Half a pint
☐ Three quarters of a pint
☐ One-pint
☐ More than one pint

80) Did you usually eat breakfast cereal? (excluding porridge and Ready Brek mentioned earlier?)

☐ Yes ☐ No

If yes, which brand and type of breakfast cereal, including muesli, did you usually eat?

List the one or two most often used

Brand	Type

81) What kind of fat did you or your wife/partner most often use for frying, roasting, grilling etc? **Select one only**

☐ Butter
☐ Lard/dripping
☐ Vegetable oil
☐ Solid vegetable fat
☐ Margarine
☐ None

If you used vegetable oil, please give type e.g. corn, sunflower.

.....

82) What kind of fat did you or your wife/partner most often use for baking cakes etc? **Select one only**

☐ Butter
☐ Lard/dripping
☐ Vegetable oil
☐ Solid vegetable fat
☐ Margarine
☐ None

If you used margarine, please give name or type e.g. Flora, Stork.

.....

83) How often did you or your wife/partner use the following spices in cooking?

SPICES (1 TEASPOON)	AVERAGE USE OVER THE LAST 5 YEARS								
	never or less than once/month	1-3 per month	once a week	2-4 per week	5-6 per week	once a day	2-3 per day	4-5 per day	6+ per day
Curry powder									
Turmeric powder									
Worcester sauce									
Mix herb dried									
Oregano dried									
Thyme dried									
Rosemary dried									
Tarragon dried									

84) How often did you eat food that was fried at home?

☐ Daily
☐ 4-6 times a week
☐ Never
☐ 1-3 times a week
☐ Less than once a week

85) How often did you eat fried food as a takeaway or away from home?

☐ Daily ☐ 1-3 time a week
☐ 4-6 times a week ☐ Less than once a week
☐ Never

86) What did you do with the *visible fat* on your meat?

☐ Ate most of the fat ☐ Ate as little as possible
☐ Ate some of the fat ☐ Do not eat meat

87) How often did you eat grilled or roast meat?

☐ Times a week
☐ Do not eat meat

88) How well cooked did you usually have grilled or roast meat?

☐ Well done/dark brown ☐ Lightly cooked/rare
☐ Medium ☐ Did not eat meat

89) How often did you or your wife/partner add salt to food while cooking?

☐ Always ☐ Usually ☐ Sometimes
☐ Rarely ☐ Never

90) How often did you add salt to any food at the table?

☐ Always ☐ Usually ☐ Sometimes
☐ Rarely ☐ Never

91) Did you regularly use a salt substitute (e.g. LoSalt?)

☐ Yes ☐ No
If yes, which brand .....

92) Did you use soy margarine?

☐ Yes *(go on to question 93)* ☐ No *(go on to question 94)*

93) How often did you use soy margarine (at least a teaspoon or more)?

☐ Never ☐ 3 times per month
☐ Once a week ☐ 2-4 times per week
☐ Once a day ☐ 2-3 times per day

94) Did you use soy sauce?

☐ Yes *(go on to question 95&96)* ☐ No *(go on to question 96)*

95) How often did you use soy sauce (at least a teaspoon or more)?

☐ Never ☐ 3 times per month
☐ Once a week ☐ 2-4 times per week
☐ Once a day ☐ 2-3 times per day

The following question asks about vitamin supplements and other functional foods you have taken.

96) Have you taken any vitamins supplements or functional food **during the last 5 years?**

☐ Yes *(please complete the table below)* ☐ No *(go on to question 97)*

Vitamin and supplements	**Average frequency Tick one box per line to show how often on average you consumed supplements**					
	Y/N	**Dose or quantity (no. of pills/capsules, teaspoons, or glass consumed each time)**	**Never or less than once a month**	**2-4 per week**	**Once a day**	**2-3 per day**
Multivitamins and minerals						
Selenium [not as part of multivitamins]						
Vitamin C [not as part of multivitamins]						
Calciferol						
Fish oil						
Saw palmetto						
Garlic as tablet						
Pomegranate drink						
Soy-based drink						
Tomato juice						
Other (please specify)						

We are particularly interested in your patterns of consumption of the following foods ***over your lifetime.***

97) How has your use of the following foods changed over your lifetime?

Food	Age	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
Whole milk	In your 20s									
	In your 30s									
Butter	In your 20s									
	In your 30s									
Margarine	In your 20s									
	In your 30s									
Fruits	In your 20s									
	In your 30s									
Vegetables	In your 20s									
	In your 30s									
Meat	In your 20s									
	In your 30s									
Whole wheat bread	In your 20s									
	In your 30s									
Alcohol	In your 20s									
	In your 30s									

May we have your permission

- To contact you if we need further information to resolve any queries?

☐ Yes Contact telephone number:.....

☐ No Email:.....

- To look at your medical record

☐ Yes ☐ No

If you are planning to move house in the near future, please may we have your new address?

My new address will be.....

..... Post code.....

New telephone number (if known).....

E-Mail: .....

Thank you very much once again for taking the time and trouble to fill in this questionnaire, your help is really appreciated and will be invaluable to this research project.

Please return your answers in the pre-paid envelope as soon as possible to:

Dr Aneela Rahman
Division of Epidemiology and Public Health
School of Community Health Sciences
Queen's Medical Centre
University of Nottingham
Nottingham NG7 2UH

Tel 0115-8230495