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Analysis of the incidence and patient survival for prostate cancer in the West of Scotland

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Thesis is submitted in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD)

Public Health

Institute of Health & Wellbeing

College of Medical, Veterinary & Life Sciences

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Abstract

Prostate cancer has emerged as the most frequently diagnosed cancer, except for non-melanoma skin cancer, among men in many Western countries in the last decade. In the United Kingdom (UK), prostate cancer accounts for nearly a quarter of all new male cancer diagnoses. Increasing age and some genetic and ethnic risk factors have been identified but few modifiable risk factors are known. The introduction of Prostate Specific Antigen (PSA) testing has increased the detection of previously undiagnosed disease but its contribution to the observed increases in prostate cancer incidence is not clear. Considerable variations in the incidence of prostate cancer have been observed in different geographic regions and socio-economic groups across the UK but it is not known whether, or to what extent, these may be attributed to differential uptakes of PSA testing. Prostate cancer is the third most common cause of cancer death in men but many cases do not progress. There is therefore an important clinical need for better prognostic markers so that the increasing numbers of men with prostate cancer can be appropriately managed.

This thesis begins with a descriptive epidemiological study using cancer registry incidence data from the West of Scotland from 1991 to 2007. The aim was to determine whether the incidence of prostate cancer was continuing to rise and to describe any demographic or socio-economic patterns that might suggest particular at-risk groups. To understand whether any socio-economic differentials in incidence might be due to PSA testing, I examined Gleason grade-specific prostate cancer incidence by socio-economic groups over time. Socio-economic circumstances were measured using census-derived Carstairs scores. Overall (age adjusted) prostate cancer incidence increased by 70% from 44 per 100,000 in 1991 to 75 per 100,000 in 2007, an average annual growth of 3.59%. This pattern was driven by significant increases in both low and high grade cancers with no convincing change in their proportions over time. Incidence was inversely associated with deprivation with the highest rates among the most affluent groups.

To explore the role of potentially modifiable risk factors on prostate cancer incidence, the Midspan and Collaborative prospective cohort studies were analysed. An analysis of the relationship between cholesterol and prostate cancer incidence was conducted on the Midspan cohort, which comprises 12,926 men who were enrolled between 1970 and 1976 and followed up to 31st December 2007. Cox Proportional

Hazards Models were used to evaluate the association between baseline plasma cholesterol and Gleason grade-specific prostate cancer incidence. Following up to 37 years' follow-up, 650 men developed prostate cancer. Their baseline plasma cholesterol level was positively associated with hazard of high grade (Gleason score ≥ 8) prostate cancer incidence (n=119). The association was greatest among men in the 4th highest quintile for cholesterol, 6.1 to <6.69 mmol/l, Hazard Ratio 2.28, 95% CI 1.27 to 4.10, compared with the baseline of <5.05 mmol/l. This association remained significant after adjustment for age, body mass index, smoking and socio-economic status.

Evidence on the possible role of tea and coffee consumption in the development of prostate cancer remains limited to a small number of studies with short follow-up and small numbers of cases. Therefore to understand the relationship of tea and coffee consumption with overall as well as grade-specific prostate cancer, a prospective cohort study of 6016 men was carried out, who were enrolled in the Collaborative cohort study between 1970 and 1973 and followed up to 31st December 2007. Three hundred and eighteen men developed prostate cancer in up to 37 years' follow-up. I found a positive association between consumption of tea and overall risk of prostate cancer incidence (p=0.02). The association was greatest among men who drank ≥ 7 cups of tea per day (HR 1.50, 95% CI 1.06 to 2.12) compared with the baseline of 0-3 cups per day. However, I did not find any significant association between tea intake and low (Gleason < 7) or high grade (Gleason 8-10) prostate cancer incidence. Higher coffee consumption was inversely associated with risk of high grade disease (HR 0.46, 95% CI 0.21-0.99) but not with overall risk of prostate cancer. These associations remained significant after adjustment for age, Body Mass Index, smoking, social class, cholesterol level, systolic blood pressure and alcohol consumption.

Although survival of prostate cancer patients has improved over time, little is known about the major prognostic factors. To understand the socio-economic differences and major determinants of survival, an investigation was carried out using cancer registry incidence data from the West of Scotland from 1991 to 2007, linked with General Registrar Office (Scotland) death records up to 31st December 2008. Socio-economic circumstances were measured using the Scottish Index for Multiple Deprivation (SIMD). Age, sex and deprivation specific mortality rates were obtained from General Registrar Office for Scotland (GRO(S)). One, three and five year relative survival was estimated using the complete approach. Survival gradients across

deprivation quintiles were estimated using linear regression, weighted by the variance of the relative survival estimate, using STATA software (StataCorp, version 11). Five year relative survival increased from 58.2% to 78.6% in men over the same period (an average deprivation adjusted increase of 10.2% between six years periods). Despite substantial improvements in survival of prostate cancer patients, there was a deprivation gap (that is, better survival for the least deprived compared with the most deprived) between the three time periods. The deprivation gap in five year relative survival widened from -4.76 in 1991-1996 to -10.08 in 2003-2007. Age, Gleason grade and socio-economic status appeared as significant determinants of survival.

There is some evidence that systemic inflammation may be associated with survival in patients with prostate cancer although its relationship to tumour grade and socio-economic circumstances has not been previously studied. I therefore investigated the association between inflammation-based prognostic scores and survival, using the modified Glasgow Prognostic Score (mGPS) and Neutrophil Lymphocyte Ratio (NLR) as well as Gleason grade. The patient cohort within the Glasgow Inflammation Outcome Study who had a diagnosis of prostate cancer was included in this study. The mGPS is a categorical score constructed by combining serum C-reactive protein and albumin levels, while the NLR is obtained by calculating the ratio of neutrophils to lymphocytes. The relationship between mGPS and NLR and five-year relative survival was explored after adjusting for age, socio-economic circumstances and Gleason grade. Of the 897 prostate cancer patients in the Glasgow Inflammation Outcome Study, 422 (47%) died during a maximum follow-up of 6.2 years. Systemic inflammation had a significant prognostic value. The mGPS predicted poorer 5-year overall and relative survival independent of age, socio-economic circumstances, disease grade and NLR. Raised mGPS also had a significant association with excess risk of death (mGPS 2: Relative Excess Risk = 2.08, 95% CI 1.13-3.81) among aggressive, clinically significant prostate cancer (Gleason score 8-10). Prostate cancer patients with a raised mGPS had significantly higher risks of death overall as well as for high grade disease. Inflammation-based prognostic scores can potentially predict patient outcome and a further prospective study is warranted to assess their clinical value.

Although the study of the epidemiology of prostate cancer is complicated by changing diagnostic sensitivity and disease grade definitions, the increasing number of men diagnosed with the disease demands continuing research into understanding risk

factors, prognostic factors and more effective treatment. However, it seems unlikely that a simple, modifiable risk factor exists for prostate cancer and that PSA testing and an aging population will continue to drive increasing incidence.

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Dedication

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Author's Declaration

This thesis is submitted in fulfilment of the requirement for the degree of Doctor of Philosophy at the University of Glasgow. Unless stated otherwise, the work is that of the author. Parts of the research work included in this thesis has been published or submitted with co-authors. The following publications and presentations originated from this thesis.

Publications

1. **Shafique K**, Proctor MJ , McMillan DC , Qureshi K, Leung H, Morrison DS. Systemic inflammation and survival of patients with prostate cancer: evidence from the Glasgow Inflammation Outcome Study. *Prostate Cancer & Prostatic Diseases* 2012; 15, 195-201.
2. **Shafique K**, McLoone P, Qureshi K, Hart CL, Leung H, Morrison DS. Cholesterol and the risk of grade-specific prostate cancer incidence: evidence from two large prospective cohort studies with up to 37 years' follow up. *BMC Cancer* 2012,12:25.
3. **Shafique K**, McLoone P, Qureshi K, Hart CL, Leung H , Morrison DS. Coffee consumption and prostate cancer: further evidence of inverse relationship. *Nutrition Journal* 2012,11:42.
4. **Shafique K**, McLoone P, Qureshi K, Hart CL, Leung H , Morrison DS. Tea consumption and the risk of overall and grade-specific prostate cancer: a large prospective study of Scottish men. *Nutrition and Cancer* 2012 (Epub ahead of print: DOI: 10.1080/01635581.2012.690063)
5. **Shafique K**, Oliphant R, Morrison DS. The impact of socio-economic circumstances on overall and grade-specific prostate cancer incidence: a population-based study. *British Journal of Cancer* (accepted, in press)
6. **Shafique K**, Morrison DS. Socio-economic inequalities in survival of patients with prostate cancer: role of age and Gleason grade at diagnosis. Submitted

Abstracts and Presentations

1. **Shafique K**, Oliphant R, Morrison DS. Trends of prostate cancer incidence by disease grade and socio-economic circumstances in the West of Scotland from 1991-2007: joinpoint analysis. *Proceedings of the Annual General Meeting of UK Association of Cancer Registries, June 2011.*

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2. **Shafique K**, McLoone P, Qureshi K, Hart CL, Leung H, Morrison DS. Cholesterol and the risk of grade-specific prostate cancer: evidence from two large prospective studies with up to 37 years' follow-up. *Conference Proceedings published in Journal of Epidemiology and Community Health, August 2011.*

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3. **Shafique K**, McLoone P, Qureshi K, Hart CL, Leung H, Morrison DS. Tea consumption and the risk of overall and grade-specific prostate cancer: a large prospective study of Scottish men. *Conference proceedings of the American Institute for Cancer Research (AICR) Annual Research Conference, November 2011.*

Paper presented at AICR annual conference on Food, Nutrition, Physical Activity and Cancer, 2-4 November 2011, Washington DC, United States of America.

4. **Shafique K**, Proctor MJ, McMillan DC, Qureshi K, Leung H, Morrison DS. Systemic inflammation and survival of patients with prostate cancer: evidence from the Glasgow Inflammation Outcome Study. *Conference proceedings of the American Association for Cancer Research (AACR) Annual Meeting, April 2012.*

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Abbreviations

ASR	Age-Standardised Ratio
CI	Confidence Interval
DEPCAT	Carstairs Deprivation Category
EASR	European Age-Standardised Rate
HPFS	Health Professional Follow-up Study
HR	Hazard Ratio
ICD	International Classification of Diseases
ISD	Information Services Division
NHS	National Health Service
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OR	Odds Ratio
PCPT	Prostate Cancer Prevention Trial
PSA	Prostate Specific Antigen
SIMD	Scottish Index of Multiple Deprivation
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

1 Introduction

1.1 Chapter outline

This chapter will briefly describe prostate cancer (PC), its diagnosis and management. Furthermore, risk and prognostic factors for PC, and finally the aims and objectives of this thesis will be described.

Section 1.1: briefly describes the prostate gland anatomy and pathology, particularly PC. Furthermore, this section deals with the clinical presentation, diagnosis and treatment of PC.

Section 1.2: describes the cancer registration process and its benefits, establishment of the Scottish Cancer Registry and measures of cancer burden, particularly incidence.

Section 1.3: describes the literature on burden of PC and international variations in incidence of PC.

Section 1.4: summarises the literature on what is known about the risk factors associated with the development and progression of PC.

Section 1.5: discusses factors associated with survival of PC patients.

Section 1.6: summarises the findings of existing literature and their limitations.

Section 1.7: states the aims and objectives of this thesis.

In this section, a short overview of the anatomy and physiology of the prostate gland is presented along with a discussion on the diagnosis and management of PC.

1.1.1 Prostate gland

The prostate gland is a small, walnut sized and shaped gland located just below the urinary bladder in males. It surrounds the urethra which is a tube connecting the urinary bladder to the genitals for the removal of fluids out of the body (McNeal, 1980; McNeal and Bostwick, 1984). The prostate gland has a fibromuscular function to restrict the urine but the principal function of gland is secretory in nature. It produces a number of essential proteins for the function of sperm such as acid phosphatase, citric acid and bioavailable zinc (Devens *et al.*, 2000). The prostate gland makes some of the highest amounts of polyamine, which contribute to the regulation of sperm pH, preserving a mildly alkaline environment for the sperm within the acidic female cervix (Devens *et al.*, 2000).

The prostate gland comprises three zones, which are composed of relatively simple secretory structures - the central, peripheral and transitional zones. Significant distinctive gene expressions have been observed between these three zones (McNeal, 1981). Transitional zone is the most common site for proliferative disorders i.e. benign prostatic hyperplasia (BPH), while majority of PCs originate in the peripheral zone of the prostate gland (McNeal, 1980).

1.1.2 Prostate cancer

The vast majority (approximately 95%) of prostatic tumours are adenocarcinomas. 'Adeno' signifies the tumour "pertaining to the glandular structure" while carcinoma relates to the origin of a cancer from the prostatic epithelium (McNeal and Gleason, 1991).

1.1.3 Diagnosis of prostate cancer

Investigation for PC can be prompted by clinical symptoms or by screening of at risk individuals by clinical examination and/or serum Prostate Specific Antigen (PSA) tests. However, the definitive diagnosis can only be made by the

histological examination of prostatic tissue obtained by biopsy. In the following subheadings, I will briefly describe the clinical presentation and role of diagnostic tests with particular emphasis on PSA testing in diagnosis of PC.

1.1.3.1 Clinical presentation

Early PCs are unlikely to produce any symptoms, however progressed disease may present with specific lower urinary tract symptoms including frequent urination, nocturia (increased frequency of urination at night), haematuria (blood in urine) or dysuria (pain during urination)(Frankel *et al.*, 2003). The pattern of clinical presentation of PC has dramatically changed over time and now the majority of PC cases remain asymptomatic and malignancy associated signs and symptoms are less common at the time of diagnosis. The clinical presentation of PC changed significantly since 1990s due to increased utilisation of PSA and prostatic biopsies, aimed to detect early stage disease and in most cases small tumours in asymptomatic cases (Frankel *et al.*, 2003).

1.1.3.2 Diagnostic testing and Prostate Specific Antigen

Diagnostic methods to detect an early stage PC included the digital rectal examination (DRE), PSA testing and transrectal ultrasound guided prostatic biopsies. The main limitations of digital rectal examination were the significant inter- (and even intra-) examiner variability, and most PCs detectable by DRE tended to be locally advanced, namely $\geq T3$ disease (Hoffman, 2011). Since the introduction of PSA testing in late 1980s, digital rectal examination is replaced by PSA testing as the main diagnostic tool (Crowell *et al.*, 2011).

PSA is a glycoprotein which is present in small quantities in the serum of men with healthy prostates. Its level is often raised in prostate disorders including PC. PSA testing was not initially envisioned as a screening strategy rather its first use was for the evaluation of treatment responses in men with PC (Crowell *et al.*, 2011). Since the advent of PSA testing, the spectrum of PC cases has changed in many Western countries including the USA and the UK: At the population level, significantly more men are now diagnosed with localised and low grade disease than previously. Furthermore, a significant reduction in mortality has also been attributed to PSA screening in the US, where PSA screening was employed at the population level (Hoffman, 2011). Results

reported by randomised controlled trials in recent years have produced debatable benefit for large scale routine population-wide PSA screening. The European Randomised Study of Screening for PC showed a moderate reduction in mortality (20%) during 9 years of study period (Schroder *et al.*, 2009). However, the absolute benefit of screening was only 0.7 deaths per 1000 men, suggesting that 1410 men would need to be screened approximately twice over a period of 9 years to prevent 1 death from PC (Schroder *et al.*, 2009). In contrast, the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, another large study, did not show any significant benefit of screening by PSA (Andriole *et al.*, 2009). It is worth noting that data from the PLCO study was compromised by significant contamination of the control arm with unscheduled PSA testing.

Although, there was some evidence of potential benefit from PSA screening, significant harms may also result from associated with over-diagnosis. Initially, a PSA value of >4.0 ng/ml was considered abnormal, though lower levels have also been proposed subsequently but no clinical benefits have been observed in diagnosis with modified cut offs. There are several major limitations of the PSA test as a screening tool. First, there is a high risk of false positives associated with abnormal PSA levels. Besides PC, other causes of elevated PSA levels include BPH, prostatitis, urinary tract infection, perineal trauma or recent use of instrumentation of the urinary tract, including digital rectal examination (Hoffman, 2011). Moreover, a normal PSA test does not rule out PC nor any clear cut-off value at which men can be assured that they do not harbour PC (Crowell *et al.*, 2011). Patients with abnormal PSA test results are typically investigated further by transrectal ultrasound guided prostatic biopsies in order to definitively diagnose PC in around 15% of patients. Biopsies may result in significant adverse effects including bleeding (haematuria, haemospermia), pain and infection.

The biggest challenge which is considered as the most significant limitation of PSA testing is that 23 to 42% of the PSA-detected cases may be over-diagnosed because on the basis of life expectancy at the time of diagnosis and natural history of the cancer in the absence of screening, it would be expected that these men may never present with a symptomatic disease during their lifetime (Crowell *et al.*, 2011; Hoffman, 2011).

So given these benefits and harms, there is no national programme of PSA-based testing in the UK. However, it is recommended that patients should be involved in the decision making process of testing after informing the possible benefits and harms of testing.

1.1.3.3 Prostate cancer stage and grade

Disease stage is a measure of extent of the cancer locally within the gland and its invasion around the prostate itself and more distally as metastatic lesions. The TNM classification is used to stage PC, where T represents tumour and its invasion into adjacent structures, N represents if the regional lymph nodes are involved or not, and M describes the presence or absence of distant metastasis. Gleason sum score is the score based on histological pattern of tumour which is widely used as a measure of aggressiveness of cancer (McNeal and Gleason, 1991). This score is sum of the assigned grades ranging from 1-5 to the most common and the second most common morphologic tumour patterns respectively. Gleason score (range 2-10) is a highly useful prognostic factor for PC patients (Sogani *et al.*, 1985). Risk stratification of men with localised PC is done by combining the PSA, Gleason grade and clinical stage which include low risk men (PSA < 10ng/ml and Gleason grade \leq 6 and clinical stage T1-T2a), intermediate risk men (PSA 10-20ng/ml or Gleason grade = 7 or clinical stage T2b-T2c) and high risk men (PSA > 20ng/ml or Gleason grade 8-10 or clinical stage T3-T4). These risk stratifications then guide the treatment decisions.

1.1.4 Treatment of prostate cancer

There are a variety of treatment modalities for PC, with some options more suitable for individual patients. The treatment choice strongly is often influenced by the risk of patients to progress or die of the disease as judged by patient's age, Gleason score, tumour stage and serum PSA levels. For early PC, the main treatment modalities include surgery, radiotherapy and active surveillance. For patients with less favourable general health status, androgen ablation hormone therapy or PSA monitoring (watchful waiting) can be considered.

1.1.4.1 Radical prostatectomy

Surgical treatment has significant benefits and intention of treatment is usually curative. Radical prostatectomy (removal of prostate gland) allows a complete pathological assessment of tumour. Furthermore, extension to surrounding structures and presence of surgical margins can also be assessed by this procedure (Heidenreich *et al.*, 2011). Following a radical prostatectomy, PSA should not be detectable as any rise in PSA indicates the recurrence of disease. Given the benefits of surgical treatment, side effects can also occur as urinary leakage, impotence and urinary incontinence. Sexual dysfunction can occur in 32% to 53% of cases receiving surgical treatment (Knight and Latini, 2009). To minimise the adverse effects of radical prostatectomy, laparoscopic prostatectomy has been introduced as a less invasive surgical approach and showed some benefits compared to open radical prostatectomy. Guidelines now suggest that patients must be engaged in decision making process of most appropriate therapy after sharing the possible harms and benefits associated with treatment.

1.1.4.2 Radiotherapy

External beam therapy or brachytherapy are commonly used radiological approaches. Radiotherapy is also used with a curative intent as radical prostatectomy. Advantages of using external beam therapy include reduction of risks associated with surgical therapy i.e. no risk of anaesthesia, no inpatient hospital stay and may even be used in men with co-morbidities (Heidenreich *et al.*, 2011). Urinary incontinence rate is lower in external beam therapy compared with prostatectomy. Sexual dysfunction can also result following radiation therapy. A main problem associated with external beam therapy is the risk of radiation induced damage to the rectum, which is behind the prostate, and the bladder. These radiations can have serious early and late rectal complications, which can be avoided by brachytherapy (the placement of radioactive pellets within the prostate).

1.1.4.3 Active surveillance

Currently, active surveillance is considered usually for men with low PSA-level, localised disease and Gleason score ≤ 6 (Albertsen, 2010). These patients are

monitored with an intention that if there are any signs of disease progression, active treatment or intervention will be started. Follow-up of these men on active surveillance includes PSA-testing, digital rectal examination and sometimes prostatic biopsy (Albertsen, 2010;Heidenreich *et al.*, 2011). This approach prevents the serious side effects associated with different treatment modalities. Given that in PSA-era most patients are diagnosed with small and asymptomatic tumours which may not progress, this approach seems reasonable. However, the most significant disadvantage of this approach is men are not “cured” from the cancer and they have to live with the disease which can have psychological effects. Some evidence suggests that men on active surveillance had highest quality of life compared with other treatment modalities for localised PC (Albertsen, 2010;Hayes *et al.*, 2010). Although, active surveillance has emerged as a good treatment option, it remains difficult to predict the tumour progression of individual patients, which might compromise the confidence of a cure subsequently.

1.1.4.4 Hormonal therapy

Hormonal therapy was previously used to treat the metastatic PC cases but in more recent days androgen deprivation therapy had become the second most commonly used treatment modality after the surgery (Krahn *et al.*, 2011). Some evidence suggested that hormonal therapy prolongs the survival of PC patients but significant side effects are also reported in recent years (Isbarn *et al.*, 2009). Because androgens are essential for the physiological activity of many body functions so the androgen deprivation therapy has side effects including loss of libido, erectile dysfunction, fatigue, depression, osteoporosis, new onset diabetes and hypertension and even increase the risk of cardiovascular mortality (Isbarn *et al.*, 2009). Beyond the survival improvements, these side effects significantly affect the quality of life of men receiving androgen deprivation therapy and some suggested that the possible benefits and harms should be discussed with the patients before initiation of treatment.

1.1.4.5 Concluding remarks on treatment

Comparison of different treatment modalities is a critical objective and has significant implications for clinician as well as the patients. Treatment goals are

to prevent death and disability from prostate cancer while minimizing intervention-related complications (Wilt *et al.*, 2008). Most of the evidence on comparative effectiveness of radical treatment and active surveillance or watchful waiting has emerged from observational studies. These studies are subject to bias that are caused by selection of patients into treatment for reasons related to expected survival (i.e. patients with a better prognosis may be more likely to receive radical treatment). Furthermore, most observational studies failed to adequately control for important confounding factors (Hadley *et al.*, 2010;Wilt *et al.*, 2008). The randomised control trial is considered the most valid methodology for assessing treatments' efficacy; however, little evidence is available from these trials on the comparative effectiveness and harms of treatment for clinically localised PC, particularly in men with PSA-detected disease.

Recent report from Prostate Cancer Intervention versus Observation Trial (PIVOT), suggests that among men with localised PC detected during the early era of PSA testing, radical prostatectomy did not significantly reduce overall and PC mortality, as compared with observation, through at least 12 years follow-up (Wilt *et al.*, 2012). These findings were in contrast with the Scandinavian Prostate Cancer Group 4 (SPCG-4) trial of radical prostatectomy versus watchful waiting in men with PC. In SPCG-4 trial, men treated with radical prostatectomy showed lower all-cause mortality (a difference of 6.6%, 95% CI -1.3 to 14.5), lower PC-specific mortality (a difference of 6.1%, 95% CI 0.2-12.0) and lower incidence of distant metastasis (a difference of 11.7%, 95% CI 4.8-18.6), compared with watchful-waiting group (Bill-Axelsson *et al.*, 2011b). Higher proportion of men detected before widespread PSA-testing, lower percentage of nonpalpable tumours (stage T1c, 10%) and higher percentage of men with PSA > 10ng/ml in SPCG-4 trial, may explain the differential results of PIVOT and SPCG-4 trials. Despite the findings of these trials, treatment of early-stage PC remains controversial, especially for tumours detected by means of PSA-testing.

In recent years, significant advances have taken place in management of PC patients. However no definitive treatment is available which suits every case of PC. These treatment modalities are used as a single treatment modality or in combination in range of clinical scenarios. Recent guidelines suggest that every

treatment option has its own benefits and risks, so individual patients should be included in the decision making process for selection of treatment.

1.2 Cancer registration

International Agency for Research on Cancer described cancer registration as the “systematic collection, storage, analysis, interpretation and reporting of data on subjects - performed by cancer registry organisation” (Jensen and Storm, 1991). Cancer registries can be broadly classified into hospital-based and population-based registries.

The basic aim of both of these registries is to collect information on cancer patients. The purpose of hospital-based registry is narrow and includes planning, administration and monitoring of hospital services and resources. The data collected in hospital-based registries is less beneficial for epidemiological studies as it is generally not possible to clearly define the catchment area of the hospital and the cases in one particular hospital might not truly represent the whole population in that region (Jensen and Whelan, 1991). Population-based registries collect information on all new cancer cases in a defined geographical region. As the data in this registry originate from a defined geographical region, the denominator population from which cancer patients came can be defined more clearly. Thus, these data can be used for descriptive epidemiological studies and inform public health purposes including health need assessment, allocation of resources, research on aetiological factors and evaluation of preventive services (Jensen and Whelan, 1991).

Cancer registries routinely collect the information on demographic profile of cancer cases, including their age, sex, post-code of residence and date of birth. Furthermore, disease related characteristics are also collected including date of diagnosis, tumour type, site, primary or secondary tumour and cancer grade and stage (however their accuracy and completeness significantly vary between registries). In this thesis, only population-based cancer registry will be considered for further discussion.

There are several benefits of using the routinely collected data by the cancer registries. Cancer registries collect the information of newly diagnosed cancer

cases. Population level coverage of cancer registry is a particular advantage, which estimates the incidence rates and prevalence from whole population and not from a sample (Bain *et al.*, 1997). So the estimates made by the cancer registry data are more likely to be exact, depending on the quality of data. Another advantage is the availability of routine data for a long period of time and this is particularly advantageous when investigating the trends of disease burden over time (Bain *et al.*, 1997) Furthermore, large number of records in population-based cancer registries reduce the statistical problems of sampling error and selection bias (Bain *et al.*, 1997). However the usefulness of these data is based on their quality so it is essential to understand the various factors determining the quality of data, particularly the completeness and accuracy of the collected data. As all the analysis in this thesis will be based on the cancer data of Scottish Cancer Registry, therefore its development and data quality issues will be discussed first.

1.2.1 Scottish cancer registry

The Scottish Cancer Registry was established in 1958 and has been collecting information for more than 50 years now. Cancer registration database currently holds the records of 1,200,000 cancer patients and on an average, 40,000 registrations are made per annum in Scotland (Information Services Division, 2011). This registry is responsible for the registration of all newly diagnosed malignant neoplasms in residents of Scotland (Information Services Division, 2011). Historically there were five semi-independent cancer registries in Scotland before 1997, since then data are pooled together as the Scottish Cancer Registry. Reorganization took place and a single cancer registry was established which is independently collecting data since January 1st, 1997. Part of this reorganization, registry also started collecting additional information about the disease stage (only for breast, cervical and colorectal cancers), treatment including radio and chemotherapy for all the patients (Information Services Division, 2011). Several in-house studies by authors of Scottish Cancer Registry have assessed the completeness and reliability of the Scottish Cancer Registry data. A study in 1990 accessed the data of a computer generated random sample of 2,021 cancer patients and compared the cancer registry records with relevant medical records (Brewster *et al.*, 1994). Discrepancy rate was different between

different variables - 7.7% in histological verification status, 5.4% in ICD-9 site codes and 14.5% in ICD-0 morphology codes were recorded (Brewster *et al.*, 1994). However, the Scottish Cancer Registry data showed a high level of accuracy on the whole - 97.2% of the records were accurate and overall discrepancy rate remained 2.8% (Brewster *et al.*, 1994). Another study looking at the accuracy of colorectal cancer patients in Scotland reported similar findings: 95% of the data was found to be accurate (Brewster *et al.*, 1995).

Three studies, independent of Scottish Cancer Registry, of cancer ascertainment of malignant tumours have also been published. One of these studies compared the data of cutaneous malignant melanoma cases following screening as part of a health education programme. This study included cases of seven different health boards from England and one health board of Scotland. Case ascertainment was found 96% for invasive malignant melanoma and 100% for in situ melanoma in Scottish Cancer Registry (Melia *et al.*, 1995). However, case ascertainment remained 74% in English cancer registries (Melia *et al.*, 1995). In contrast to these, two independent studies reported that registered cases of malignant melanoma and primary intracranial tumours in Scottish Cancer Registry were significantly underestimated (Counsell *et al.*, 1997; Lucke *et al.*, 1997).

In general, the quality of data in Scottish Cancer Registry has been assessed for many different tumours, suggesting high level of completeness and accuracy. Very few cancer registries conduct studies to assess the data quality and publish their results. However where literature is available, data quality of Scottish Cancer Registry seems fairly comparable with other cancer registries.

1.2.2 Measures of cancer burden

The burden of cancer on society is used to describe the epidemiological quantification of occurrence of disease in a given population. Different measures are used for the estimation of cancer burden.

Incidence:

Incidence describes newly diagnosed cases of cancer in a defined population over a specified period. Incidence rates of a cancer mainly reflect the distribution of risk factors in population and diagnostic abilities of health services. So the incidence rates are useful measure of burden, where the prime objective is to reduce the risk of cancer through successful primary prevention. Similarly, efforts for successful early detection of cancer can also be examined by estimating incidence rates.

Prevalence:

The prevalence of cancer is the number of individuals living in a population, who have had a diagnosis of cancer. A time cut-off is usually applied to estimate number of cancer cases in a defined population diagnosed during 5, 10 or 15 years and referred as “limited-duration prevalence”. Prevalence is a useful measure for administrative and planning purposes. For example, successful primary prevention efforts reduce the prevalence by reducing the incidence of cancer, while improvements in services - early diagnosis and advances in treatment, increase the prevalence.

Survival:

Cancer survival relates to the time course of disease following the diagnosis, extending to death due to cancer itself or other causes. Cancer survival is usually expressed as the proportion of patients alive at five years or ten years after diagnosis. Using population-based data, cancer-specific survival is usually expressed as relative survival, which is a ratio of the observed survival for a group of cancer patients to the survival expected for people of the same age, sex and socioeconomic status in the general population. Cancer survival is perhaps the most widely used measure of the effects of different factors i.e. timely diagnosis, effectiveness of treatment, socioeconomic circumstances and other factors related to health services.

In practice, incidence data provide better overall measure of burden of disease in a population, so in this thesis we will focus on incidence. Also, a main component of this thesis is concerned with the aetiological factors associated

with PC - therefore incidence would be a more appropriate measure to reflect the risk of developing disease.

1.2.2.1 Incidence

Incidence of a cancer represents the occurrence of new cases arising in a given period in a specified population. Incidence basically represents the risk of developing a cancer due to various underlying factors (Last, 2001). The particular advantage of incidence rate is that it allows comparison of risk and burden between populations, countries and time periods. Many factors can influence the incidence rate including diagnostic intensity, coding and reporting. These factors can cause an underestimation or over-estimation of incidence and may affect the comparison between population groups and time periods (Rothman et al. 2008).

To calculate the incidence rate of a cancer, for example PC, following information is required, i.e. number of individuals diagnosed with a cancer, population from which individuals come from and the time period over which the data were collected (Rothman et al. 2008). All these parameters can directly affect the incidence rates of a population. Different types of incidence rates can be calculated using this information i.e. crude incidence rate and age standardised incidence rates.

Crude incidence rate is the number of new cases occurring in a year and usually per 100,000 persons in a population. Population at risk is an important factor in calculating incidence rates (Bonita et al., 2006). Ideally, these should only include people who are potentially at risk of developing a cancer. For instance, females should not be included when calculating the crude incidence rates for PC. The crude incidence rate is a reliable measure of frequency of disease in a population. However, in the example of PC which typically affects men over 50 years of age, crude incidence rate can heavily be influenced by the age structure of a population. In a population where the majority of men are young, crude incidence rate is likely to be low and opposite would be true if higher proportion of men in a population is old. Similarly, if age-structure of a population is varying over time, difference in crude incidence rates could be because of a change in age structure rather than the risk of cancer.

Therefore, crude incidence has a limited use as it cannot effectively compare the burden of disease between populations, cancer registries and over time, as it does not take into account the aging structure of a population (Rothman et al., 2008). Comparing the rates of incidence between populations, or between time periods or sub groups of population, the crude estimates can be misleading. We need a 'Standard Population' with which we can calculate age-standardised rates. For such comparisons, age-standardised rates are used.

Age-standardisation controls for the changing age structure of population and this is the only viable method to compare the rates over time, between populations and within population groups. There are two different methods of age-standardisation: the direct and the indirect method of standardisation. The indirect method is most commonly used to calculate the expected mortality rates for an index population, i.e. age specific mortality from a reference population. The direct method adjusts for the differences in age-structure of the populations, and it is therefore widely used to compare the incidence rates between populations and within population over time. The direct standardisation is calculated by estimating the crude incidence rates for each age-group (usually 5-years groups), followed by normalising/correcting these rates to the numbers for the respective age specific groups within a fixed reference 'standard population' of 100,000 people, thus giving an incidence for each of the age-groups in the standard population (Waterhouse et al., 1976). The age-group specific incidence rates are then added together to calculate the overall incidence rates for standard population (100,000). Thus age-standardised rates can be considered as a weighted average of age-specific rates, the weights being taken from the standard population (Waterhouse et al., 1976). Standard population can be chosen arbitrarily; the European Standard Population (which gives European Age-Standardised Rates) and the World Standard Population are two common options (Waterhouse et al., 1976). The European-standard population represents the age structure of most of the European countries and have been assessed in relation to the Scottish population and found broadly comparable (Harris et al., 1998).

1.3 International variations in incidence of PC

Worldwide, 913,000 new cases of PC occurred in 2008, ranking it among the top five commonest cancers globally (Ferlay et al., 2010). Lung cancer is the most common cancer among men worldwide but in developed world, PC is now the commonest cancer among men with 658,000 cases in 2008 (Ferlay et al., 2010). The incidence of PC varies significantly in different countries. Generally, more developed countries have a higher incidence compared to less developed countries. In the year 2008, the age standardised rate (world population) was more than five times higher in the developed world (63 per 100,000) when compared with less developed world (12 per 100,000) (Ferlay et al., 2010).

Worldwide incidence varied by 25-fold in 2008 with the highest rates observed in Australia and New Zealand and lowest in Micronesia and Polynesia. These large variations in incidence could be due to a combination of underlying factors, including genetic susceptibility, exposure to unknown risk factors and artefactual increases by testing for PC in different countries (Gronberg, 2003). Access to and quality of the healthcare services can at least partially explain the large differences in incidence rates between the developed and less developed countries.

PC is a condition which is strongly associated with increasing age - approximately 75% of the total cases occur among individuals of more than 65 years of age. It is therefore significantly more common in those countries where the proportion of elderly population is higher (Ferlay et al., 2010). However the lower incidence rates in developing countries is not only because of the lower proportion of elderly population and lower detection but also because of poor recording of cancer cases. In year 2006 only 21% of the worlds' population was covered by population-based cancer registries, with very low level of coverage in Asian and African countries, 8% and 11% of the total populations respectively (Ferlay et al., 2010). Although the general idea of disease burden seems reasonably straightforward, the burden can be measured or presented using multiple dimensions.

In addition, the quality of cancer registration and accuracy and completeness of cancer data could explain the difference in incidence rates between countries. For example, a few decades earlier, when reliable cancer registration data did not exist in the African countries, rates of PC in Africa were taken as approximately similar to that in the Asian countries (Gronberg, 2003). However, one decade ago, PC was reported as very common in Uganda (Wabinga *et al.*, 2000), and the most common cancer among men in Nigeria (Ogunbiyi and Shittu, 1999). Migration studies have suggested that men who moved from Japan (a country with low incidence of PC) to the US (a country with higher incidence of PC), experienced an increase in incidence (Gronberg, 2003). These findings suggest that differences observed between countries and racial groups may be due to the differences in lifestyle and dietary factors.

Most up to date cancer statistics have shown variations in incidence rates of PC between countries of the developed world. Highest rates were observed in Australia, New Zealand, Western and Northern Europe and North America (Ferlay *et al.*, 2010). Southern and Eastern European countries experienced lower incidence rates compared with other developed world countries (Ferlay *et al.*, 2010).

Age standardised incidence rates of PC have dramatically increased in last two decades in the UK and Europe (Bray *et al.*, 2010). These increases have largely been attributed to the opportunistic testing of asymptomatic PC by PSA (Bray *et al.*, 2010; Brewster *et al.*, 2000; Carsin *et al.*, 2010). A decline in mortality rate has also been observed which is also attributed to the PSA based testing, which led to earlier diagnosis and prompt treatment of localised disease (Collin *et al.*, 2008; Hussain *et al.*, 2008).

In the UK, PC is the most commonly diagnosed cancer, excluding non-melanoma skin cancer, in men and accounts for nearly a quarter (24%) of all new male cancer diagnoses (Cancer Research UK, 2008). As variations in incidence rates are noted within the developed countries, similar variations have been observed within the four nations within the UK. Wales observed highest incidence rate in 2008 (age-standardised rates, 119.9 per 100,000) while lowest were observed in Scotland (age standardised rates, 85.7 per 100,000) during the same year

(Cancer Research UK, 2008). As there are no policy guidelines for the mass screening on population level, so the observed differences in the UK are attributed to differential uptake of PSA-testing (Westlake and Cooper, 2008).

It is worth noting that, as these rates are age-standardised, these estimates have accounted for the changing age-structure of the population. Therefore, any differences observed between countries are unlikely due to the aging population. The apparent increase then can be attributed to a real increase in risk of the disease and/or an artefact of increased detection of cases by testing. The observed increase in incidence of PC in 1970s and 1980s has partially been attributed to the transurethral resection of prostate (TURP) for the treatment of BPH, which led to incidental finding of PC in approximately 10% of the cases (Brewster *et al.*, 2000;Quinn and Babb, 2002). In late 1990s and more recently, differences in incidence rates within the UK countries are mainly attributed to varying intensity and utilisation of PSA testing in different countries. However, the PSA issue still remained unresolved whether the observed increasing rates are merely because of increased detection or due to a true increase in the risk of this disease.

1.4 Aetiological factors

No single factor is considered to be solely responsible for development of PC. Many risk factors have been identified which are associated with the pathogenesis and cancer development. Evidence on these risk factors and their association with PC mainly comes from observational studies. The effects of dietary components and role of some chemopreventive agents have also been investigated by randomised controlled trials. The review of evidence in this section of the chapter will be confined to the evidence of different factors and their association with the PC risk. For the purpose of simplicity, the risk factors are classified and presented as (1) Non-modifiable risk factors and (2) Modifiable risk factors.

1.4.1 Non-modifiable risk factors

The risk factors which are beyond the human control like age, family history of PC, race, socio-economic circumstances and hormonal levels are considered as

non-modifiable risk factors and they have a strong association with the risk of PC. A brief review of the evidence on these factors and their association with PC is attempted in this section.

1.4.1.1 Age

Age is one of the strongest risk factors of PC. PC is uncommon among individuals younger than 50 years (<0.1% of all patients) and more than three quarters of cases are diagnosed in men over 65 years. The largest number of cases are diagnosed in 70-74 age group (Cancer Research UK, 2008) and the cumulative risk of PC at the age of 74 years has been calculated from 0.5% to 12.8% worldwide (Ferlay *et al.*, 2010). However, post-mortem data have found different results which showed that microscopic lesions were found in half of all men in their fifties and more than 80% of men older than 80 years (Cancer Research UK, 2008). These are the men who never manifest the disease during their lifetime, suggesting that a significant proportion of men remain asymptomatic despite having the disease.

An age migration has been brought about due to earlier diagnosis of PC by PSA (Metttlin and Murphy, 1994). Due to PSA testing and screening in different countries, the whole spectrum of PC has changed in the last few decades. A relatively larger proportion of men is now diagnosed before the age of sixty years compared to few decades earlier (Metttlin and Murphy, 1994). Also, a higher proportion of men are now diagnosed at an earlier stage and grade with smaller tumour volume (Metttlin and Murphy, 1994). Whether the age and stage shift of PC patients has a beneficial effect on health and quality of life for individuals as well as at the population level remains unclear and debatable. Further research into survivorship experience of clinically presented and screen detected patients may provide valuable information on harms and benefits of early diagnosis.

1.4.1.2 Family history

Family history has now been firmly established as a risk factor for PC. PC can be grouped as one of the three groups - sporadic, familial or hereditary (Bratt, 2002). Disease is marked as familial cancer if one or more than one first-degree relative are affected by the PC. Hereditary PC refers to a subset of familial PC

that shows a pattern of cancer distribution consistent with Mendelian inheritance of a susceptibility gene (Bratt, 2002).

Several epidemiological studies have shown an augmented risk of PC for sons and brothers of men with the disease. Relative risk of an individual to develop PC increases significantly in accordance to the number of individuals affected in family, their relationship with the index case(s) and the age at which they developed the disease (Carter *et al.*, 1992). If a brother or father of an individual had PC, the relative risk in such an individual is doubled with an absolute risk of 15%. If a brother or father had the disease before the age of 60 years, then the relative risk increases three fold and absolute risk becomes 20%. The relative risk amplifies to four times and absolute risk is 30% if both father and a brother have PC (Bratt, 2002). Regarding the clinical features of patients with hereditary and sporadic PC, there are generally no differences in tumour grade and pathological stage at diagnosis.

The most prominent clinical characteristic of hereditary PC is the relatively earlier age at diagnosis. Patients from families with hereditary PC are generally diagnosed six to seven years earlier than those with sporadic cancer (Bratt, 2002). This could be attributed to the increased awareness of symptoms and more enthusiastic participation in testing, both of which result in earlier diagnosis of hereditary cases not only at a lower age but also at a lower grade and in localised form. In terms of comparing the survival of these patients, no significant difference was observed in earlier studies between men who had familial or sporadic PC (Gronberg *et al.*, 1998; Hanlon and Hanks, 1998). However, survival comparison between these two groups is difficult because earlier age at diagnosis with better differentiated and localised disease among hereditary cancers could lead to a longer survival, i.e. lead time bias.

Similar to other malignancies, particularly solid tumours, PC is a complex disease with its initiation arising from interaction between genetic and non-genetic factors. There have been many efforts to identify the causative gene(s) for PC, despite that most of the existing evidence is elusive (National Cancer Institute, 2011). Several candidate loci have been identified by genome-wide linkage analysis studies in high risk families, but occasionally subsequent studies failed

to confirm these candidate susceptibility loci among PC patients (National Cancer Institute, 2011).

Not only the history of PC but also, the history of colorectal or bladder cancer in parents has a higher than multiplicative interaction on an individual's risk of developing PC (Zhang *et al.*, 2009). Diagnosis of a cancer among a family member usually leads to more intense testing among other family members. Therefore, the observed higher risk of cancers among family members could be due to higher consciousness and testing for cancer, and not necessarily due to genetic composition of the individuals.

1.4.1.3 Race

Racial differences exist in the incidence of PC. Black men have a higher risk of PC development (1.5 to 2 times) compared with White men, while Caucasians are observed to have a higher risk than Asians (Brawley *et al.*, 2007; Krieger *et al.*, 1999). These differences in incidence of PC have raised a question, whether the difference in incidence of PC among various races is just a result of genetic predisposition of certain races to develop the disease or a product of differential distribution of other factors like socio-economic status of individuals, their dietary and lifestyle habits and access to health care services.

Asian men have a lower incidence of PC, while the Japanese and Chinese immigrants in Western countries experienced a higher incidence compared to their counterparts (Brawley *et al.*, 2007). If genetic pre-disposition is the major contributing factor, then the substantial difference in incidence among men of same origin, living in different countries cannot be explained. These findings have suggested the possible role of lifestyle and dietary patterns as contributing factors in disease development. Although genetics play a vital role in PC development, considerable evidence suggests that environmental factors (possibly diet and lifestyle) are important and it is the gene-environment interactions that play a central role in the development of PC (Giovannucci *et al.*, 2007; Whittemore *et al.*, 1995).

Another important consideration arises from the findings of autopsy studies which suggest that the prevalence of small PCs is relatively higher among

numerous populations, and there are little or no racial/ethnic variations in the incidence (Sanchez-Chapado *et al.*, 2003; Soos *et al.*, 2005). These findings lead to further questions about the factors which promote these small slow growing tumours and how they differ from the factors responsible for the development of larger and clinically significant disease. Again, multiple factors including androgen level in the body, lifestyle factors and diet are considered to be associated with differential tumour biology among different races but the evidence on these remains mostly equivocal (Brawley *et al.*, 2007).

1.4.1.4 Socio-economic circumstances

Socio-economic circumstances have been related to the incidence of many cancers including PC. It is unclear whether the increased incidence in specific socio-economic groups reflects real risk factors being more prevalent in some groups (discussed later) or simply results from the readiness to diagnose the condition.

Prostatic carcinogenesis is believed to be a multistep process. Along with race, evidence suggests that lifestyle and environmental factors do contribute in this carcinogenic process. Studies have also indicated that the differences in risk of PC between different racial origins are mainly driven by the socio-economic circumstances of the individuals (Dale *et al.*, 1996). Many other factors are thought to be associated with the socio-economic differences in cancer development. For prostate particularly where the aetiology is poorly understood, the involvement of socio-economic status in the risk of disease can be due to the differential distribution of currently unknown risk factors - environmental exposures such as diet and sexual activity being the examples of such risk factors.

Another important aspect in context of socio-economic circumstances is the capacity to access the health care services and quality of testing services available to different socio-economic groups. These obviously vary in different countries. For instance, in the US, where access to services mainly depends on the ability to pay for a medical insurance, individuals of low socio-economic circumstances are less likely to have good access to health services and ultimately are less likely to be diagnosed earlier (Dale *et al.*, 1996).

Surprisingly, in the UK, where National Health Services is being financed by central Government and services are free at the point of use for everyone, similar socio-economic disparities in incidence of different cancers and other chronic disease have been observed. It has been reported from England that most affluent people are more likely to have higher incidence of the PC compared with the most deprived group (Dutta *et al.*, 2005). Differential use of PSA testing may explain these differences between socio-economic groups. However, other factors which could be the higher level of education, health consciousness and heightened awareness about the disease among most affluent people are hardly examined in most of the PC research in this country. There has been no published data from Scotland on the incidence trend of PC in relation to the socio-economic circumstances. However, evidence suggests that the health of Scottish population is poorer than the rest of the UK (Hanlon *et al.*, 2005).

Area based measures of socio-economic circumstances:

In most of epidemiological research socio-economic circumstances of individuals are measured by using variety of different indexes such as education, income, car and house ownership. Area-based indices are also widely used as a measure of socio-economic circumstances. Many deprivation indices have been derived since the 1980s and there has been a wide debate on the use of these indices. Area-based measures of socio-economic circumstances are usually derived using the census and administrative data. Carstairs and Morris devised an area-based measure of socio-economic status which was based on the data of 1981 and 1991 Censuses respectively. Carstairs scores are basically un-weighted combinations of four Census variables namely unemployment, overcrowding, car ownership and low social class (Carstairs and Morris, 1989; Morgan and Baker, 2006). Each of the four variables are transformed or standardised to a common scale (i.e. with a mean of zero and standard deviation of one) so that the value of no one variable dominates the overall score of individuals (Morgan and Baker, 2006). In Carstairs score, deprivation group 1 represents the most affluent while the 7 represents the most deprived.

In Scotland, another area-based measure - Scottish Index of Multiple Deprivation (SIMD) is widely used. This is a postcode based measure of socio-economic circumstances derived by post code of residence. The SIMD score is based on detailed information on seven key domains including income and benefits, employment in working age population, health and healthcare utilisation, education attainment, access to services and transport, recorded crime rates and housing quality and overcrowding (Scottish Government, 2006). SIMD quintiles are commonly used, 1 representing the least deprived quintile and 5 representing the most deprived quintile.

All area-based measures assume that the individuals with a living area experience similar socio-economic circumstances, and that the 'background' risk factors of the population are evenly distributed within the area. However, there is an on going debate that the choice of area-based measure can influence the magnitude of deprivation gradient in health between different socio-economic groups. The choice of measurement index can impact on the observed

deprivation gradient in incidence and survival between groups of cancer sufferers (Donnelly and Gavin, 2011). These measures may not be truly representing the socio-economic circumstances of individuals even though they can provide valuable information about factors at the population level, which is of particular importance when considering access to the health care services, and utilisation of services.

1.4.1.5 Hormones as risk factors

Although there is sufficient biological evidence that hormones, particularly the androgens play a vital role in the development of PC but most of the epidemiological evidence remained inconclusive in a hormone dose to cancer risk context (Hsing, 2001). Testosterone and dihydrotestosterone are the two most important androgens of adult males. Testosterone is the major circulating male hormone, while dihydrotestosterone is synthesised in tissues. The latter is derived from testosterone mainly in the prostate gland and skin by the 5 alpha reductase isoenzymes type 1 and type 2 (Hsing, 2001). Physicians' Health Study observed a strong trend of increased PC risk with increasing levels of plasma testosterone (ORs by quartile = 1.00, 1.41, 1.98, and 2.60 (95% CI = 1.34-5.02); P for trend = 0.004) and an inverse trend in risk was seen with increasing levels of sex hormone binding globulin (ORs by quartile = 1.00, 0.93, 0.61, and 0.46 (95% CI = 0.24-0.89); P for trend = 0.01) (Wolk *et al.*, 1997). Epidemiological evidence on hormones and PC risk initially emerged from case-control studies but later on most of the studies reported inconsistent evidence (Hsing, 2001). A main limitation inherent in the case-control design of such studies was the inability to obtain the hormonal status of participants either before diagnosis or (even harder) before the onset of prostate carcinogenesis, as the disease process or disease itself might have altered the hormonal profile among patients in such a study design.

A meta analysis of 9 prospective studies reported that there was no significant evidence that the serum testosterone concentrations were different between PC cases and controls, with a pooled risk ratio 0.99 (95% CI 0.95-1.02) (Eaton *et al.*, 1999). Methodological limitations could partially explain the mixed results in different studies. For instance, intra-person and laboratory variations can affect the measurement of hormonal levels between different studies. Similarly, the

timing of measurement of hormone level could also explain the difference between studies. For example, if testosterone is a major risk factor for the development of disease, then the most appropriate timing of sampling might be the age between 15 to 23 years (Gronberg, 2003).

1.4.2 Modifiable factors

Modifiable risk factors have been substantially examined for their relationship with the development and progression of PC. Generally, to date, there is no known means of preventing PC, and no well established modifiable risk factor is known to alter the risk of this cancer. Factors studied in details fall broadly in the following classes: dietary factors (tea coffee, fat, meat intake, lycopene, soy and vitamins), lifestyle and co-morbidities (smoking, alcohol, physical activity, obesity and diabetes), and medications and supplements (statins, finasteride, non-steroidal anti-inflammatory drugs and vitamin).

1.4.2.1 Tea and coffee as risk factors

Tea and coffee are among the most popular beverages worldwide and have been investigated for their role in PC development. These beverages are also among the few potentially modifiable risk factors for PC but the epidemiological evidence is inconclusive and therefore no recommended guidelines are available for their consumption. Preparation of these beverages also differs between various regions of the world. Both tea and coffee are thought to be protective factors against the PC but the evidence has not achieved that level to recommend their use for the prevention of PC (Lee et al., 2009).

Tea (*Camellia Sinesis*) is one of the most popular and commonly consumed beverages in the world (Bokuchava and Skobeleva, 1980). Green tea is more commonly consumed in Asian countries while black tea is predominantly used in Western countries. Green tea is prepared from the dried leaves of the plant, whereas the preparation of black tea includes crushing of leaves and a fermentation process (Bokuchava and Skobeleva, 1980). These differences in the preparation process are responsible for variations in the taste and chemical composition of teas and may also influence their carcinogenicity. Tea consumption has been investigated for its possible effects on health outcomes in

the last three decades (Mckay and Blumberg, 2002). Most of the in vitro cell culture, in vivo animal and clinical interventional studies investigated the effect of green tea or purified extracts on PC carcinogenesis and reported its chemopreventive effect but results from epidemiological studies on green tea consumption and carcinogenesis are mixed (Henning *et al.*, 2011;Mckay and Blumberg, 2002). Population-based studies on the role of tea and PC risk have shown mixed results, some showing a positive association (Sharpe and Siemiatycki, 2002), some negative (Jain *et al.*, 1998;Severson *et al.*, 1989) while others found none (Ellison, 2000;Heilbrun *et al.*, 1986;La *et al.*, 1992;Villeneuve *et al.*, 1999).

Recent review on tea and PC suggested that tea is a healthier alternative to coffee as evidence on a preventive effect of tea has been more pronounced in epidemiological evidence (Lee *et al.*, 2009). Most of the laboratory and epidemiological studies which provided stronger evidence on protective effects of tea were carried out on green tea which is more common in some Asian countries including China and Japan. Extracts of tea have been widely used in both in vivo and in vitro studies have and found significant effect on cancer cell death. On the other hand, black tea, which is much more common in most of the Western countries has not been widely studied and evidence on black tea and PC is limited to few studies with smaller number of cases and short follow-ups (Chhabra and Yang, 2001).

Evidence for an association between black tea and PC incidence is much weaker than that for green tea (Henning *et al.*, 2011). Research is either limited to case control studies (Ellison, 2000;Jain *et al.*, 1998;Villeneuve *et al.*, 1999), which are prone to biases, or cohort studies (Heilbrun *et al.*, 1986;Kinlen *et al.*, 1988) with small number of PC cases, short follow-up periods and inadequate adjustments for potential confounding effects.

A meta-analysis of twelve epidemiological studies (eight case-control and four prospective cohorts) (Park *et al.*, 2010) and reviews on role of coffee in PC risk (Lee *et al.*, 2009;Dagnelie *et al.*, 2004) remained inconclusive. However, a recent study on coffee consumption and PC risk, from a large, prospective cohort (Wilson *et al.*, 2011), reported a weak inverse association with overall

risk and strong inverse association between higher coffee intake and aggressive as well as lethal PC (Wilson *et al.*, 2011). Although the authors did not recommend that coffee consumption should be increased to reduce the risk of PC. However, study provides the evidence that future research should investigate the role of these factors in relation to grade-specific incidence of PC.

Coffee contains several hundreds of volatile and non-volatile compounds which have the tendency to modify the effect of many other substances in human body (including dietary components), but we often know little or nothing at all which substance or groups of substances will be affected in which direction and that is mainly due to extremely complex biological processes (Porta *et al.*, 2003; Spiller, 1984). Given that coffee compounds have very strong metabolic, physiological, cellular and molecular effects, clinical and epidemiological data from large human groups should be carefully analysed for interactions (Porta *et al.*, 2003).

Common limitations of the studies on tea/coffee and PC risk are short follow-up of studies and lack of Gleason grade information. Considerable interest has developed in recent years to explore how some of the dietary and lifestyle factors are associated with the biology of prostate tumours and certain behaviours are linked with more aggressive or fatal disease.

1.4.2.2 Fat intake

Dietary components are considered important in the aetiology of PC. Increased rates of PC among Japanese and Chinese immigrants in the US suggested a significant role for dietary and lifestyle habits in the development of PC (Gronberg, 2003).

Many observational studies examined the role of fat intake in aetiology of PC. Earlier studies showed some positive associations while the data presented from larger prospective cohorts in more recent years suggested no relationship between fat intake and PC. The Health Professional Follow-up Study, a prospective study of 51529 men in the US reported that total fat intake was directly related with advanced stage PC (RR = 1.79, 95% CI = 1.04 -3.07) (Giovannucci *et al.*, 1993). Mono-unsaturated fat and saturated fat were also positively associated with the advanced stage PC (Giovannucci *et al.*, 1993).

These results remained consistent even after adjustments for age, energy intake, BMI, marital status and history of vasectomy. The interesting fact is that fat intake might be different between different racial or socio-economic groups; however this study did not account for potential effect socio-economic status and race.

The Malmo Diet and Cancer study in Sweden, a large prospective cohort study, reported no significant association between fat intake and overall PC risk (Wallstrom *et al.*, 2007). Some biological research has provided evidence of a protective role of fish fat in PC, but the Malmo Diet and Cancer study showed that Eicosapentaenoic acid and Docosahexaenoic acid (DHA), predominantly found in fatty fish, were associated with increased risk of PC (HR for highest vs lowest quintiles of DHA = 1.35, 95% CI 1.07-1.69) (Wallstrom *et al.*, 2007). The main limitation of this study was that majority of the participants were younger than 50 years and median follow-up time was only 11 years. The role of fat consumption in carcinogenesis might even start long before the actual manifestation of the cancer. Therefore, studies with shorter follow-up are unlikely to capture any real associations.

The European Prospective Investigation into Cancer and Nutrition (EPIC), another large multicenter prospective study of 142,520 men, also did not find any significant relationship between dietary fat intake and the risk of PC (Crowe *et al.*, 2008). The EPIC study also had a relatively short follow-up period (median follow-up at 8.8 years) and the risk estimate significantly differed when stratified analysis was performed based on the data from different countries. However, the question still remained unanswered whether this heterogeneity was attributable to the true biological differences of individuals between different countries or just random variation (Crowe *et al.*, 2008).

In summary, most studies have provided mixed results on the relationship between fat intake (total, monounsaturated, polyunsaturated) and PC risk.

1.4.2.3 Plasma cholesterol as a risk factor

It has been observed for about a century that the levels of cholesterol, fatty deposits, lecithin and some other lipids in the diseased prostate are elevated

(White RM, 1909). Several studies have explored the relationship between plasma cholesterol levels and the incidence of PC and its associated mortality with inconsistent conclusions (Bravi *et al.*, 2006; Hiatt and Fireman, 1986; Kark *et al.*, 1982; Knekt *et al.*, 1988; Davey Smith *et al.*, 1992; Thompson *et al.*, 1989). Some found a positive association between cholesterol and PC mortality (Batty *et al.*, 2011; Bravi *et al.*, 2006) while others revealed either an inverse relationship (Kark *et al.*, 1982; Thompson *et al.*, 1989) or no overall association with incidence (Hiatt and Fireman, 1986; Knekt *et al.*, 1988). The imprecision of death record data may make it difficult to differentiate between risk factors for a variety of causes of mortality among PC patients and mortality from PC itself. The well-established relationship between serum lipids and cardiovascular risk (Preiss, 2009), for example, may confound the apparent positive association between cholesterol and mortality in PC patients.

A few decades ago, there was concern that a low circulatory cholesterol concentration as a result of statins use, which is cardio-protective, might increase the risk of some non-cardiac events particularly cancers. Some of these studies reported an inverse association between cholesterol and PC (Kark *et al.*, 1982; Thompson *et al.*, 1989). These studies might have been influenced by the “reverse causality” - i.e. cholesterol was modified by undiagnosed disease and not a causal factor for it, may have partly explained their observations.

In general, the evidence on the role of cholesterol in prostate carcinogenesis remains equivocal and limited. A few studies have investigated the role of risk cholesterol in relation to grade-specific PC risk. There is no study published on the role of cholesterol on grade-specific PC risk from the UK population to date. Further evidence is required before making any recommendations about statins or cholesterol level management in relation to PC.

1.4.2.4 Smoking

The role of lifestyle has been widely studied in relation to different cancers and considered very important in disease development. Evidence of these factors with regard to PC is equivocal. One important fact which needs to be considered is the competing risks. Individuals with health risk behaviours like smoking, sedentary lifestyle and higher alcohol intake may be at a higher risk of death

due to other chronic diseases. If this is the case then evidence should suggest lower risk of PC among those who had high alcohol intake, smoking habits and physical inactivity. Therefore, some of the evidence on these factors will be briefly reviewed in the following section

Carcinogens in tobacco directly affect the sex hormone and growth factor profiles which can ultimately lead to altered risk of PC. Evidence on smoking and its association with overall risk of PC is inconsistent. However, smoking has a stronger relationship with advanced and fatal PC (Watters *et al.*, 2009;Zu and Giovannucci, 2009;Huncharek *et al.*, 2010). In a large prospective study, current and former smokers had a significantly lower risk of developing non-advanced PC (18% and 11% respectively) (Watters *et al.*, 2009), while ‘current’ smoking status had a significantly higher risk (Huncharek *et al.*, 2008) of fatal PC (Watters *et al.*, 2009). Consistent with this, a meta-analysis of 24 prospective studies which enrolled 21,579 PC patients reported that the current smokers had 14% higher risk of fatal PC than the non-smokers (Huncharek *et al.*, 2010), Additionally they reported the dose-response effect of smoking and concluded that the heavy smokers had 24% to 30% higher risk of death from PC (Huncharek *et al.*, 2010).

1.4.2.5 Alcohol

Alcohol consumption and its association with cancer risk has been extensively studied in epidemiological research, however there is little evidence on its role in PC risk. Alcohol use might have adverse and protective effects on prostate carcinogenesis because experimental evidence suggests that ethanol alters the sex hormones profile in such a way that the growth of prostate cells is reduced, while it can enhance the early stage carcinogenesis due to the oxidative stress it causes (Baglietto *et al.*, 2006).

Multiple studies have suggested that alcohol consumption has no association with the overall risk of PC (Gong *et al.*, 2009;Baglietto *et al.*, 2006), while results from the Prostate Cancer Prevention Trial (PCPT) suggested that heavy drinking (>4 or 5 drinks per day) doubles the risk of advanced PC (Gong *et al.*, 2009). Results of a meta analysis published on alcohol use and PC risk were also inconsistent, i.e. suggestive of no association of alcohol consumption and the risk of PC and mortality (Middleton *et al.*, 2009).

1.4.2.6 Physical activity

The exact mechanism by which physical activity may influence the risk of PC is unknown. However, there are some speculations that physical activity affects certain hormones which are associated with prostate carcinogenesis. However, epidemiological studies on the strength of effect are inconclusive.

Recent evidence from a large prospective study reported that exercise at the baseline or during adolescence was not significantly associated with total, advanced or fatal PC risk (Moore *et al.*, 2008). Results from Health Professionals Follow-up Study suggested that there were no association between the vigorous physical activity and PC risk, although there was some risk reduction in fatal PC but not statistically significant (RR 0.59, 95% CI 0.35-1.01)(Giovannucci *et al.*, 2007). A recently published prospective study measured the lifetime physical activity and observed its association with PC risk (Orsini *et al.*, 2009). They reported that lifetime vigorous physical activity was associated with increased risk of low grade and non advanced cancer while it reduces the risk of advanced and fatal PC (Orsini *et al.*, 2009).

1.4.2.7 Diabetes mellitus

Diabetes has been found to reduce the risk of PC, both low and high grade disease. The PCPT, a large randomised control trial, reported a 47% risk reduction of low grade disease and 27% reduction in risk of high grade PC among those who had a history of diabetes mellitus (Gong *et al.*, 2006). The main concerns on these findings from PCPT were the short follow-up of the individuals and extensive screening of study participants as everyone had to have a prostate biopsy at the end of study. Individuals, with a history of diabetes mellitus may have introduced a survival bias as these would have been those who were otherwise healthy and escaped from death due to other diabetes related causes, for example cardiovascular mortality.

A multiethnic cohort study carried out on 5941 PC patients reported that diabetics had a significantly lower risk of PC than non-diabetics (RR = 0.81, 95% CI: 0.74, 0.87; P < 0.001) (Waters *et al.*, 2009). Similar findings of protective effect of diabetes mellitus on PC have also been reported from Health Professional Follow-up Study (Kasper *et al.*, 2009) and Prostate, Lung, Colorectal

and Ovarian (PLCO) cancer screening trial (Leitzmann *et al.*, 2008). Interestingly, most of these studies relied on self reported diabetes mellitus. Individuals who had a diagnosis of diabetes mellitus are likely to also take medication (including aspirin and statins to reduce the risk of cardiovascular events) and may also make lifestyle and dietary modifications to manage their disease. These studies did not account for the effect of drugs in use by the participants. In addition, the apparent association between diabetes mellitus and PC may have been confounded by some unknown factors as well.

More recently, these findings have also been challenged by studies published from national insurance data of Taiwanese men and also from a prospective study, which reported a significantly higher risk of PC in patients who had a history of diabetes (Lee *et al.*, 2011; Tseng, 2011). Ohsaki cohort study of Japanese men also reported similar findings of increased of advanced stage disease among diabetic patients (Li *et al.*, 2010).

The biological mechanism which is thought to underlie the relationship between diabetes and PC is the reduction in concentration of insulin like growth factor-1 and testosterone. As the evidence from different populations showed contrasting findings, the question still remains unanswered that whether the observed associations are real or affected by some residual confounding or biases.

1.4.2.8 Body size and prostate cancer risk

Body size has been extensively studied in relation to the risk of PC. Different measures of body size are used. Height, BMI (general obesity) and WHR (central obesity) are the common methods to quantify the body size.

A meta-analysis on 56 observational studies reported that BMI was positively associated with the risk of advanced disease (random effects RR 1.12 per 5 kg/m² increment, 95% CI 1.01-1.23) but not with localized disease (random effects RR 0.96 per 5 kg/m² increment, 95% CI 0.89-1.03) (MacInnis and English, 2006). This meta-analysis also suggested that height was marginally significant and increasing height was related to increased risk of PC (MacInnis and English, 2006).

Possible mechanism linking obesity and PC is the complex interaction of obesity with the testosterone and androgens (Mistry *et al.*, 2007). Another meta-analysis of 58 observational studies also suggested an increasing risk of PC with height (Zuccolo *et al.*, 2008).

Recent findings from US national surveys indicate the fact that the observational investigations of obesity and PC may have under-estimated the observed associations between obesity and PC incidence. PC diagnosis is now made by prostatic biopsy, while in the first place, an indication for biopsy is increased level of PSA. Data from three national surveys suggested that obese men were 17% more likely to have lower PSA (lower than the threshold for biopsy indication < 4ng/mL) compared with lean men with a desirable BMI (Parekh *et al.*, 2010). Possible mechanism involved in this association is that obese individuals tend to have low testosterone and that could lead to lower PSA. Another explanation is the blood dilution among obese individuals that may lead to a lower PSA level and ultimately lower reported incidence. Prostate testing for cancer and treatment study (ProtecT) from the UK reported that obese men were less likely to have low grade PC, however no association was observed between high grade or advanced PC (Dimitropoulou *et al.*, 2011).

Taken together, the findings of recent US survey and earlier observational studies, obesity's relationship with high grade disease seems plausible as obese individuals are more likely to have lower PSA. As a result, chances of earlier detection reduce and obese men may present at a later stage with more aggressive disease, which has been reported from large cohorts (Gong *et al.* 2006).

Obesity, dietary habits and lifestyle are strongly related with hormones including leptin, insulin and insulin like growth factors. Insulin and leptin have also been examined for their association with the risk of developing PC. Insulin is mainly known to increase the risk of different cancers through its effect on cell proliferation, differentiation and apoptosis. The existing epidemiological evidence has not as yet established a clear causal association of these hormones with PC (Albanes *et al.*, 2009;Hsing *et al.*, 2001;Nandeesh, 2009).

In the recent years, insulin like growth factor (Gennigens *et al.*, 2006) family has been identified as a factor which is not only associated with the overall risk of PC but also suggested to be a key factor in metastatic disease. Substantial biological evidence has suggested that increased level of IGF-I and II increase the risk of PC development whereas a recent meta analysis of 12 large prospective studies showed only a moderate increase in the risk of PC (Gennigens *et al.*, 2006). Biological evidence suggests that IGFs may possess a tendency to induce prostatic epithelial proliferation. However, IGF-1 has shown a significant relationship with PSA (Oliver *et al.*, 2004) even among healthy individuals with no evidence of PC. The IGF system therefore might be a link between the lifestyle and dietary factors and PC. Consumption of high amount of fat, proteins and dairy products has been related to the IGF-1 (Key, 2011). Heavy consumption of these aforementioned products along with a sedentary lifestyle could lead to increased production of insulin that in turn can raise the level of IGF, thus explaining how IGF could be a risk factor of PC (Key, 2011).

1.4.2.9 Meat intake

Evidence on the role of meat intake in the aetiology of PC is “limited-suggestive” of increased risk with increased consumption, while the evidence on red meat is even at a lower level of “limited-no conclusion” (Sinha *et al.*, 2009). The increased risk due to higher consumption of meat is due to the high fat content of red and processed meat. Several mechanisms have been proposed which can increase the risk of PC with higher consumption of fat. One explanation is that higher fat intake can increase the level of sex hormones, which is possibly linked with the PC risk (Giovannucci *et al.*, 1993).

A population-based case control study conducted in the US showed a higher risk of PC among Black Americans due to higher consumption of meat (Hayes *et al.*, 1999). The increased intake (grams/day) of meat was shown to double the risk of PC among Black Americans, (P trend = 0.007) but not in Whites (Hsing *et al.*, 2001). However, these findings were not replicated from a nationally representative sample, which reported no association between meat and animal fat intake with PC (Tseng *et al.*, 2004). More recently, the evidence from prospective studies also provided mixed results of no association or positive association (Rohrmann *et al.*, 2007).

Several limitations are inherent in these studies, which could be attributed to mixed results. First, although most studies used validated questionnaire based methods to collect the information of meat consumption, the possibility of measurement error in assessing the dietary intake could not be completely ruled out. Also, cooking practices are very different between different populations, and these cooking practices along with the addition of other ingredients in food could also alter any potential link between meat intake and PC (John *et al.*, 2011).

Interestingly, recently published data from multiethnic cohort suggested no evidence of relationship between intake of meat, or well cooked meat with the risk of PC. Furthermore, they could not find any significant relationship between exposure to heterocyclic amines and PC risk (John *et al.*, 2011; Sharma *et al.*, 2010).

1.4.2.10 Lycopene

Lycopene is an acyclic isomer of beta-carotene for which the main source is tomato and its products. Other sources of lycopene include pink grapefruit, watermelon, rosehip, apricot, and guava but the amount of lycopene content among these is little compared to tomato. Besides blood plasma, lycopene is concentrated in adrenal gland, testes, liver and in the prostate gland. It is the most predominant carotenoid, where it functions as a potent antioxidant and protects the cells, lipid layers and proteins from oxidative damage. Earlier, epidemiological studies showed a significant risk reduction of PC from 15% (Giovannucci *et al.*, 2002) to 25% (Gann *et al.*, 1999) among those consuming a diet rich in lycopene but later many prospective studies observed no association between lycopene and overall PC risk (Haseen *et al.*, 2009; Schuurman *et al.*, 2002). Null findings from many prospective studies could be explained by many factors including small number of cases particularly advanced stage disease, where lycopene has shown higher preventive value. In some studies, lycopene intake was too low to observe a possible threshold effect, and finally the widespread use of PSA testing has made it difficult to understand the true causes of PC, as many more cases are now diagnosed on a low grade and stage with very small tumour size which otherwise might remain asymptomatic during lifetime of the individual. Furthermore, self reporting of tomato intake and its products

(which are rich in lycopene) can bias the results as the exposure assessment may have varied due to the participants' and the interviewer's related factors.

However, some recent studies analysing serum lycopene levels rather than self reported intake of lycopene rich foods also found no association between lycopene level and PC risk. A nested case control study provided no evidence of an association between serum lycopene level and overall (OR 1.14; 95% CI, 0.82-1.58 for highest versus lowest quintile; p-value 0.28) or aggressive PC (OR 0.99; 95% CI, 0.62-1.57 for highest versus lowest quintile; p-value 0.433) (Peters *et al.*, 2007).

Recent findings from PCPT (Mellon, 2005) also suggested no association between serum lycopene level and the risk of overall as well as grade-specific risk (Kristal *et al.*, 2011). PCPT had a follow-up of 7 years; the question however still remained unanswered that for a disease like PC, where natural history is very long and histological lesion starts decades before the presentation, whether these factors being studied before the manifestation are truly related to the incidence of PC or its progression and clinical presentation.

In general, systematic review of epidemiological evidence provided insufficient evidence that either the tomato products or the lycopene has any significant role in prevention of PC or any benefit associated with the presentation of PC (Haseen *et al.*, 2009).

1.4.2.11 Soy intake as a risk factor

Differential incident rates of cancer between populations have drawn the attention of research community to the dietary intake and the risk of chronic diseases including cancer. Soy is a plant based dietary ingredient rich in protein, and is widely consumed in Asian populations. Laboratory studies have suggested that isoflavones within soy derived food have strong antioxidant and anti-inflammatory actions, both of which are thought to control survival of PC cells (Hsu *et al.*, 2010).

Most of the studies, published from Asian countries, have indicated a preventive (or protective) role for soy in the development of PC (Lee *et al.*, 2003). A risk

reduction of up to 42% (Lee *et al.*, 2003) in PC has been observed in Chinese population among those who had higher intake of soy. A recently published study which included 4404 PC patients suggested that the risk reduction of PC was attributed to legumes intake and probably not because of the isoflavones in the soy products (Park *et al.*, 2008).

Strong evidence has emerged from studies carried out in the Asian populations. However, these findings were not found to be consistent in the Western population. In a recent meta-analysis of epidemiological studies, it has been suggested that the preventive effect of soy food was only seen for non-fermented food where the risk reduction of up to 30% was observed whereas in fermented food there was no evidence of an association between higher intake of soy food and PC risk (Yan and Spitznagel, 2009). This review also highlighted that the risk reduction was only observed in studies conducted in Asian countries, while there were no evidence of protective effect in Western studies. It was therefore suggested that the type of soy food and its compositional difference may have some role in protective effect (Yan and Spitznagel, 2009).

1.4.2.12 Statins

Many observational studies reported the protective role of statins on PC (Boudreau *et al.*, 2008;Murtola *et al.*, 2007). Large population-based studies have supported the hypothesis that long term use of statins (series of small molecule inhibitors of the 3-hydroxyl-3-methylglutaryl coenzyme reductase, a central enzyme in cholesterol synthesis) reduce the risk of advanced PC (Jacobs *et al.*, 2007;Murtola *et al.*, 2007;Platz *et al.*, 2006). In addition, the duration of statin use has also been linked with reduced risk of high grade PC (Platz *et al.*, 2006). A major confounding factor is that the statin users tend to have a lower level of PSA when compared to those on statin treatment (Mondul *et al.*, 2010). This relationship between statins and PSA could be a reason for the lower observed incidence of overall and advance grade PC among PC patients. Contrary to these, no association between the statin use and the risk of overall as well as high grade or stage PC has been reported in more recent studies (Agalliu *et al.*, 2008;Boudreau *et al.*, 2008).

Two pathways implicated in prostate carcinogenesis have been suggested as potential targets for statins mediated effects. One pathway is the anti-inflammatory properties of statins as inflammation has been associated with the development of PC (Maitland and Collins, 2008). A study on 236 PC patients reported significantly lower intratumoral inflammation among the preoperative statins users than nonusers (Banez *et al.*, 2010). In the second pathway, reduced levels of cholesterol (the principle effect of statins) might have some impact on prostate carcinogenesis. Statins have been widely used to reduce the cholesterol level in individuals in order to modulate the risk of cardiac events.

1.4.2.13 Finasteride and prostate cancer

Finasteride is a 5-alpha-reductase inhibitor - a group of drugs with anti-androgenic activity. This is frequently used for the treatment of benign prostatic hyperplasia. This drug reduces the level of dihydrotestosterone which is synthesised in the peripheral tissues. Evidence suggests that Finasteride is protective against PC. A large observational cohort study carried out in Finland reported a significant preventive effect of Finasteride on Gleason 2-6 tumours while there was no significant reduction in overall PC risk, particularly for higher grade disease (Gleason 7-10 tumours)(Murtola *et al.*, 2009).

The PCPT, a randomised controlled trial established in the US in 1993, was one of the largest randomised trials which were conducted to investigate the chemopreventive effect of finasteride on PC risk. A total of 18,882 healthy individuals were recruited in this trial, who had a normal digital rectal examination and PSA level of less than 3ng/ml (Mellon, 2005). The primary end point of this trial was to estimate the prevalence of PC in the treatment arm (Finasteride group) and in placebo group. After seven years of treatment and follow-up, the PCPT reported a significant reduction (24.8%) in the risk of PC among the treatment group compared with the placebo arm (Thompson *et al.*, 2003). However, another striking finding of the study was that men in the Finasteride group experienced significantly higher risk of aggressive PC (Banez *et al.*, 2010) compared with the placebo group (Thompson *et al.*, 2003). Furthermore, some sexual side effects were significantly higher among the Finasteride group. These findings were widely debated upon among the

urological experts and finasteride was not recommended to be used routinely for preventive purposes (Mellon, 2005).

1.4.2.14 Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory (NSAID) medications are one of the most commonly used over-the-counter drugs. Experimental studies suggest that these drugs, particularly aspirin may have a chemopreventive effect (Yoo and Lee, 2007). While the biological mechanism is not clearly understood yet, there is some evidence that these drugs enhance the apoptotic activity (programmed cell death) in cancerous cells (Yoo and Lee, 2007). In addition, in more recent years, inflammation has been widely studied as an aetiological factor in most cancers so anti-inflammatory properties of these drugs might have an indirect role in suppression of carcinogenic process by inhibiting the inflammatory process.

Epidemiological evidence on these remains equivocal. A UK-wide cross sectional case control study indicated that individuals taking non-aspirin NSAIDs and NSAIDs were significantly more likely to have PC with 32% and 25% excess risk compared with non-users respectively (Murad *et al.*, 2011). Interestingly, this study found no convincing evidence of an association between aspirin use and the likelihood of PC (Murad *et al.*, 2011). Precise physiological mechanism has not yet established. However using the cross sectional design does not clearly explain the risk of disease associated with the use of these drugs. Also, individuals using these drugs would be more likely to visit the services compared to non-users, it may just be a detection bias which increased the likelihood of diagnosis of PC among users of these drugs.

In contrast to this, a recent finding from Health Professional Follow-up Study, a large prospective study, suggests that men taking more than 2 tables of aspirin per week had 10% lower risk of developing PC (Dhillon *et al.*, 2011). Furthermore, men taking more than 6 tablets per week experienced 28% lower risk of high grade and lethal disease compared with non-aspirin users (Dhillon *et al.*, 2011). The main indication of aspirin use is cardiovascular diseases, so individuals using this drug might have died due to non-cancer causes and therefore not remained at risk of being diagnosed with PC. Further stratified analyses based on presence and absence of cardiovascular diseases did not

materially alter the association between aspirin and PC in this study (Dhillon *et al.*, 2011). Analysis was repeated in the same study after excluding the men dying from non-cancer causes, but the overall findings remained consistent.

The overall epidemiological and biological evidence on the use of these drugs and PC risk still remains inconclusive and further research is required to confirm these findings.

1.4.2.15 Vitamin D

Many vitamins and minerals have been studied for their preventive role against the risk of PC due to their anti-oxidant and anti-proliferative activities. Among these, selected agents are discussed below.

Experimental studies in animals have suggested that the biologically active form of vitamin D reduces the degree of proliferation of prostate cells and serum levels of vitamin D may be associated with PC risk. However, clinical data have not consistently demonstrated any link between vitamin D level and PC. Most recent evidence from a meta-analysis of 25 studies provided little evidence about the preventive effects of vitamin D against PC. Significant heterogeneity was observed between case control studies, and even in prospective studies the role of vitamin D remained inconclusive both for the overall (OR 1.14, 95% CI 0.99-1.31) as well as aggressive (OR=0.93, 95% CI 0.63-1.39) forms of PC (Gilbert *et al.*, 2011).

1.4.2.16 Vitamin E and Selenium

Selenium and Vitamin E have been proposed to have anti-tumorigenic activities in animal models. Previous evidence suggested a preventive role of selenium in PC risk (Clark *et al.*, 1996). Secondary analyses of two randomised controlled trials indicated that supplementation of vitamin E and selenium could reduce the risk of PC by up to 60 percent (Clark *et al.*, 1998; Hartman *et al.*, 1998). This preliminary evidence, reported more than a decade earlier, led to the establishment of a randomised control trial, the Selenium and Vitamin E Cancer Prevention Trial, in the US. A total of 35,533 healthy middle age men were recruited from 427 sites in the US, Canada and Puerto Rico with an intention of a maximum of 12 year follow-up (Lippman *et al.*, 2009). However, initial results

were reported at a median follow-up of 5.42 years and a maximum of 7 years. The findings suggested that there were no significant differences in risk of prostate between four groups of individuals receiving either vitamin E or Selenium or Selenium and Vitamin E in combination or a placebo (Lippman *et al.*, 2009). Furthermore, there was a statistically non-significant increased risk of PC (RR 1.13, 99% CI 0.95-1.35) in men of vitamin E group and an increased risk of diabetes mellitus (RR 1.07, 99% 0.94-1.22) among participants of selenium group. The trial was stopped after these findings and participants were informed to stop the supplements intake as there was no significant preventive effect against PC (Lippman *et al.*, 2009).

More recently, the earlier finding of this report has been confirmed with the inclusion of additional 521 PCs diagnosed in interval of first and second report. Risk of PC increased up to 17% among those taking vitamin E alone during a median follow-up of 7 years (Klein *et al.*, 2011). In summary, as with most drugs and dietary factors, the evidence on vitamins and minerals in relation to PC risk remains inconclusive. Given that the most prostate lesions remain latent for a long time even decades in some cases. Any trials with shorter follow of less than 10 years are unlikely to reveal the true risk factors of PC as the factors investigated in such trials may have been affected by the presence of asymptomatic disease. Furthermore, any factors which are related to the incidence of PC in such short follow-up studies, they may be associated with cancer progression rather than the disease development. Therefore, studies with longer follow-up are warranted to understand the aetiology of PC.

1.4.3 Concluding remarks on risk factors

Most of the evidence on risk factors of PC has originated from observational epidemiological studies. However, some experimental studies also investigated the role of different dietary factors to understand the disease process. It is essential to understand that factors associated with the development and progression of PC may not necessarily be causally responsible to 'drive' carcinogenesis. The concept of causality is vital to the understanding of cancer epidemiology and observational studies.

Sir Austin Hills put forward some aspects of associations which should especially be considered before deciding that the most likely interpretation of any observed relationship is causation (Bradford-Hill, 1965). These aspects then well known as Hill's criteria for causation include strength (current findings are robust), consistency (has the similar findings produced from different sources and settings), specificity (a cause is only related to that disease), temporality (cause appeared before the disease), biological gradient (dose-response relationship between risk factor and cancer), plausibility (biological explanations of findings), coherence (with previous research), experiment (prevention from the disease when factor is removed) and analogy (based on previous findings in some other settings or for some other diseases even) (Bradford-Hill, 1965). It is not possible that all aspects of this criterion can be fulfilled for every disease and its risk factors, particularly for most of the chronic diseases and cancer, where interaction of multiple factors is vital or required in disease initiation and progression. These criteria have been criticised in more recent years particularly due to the multi-factorial aetiology of chronic diseases and cancers. However, Hills himself suggested "that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we can accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*" (Bradford-Hill, 1965).

This framework provided by Hills more than four decades ago proved to be fundamental in the modern epidemiology. Since then, different study designs including case-control, cohort and experimental studies such as randomised controlled trials are used to investigate the associations of different factors in relation to the cancer development and its progression. Epidemiological and statistical advancements have brought about many changes in the cancer understanding and have improved the health of populations.

1.5 Determinants of survival of patients with prostate cancer

This section of the chapter will review the literature on major determinants associated with survival of PC patients. Given that the aetiology of PC is unclear,

and incidence has been increasing in last few decades, it is important to improve the survival of those who have been diagnosed with this disease. Generally, cancer survival is a term used to describe the proportion of individuals who are alive after certain period of time (i.e. usually 1-year, 5-year or 10-years) of their cancer diagnosis. Survival of PC patients has improved over time. A substantial number of studies have explored the role of different factors in survival of PC patients, which could be divided into patient related factors, disease characteristics and treatments factors. The role of lifestyle related determinants and their impact on PC survival have not been studied extensively. Most of the survival studies have been based on data collected by Cancer Registries, which do not have the information on lifestyle related factors. This could be a reason for lack of literature on lifestyle related factors in association with survival of PC patients as the registries do not routinely collect information on lifestyle habits. It is imperative to understand that patient survival depends on multifaceted interaction of many factors.

1.5.1 Patient related factors

1.5.1.1 Age

Age is one of the major determinants associated with survival of PC patients. The independent effect of age on prostate-specific survival has not been well established and some evidence also suggests that age is not independently associated with cancer specific survival, when co-morbidity and disease related factors are taken into account. Some of the survival variations between age groups could also be explained by the treatment offered to the patient, as individuals older than 75 years are less likely to receive a curative treatment (Bechis *et al.*, 2011).

Disease stage and grade are independent predictors of survival but it is important to consider that with increasing age, disease stage and grade also advances. Evidence suggests that patients diagnosed after the age of 70 years had significantly higher proportion of advance stage (52.1% vs. 33%, $p < 0.001$) and high grade (17.2% vs. 9.5%, $p < 0.001$) disease compared with those who were less than 60 years (Sun *et al.*, 2009). Indeed, in a large prospective cohort study, on competing risk regression, age did not show any significant prognostic value

after adjustment for comorbidity, disease characteristics and treatment modality (Bechis *et al.*, 2011). This study suggested that the decision of treatment should be made based on disease risk rather than the individual's age. Earlier to that, PC patients data from a population-based study in the US suggested that survival was poorer among the patients of youngest (40-44 years old) and the oldest age group (Merrill and Bird, 2002). Poorer survival among the youngest and oldest age group was mainly due to the influence of disease grade and stage (Merrill and Bird, 2002).

These findings from recent, large datasets, suggests that age has an association with disease related characteristics and treatment offered to patients. However, role of age as an independent predictor of survival of PC patients is not well established.

1.5.1.2 Socio-economic circumstances

In the UK, survival of PC patients has improved over time but socio-economic inequalities in survival have also been reported from regional studies (Hussain *et al.*, 2008; Rowan *et al.*, 2008). A deprivation gap in survival (better survival for least deprived compared with the most deprived) has been reported previously in studies carried out in England, Wales and Scotland (Rowan *et al.*, 2008; Shack *et al.*, 2007). Deprivation gap (better survival for least deprived compared with the most deprived group) in five years survival of PC in England and Wales increased from -1.2% in 1986-1990 to -7.2% in 1996-1999 (Rowan *et al.*, 2008). Hybrid analysis based on the follow-up of those diagnosed in 2000 and 2001 suggested that this gap may not widen further (Rowan *et al.*, 2008).

Scottish Cancer Registry reported that a significant deprivation gap in relative survival of PC patients exists in Scotland. Although the relative survival of PC patients improved 11% on average in every five years period during the period of 1986-2000 (Shack *et al.*, 2007). However the deprivation gap has increased every five years during this period and the difference of relative survival between the least deprived and the most deprived was 6.9% during the period of 1996-2000 (Shack *et al.*, 2007). Authors suggested that this difference can be explained by the stage of disease at the time of diagnosis and access to health care services between the two groups (Shack *et al.*, 2007). However, the study could not

assess the impact of these factors on deprivation gap in survival due to the lack of information on disease related characteristics. Another important consideration, particularly for PC, could be the age and grade at diagnosis. The role of factors on widening deprivation gap is unknown yet.

In the US, the burden of PC is disproportionate between populations of different racial backgrounds. Interestingly, race has also been linked with the survival of patients with PC. The relationship is unclear and attributed to different factors though. Various factors explain the prognostic value of race, including differential aggressiveness and disease stage at presentation, socio-economic differences and treatment disparities between different racial groups. Blacks are known to have a significantly higher PC risk, more advanced stage and high grade disease and poorer survival outcome compared with Whites in the US (Fowler, Jr. *et al.*, 2000).

A randomized controlled trial on 2,048 patients of localized PC reported that Black race was associated with a significantly higher risk of overall and disease specific death ($p = 0.04$, $RR = 1.24$ and $p = 0.016$, $RR = 1.41$, respectively)(Roach, III *et al.*, 2003). However, when adjusting for the effects of risk group and treatment, this difference was not statistically significant (Roach, III *et al.*, 2003).

Evidence from the Pre-PSA era suggested that the difference of survival between the Blacks and Caucasians was largely explained by the socio-economic status and survival was mainly dependent on the disease stage and socio-economic status (Dayal *et al.*, 1985). In more recent years, these findings have been confirmed from National Cancer Database of PC patients. Individuals who did not have a medical insurance had double risk of having high PSA and advanced stage disease compared with those who had insurance (Fedewa *et al.*, 2010). Interestingly, ethnic minorities including Asians, Hispanics and Blacks were significantly more likely to be uninsured and had advanced stage disease (Fedewa *et al.*, 2010). These differences suggest that access to medical care and capacity to pay for health care services could be an important factor in racial differences of PC survival. In context of US, Black Americans have worse survival compared with Whites. This might be attributed to their less privileged socio-

economic position and poor access to diagnostic and other health care services because access to these is mainly determined by the ability to pay (Roach, III, 1998).

In contrast a research, conducted on patients with PC where all men had equal access to health care services, showed that the overall cancer specific risk of death among Blacks vs. Whites was 1.28 (95% confidence interval CI = 1.14-1.44); for local stage, 1.23 (95% CI = 1.01-1.51), 1.30 for regional stage (95% CI = 0.97-1.75), and 1.27 for distant stage (95% CI = 1.07-1.50)(Robbins *et al.*, 1998). Similarly, findings of survival disparities have also been reported from the UK and New Zealand, where health care services are financed by the Government and are equally available for all socio-economic groups. Data from New Zealand also reported that the 5-year relative survival of PC patients was significantly different - individuals from the most deprived socio-economic groups had a 15% lower survival than those from affluent groups (Jeffreys *et al.*, 2009).

These findings suggest the role of some unknown factors in prognosis other than race, socio-economic status and access to services. These factors can be the overall health status, diet, lifestyle related characteristics which are difficult to quantify in relation to PC prognosis and are largely unexplored up till now.

1.5.1.3 Inflammation and survival

Although it is recognised that the development of cancer has a genetic basis, there is increasing recognition that the host inflammatory response is associated with the progression and survival of patients (Balkwill and Mantovani, 2001; Colotta *et al.*, 2009; Hanahan and Weinberg, 2011; Vasto *et al.*, 2008).

Many epidemiological and clinical studies suggested that patients with higher local and systemic inflammation experienced poorer survival. Different inflammatory markers have been studied in relation to the prognosis of cancer patients and reported consistent results that higher inflammation is linked with poorer survival. Neutrophil lymphocyte ratio (NLR) showed a significant prognostic value as a measure of systemic inflammation in colorectal (Kishi *et al.*, 2009), hepatocellular (Gomez *et al.*, 2008), ovarian (Cho *et al.*, 2009) and pancreatic cancer (Aliustaoglu *et al.*, 2010) patients. In particular the systemic

inflammatory response, as evidenced by an elevated C-reactive protein, has been shown to be independently associated with poor prognosis in many common solid tumours (Roxburgh and McMillan, 2010). It is therefore of interest that the systemic inflammatory response, as measured by the modified Glasgow Prognostic Score (mGPS, a combination of C-reactive protein and albumin), has been shown to have prognostic value in operable and non-operable cancers independent of site (Proctor *et al.*, 2011).

Although survival in patients with PC has improved in recent years, it is often difficult to differentiate patients who require potentially curative treatment from those who can be managed conservatively. Considerable effort has gone into identifying novel genetic and immunological biomarkers, however, these remain time consuming and not validated to be part of routine clinical practice (Castelli *et al.*, 2010; Huang *et al.*, 2010). Therefore, in general, current clinical decisions are based on readily available tumour related factors, including PSA levels, Gleason grade and clinical stage (Verhagen *et al.*, 2002).

Many biological and laboratory studies have investigated the role of inflammation in the development of PC and found a significant relationship between inflammation and risk of PC. However, clinical data on the role of systemic inflammation on prognosis of PC patients is sparse. Two earlier studies investigated the role of C-reactive protein (CRP) as a measure of systemic inflammation in relation to survival of PC, and found that men with higher levels of C-reactive protein showed poorer survival both in localised (McArdle *et al.*, 2010) as well as metastatic disease (McArdle *et al.*, 2006). However, smaller number of cases and lack of information on socio-economic status in both studies preclude any definite conclusion about the role of inflammatory markers in prognosis.

In most of the studies, it remained unclear about the host characteristics, other than tumour related factors, and their relationship with increased mGPS or NLR in cancer patients which lead to poorer survival. One hypothesis therefore is that, a pre-treatment systemic inflammatory response which may be a part of any pre-existent co-morbid condition, could lead to an excess risk of death due to non-cancer causes (Roxburgh *et al.*, 2011) Another important consideration is

that, the socio-economic status of the individuals may influence the systemic inflammation among cancer patients and could be responsible for poorer survival.

There has been a considerable amount of interest in systemic inflammation and its association with prognosis. Further research is warranted in this area with larger cohort studies with bigger samples, complete information on potential confounding and longer follow-ups.

1.5.1.4 Co-morbidity

Co-morbidity is the presence of one or more diseases in addition to the primary disease (i.e. PC in this case). Different tools are used to quantify co-morbidity. However, the Charlson Co-morbidity Index (CCI) has been widely used in literature (Hall et al., 2005).

Age and CCI were the most significant predictors of all cause mortality but not in cancer specific mortality among PC patients (Sweat *et al.*, 2002). Similar results were provided from another study which used CCI as a measure of co-morbidity in PC patients and they reported co-morbidity as the most important prognostic factor for men less than 70 years (Post *et al.*, 2001). Risk of death was twice in patients with one concomitant disease than those with no co-morbidity (95% CI, 1.0-4.3), whereas the risk was even higher among those who had two or more diseases (HR = 7.2, 95% CI 3.1-16.6) (Post *et al.*, 2001).

As co-morbidity increases the risk of all cause mortality but not cancer specific mortality, this may be due to the fact that co-morbidity increases the risk of death due to non-cancer causes among PC patients. Interestingly, co-morbidity not only influences the survival of patients due to deaths from other causes than cancer but also affects the decision making process of treatment. Individuals with serious co-morbid conditions at the time of diagnosis are unlikely to receive a curative and aggressive management of the cancer therefore, in an indirect way co-morbidity influences the cancer specific deaths. Similarly, treatment offered to patients is an important predictor of cancer specific mortality (Hall et al., 2005).

1.5.2 Disease characteristics

1.5.2.1 Cancer stage and grade

Cancer stage is perhaps one of the most important determinants of survival. PC stage is used to describe the extent of cancer, whether it is localized or extended to adjacent or distant structures. Stage of PC has a graded link with the survival i.e. highest for the focal incidental cases and worst for the metastatic disease. Significant differences in PC specific survival have been observed at 10 and 15 years follow-up according to the stage of cancer i.e. for incidental cases (100% and 90.6% respectively), for men with localized PC (73.1% and 60.8% respectively), for men with locally extended disease (23.4% and 11.4% respectively) and for men with metastatic disease (68.1% and 54.5%) (Jonsson *et al.*, 2006). These estimates have been taken from historical data, however in more recent years, survival seems to be improved for most stages particularly for localised disease, however, it remains unclear whether it is due to the better application of treatment modalities or lead time and length time biases because of PSA-testing.

Gleason grading of PC is considered as a major determinant of disease biology and prognosis. Tumour grading refers to the property of cancer independent of tumour location while prognosis is defined as the expected biological aggressive potential of a prostatic tumour to spread to other organs (Epstein, 2010). The Gleason scoring system is based on microscopic tumor patterns which are assessed by pathologist, based upon the degree of loss of the normal glandular tissue architecture (i.e. shape, size and differentiation of the glands) (Epstein, 2010). The Gleason score is a sum of primary and secondary grades representing the majority of the tumour and minority of the tumour, respectively. The Gleason sum score is represented as number ranging from 2 to 10 - the higher the score the more aggressive the tumour is likely to act. The Gleason score has been investigated for its impact on survival and reported that disease specific mean survival was highest for the Gleason score 4-5 which is well differentiated disease (i.e. 20 years), while lowest (i.e. 5 years) for the Gleason score 8-10 which is a high grade and also known as aggressive disease (Egevad *et al.*, 2002). Evidence also highlighted that not only the Gleason sum score strongly impacts on survival but individual pattern of grade was also found important with regard

to PC specific survival (Egevad *et al.*, 2002). There was a trend towards a shorter survival for Gleason 4 + 3=7 (Disease specific mean survival = 9 years) than Gleason 3 + 4=7 (Disease specific mean survival 13 years; $p = 0.16$) (Egevad *et al.*, 2002).

Population-based testing by PSA is carried out with the objective to diagnose the cancer at an earlier stage. Role of PSA based screening for cancer detection remains controversial. Recently, a study from the “Prostate Testing for Cancer and Treatment” trial (ProtecT) reported that due to PSA screening, stage and grade migration has taken place in the UK (Moore *et al.*, 2009). It was reported that patients who were included in the ProtecT, had a significantly lower stage, lower grade and low PSA level compared with the men taken from cancer registry (Moore *et al.*, 2009). Population-based PSA screening might also detect some low risk patients with PC for whom optimal treatment remains uncertain and the health services might end up over treating the patients with PC due to population-based PSA screening (Moore *et al.*, 2009).

1.5.3 Treatment and survival

Choice of treatment for PC patients is a complex process. Decision about the treatment varies from individual to individual and many factors need to be considered when selecting an appropriate therapy for an individual. These include age, disease stage and grade, overall health status and co-morbidity. Treatment modalities range from surgical resection, radiotherapy, chemotherapy to non-intervention with watchful waiting.

Careful interpretation is required when comparing the results (in terms of survival) of different treatment modalities because they are not generalisable to each other and evidence exists that patients with similar disease characteristics under the same health care system are treated differently (Fairley *et al.*, 2009). Research carried out on 60,269 low, moderate grade and organ confined PC patients compared the three treatment modalities and their impact on overall and disease specific mortality (Tward *et al.*, 2006). Prostate specific death at 10 years was 2.62 deaths/1000 person-years for those treated by surgery, 1.83 deaths/1000 person-years for brachytherapy and 8.68 deaths/1000 person-years for those with no definitive treatment (Tward *et al.*, 2006). Similarly a

systematic review comparing different radiotherapeutic modalities with regard to the PC survival reported that the risk of death was 1.50 (95% CI 1.29-1.73) for external beam radiotherapy relative to brachytherapy, and was 2.33 (95% CI 2.04-2.66) for external beam radiotherapy combined with a radioactive seed implantation relative to brachytherapy (Pieters *et al.*, 2009). As described earlier, these treatment modalities are not directly comparable as different patient groups tend to be offered different treatment modalities. Patients have significant differences in terms of their general health, disease related characteristics and existence of co-morbid conditions.

1.6 Summary of literature

PC is the most commonly diagnosed cancer after non-melanoma skin cancer, among men in the developed world. Variations in incidence between countries of developed world are mainly attributed to the varying population structure and screening practices between countries. Large variations in incidence have been observed even between different socio-economic groups within countries. In the UK, socio-economic gap in incidence of PC has been observed in England and Wales. Scotland is widely known for poorer health outcomes due to deprivation. However, no attempts have been made to investigate the socio-economic differences in incidence of PC. The overall increase in incidence of PC in the UK is mainly attributed to PSA testing. If PSA testing is responsible for observed incidence trends then a grade-shift (relatively more low-grade disease) should be observed as PSA tests detected cancer cases are theoretically expected to be low grade tumours. Grade-specific and socio-economic trends in incidence may be helpful understanding the rising incidence.

There is no single risk factor responsible for the development and progression of PC. There is a wide range of factors capable of interacting in a complex temporal manner to influence cancer development and progression. Age, race and family history are considered as strong risk factors while the evidence on other risk factors is mostly inconsistent. Evidence mainly comes from observational studies and a few randomised controlled trials. Many risk factors have been studied in case-control studies in earlier decades. PC has a very complex aetiology both for incidence and progression and initial lesions typically start decades before the clinical presentation of the disease, a fact reported by many autopsy studies. Therefore, in such a scenario case-control studies are unlikely to capture the true risk factors associated with the disease, as recall bias is inherent in this design.

Evidence emerging from prospective cohort studies and randomised controlled trials also remained equivocal for most of the commonly studied lifestyle and dietary factors. The majority of prospective cohort studies recruited middle age or elderly men and followed them up to 15 to 20 years. Men of these age groups might already have a latent lesion in the prostate gland when follow-up began.

Such studies were unlikely to unfold the true risk factors as they started follow-up on an age when men already had a latent disease. Randomised controlled trials, mostly had a follow-up of up to 10 years, therefore any factors found associated in a short follow-up may have a link with the progression or manifestation of the disease but unlikely to be related to the development of PC. In such a scenario, studies with large sample sizes with very long follow-up periods may help to understand the aetiology of PC.

Another factor which makes the aetiological studies more complex is the advent of PSA. Today, many more patients are diagnosed than ever including a pool of biologically indolent tumours. In the pre-PSA era the men who were diagnosed with PC displayed a period of progression, or transition from a small volume latent disease to a clinically significant PC. The diagnosis in pre-PSA era reflected an event while in the PSA era many cancers classified as events are not true events - rather they reflect a diagnosis of a previously unknown latent cancer. Men diagnosed with PCs in PSA era represent a more heterogeneous group of cancers, which ultimately make it more difficult to examine the same risk factors for progression which were being studied in the pre-PSA era. In this case, it is crucial to understand those factors which are associated with the aggressiveness or progression of PC.

Survival of PC patients has improved in the last two decades. Many factors have been investigated for their role in PC survival. Evidence on the role of age and race provided inconsistent results, while socio-economic status, tumour related characteristics and treatment had a main role in PC survival. Nevertheless, management of PC still remains an intricate process as to what treatment to be offered to which individual case, to achieve the best possible outcome. Prognosis has not been clearly understood despite extensive research. As incidence is increasing and no organised population level efforts can be made to prevent PC, it is therefore, crucial to understand the prognosis of those who have been diagnosed with the disease. In more recent years, systemic inflammation has emerged as a prognostic factor for patients with many different cancers; however, larger studies are required to understand its role in the prognosis patients with PC. Different inflammatory markers are used to measure the systemic inflammation including neutrophil lymphocyte ratio,

modified Glasgow Prognostic Score and platelet lymphocyte ratio. The evidence on these inflammatory markers as a prognostic factor in PC survival is limited to two studies with smaller sample size and lack of information on socio-economic circumstances. Further work in understanding the prognosis of PC patients is warranted as incidence is expected to increase due to ageing population in coming years.

1.7 Aim and objectives

The aim of this thesis is to examine the aetiological and epidemiological factors associated with incidence and survival of PC in the West of Scotland. These factors will be examined with particular attention to the socio-economic disparities both in incidence and survival. Prognosis of PC has not been clearly understood, therefore, an attempt will be made to investigate some prognostic factors associated with the survival of PC patients.

Each chapter in this thesis is designed to address specific objectives outlined as follows:

1. To undertake a descriptive epidemiological study to understand the trends in incidence of overall PC and grade specific disease in last two decades with particular focus on socio-economic circumstances.
2. To conduct a large prospective cohort study to investigate the role of cholesterol in development of overall and grade-specific PC.
3. To conduct a prospective cohort study to investigate the role of dietary factors, tea and coffee, on overall and grade-specific PC incidence.
4. To carry out an epidemiological study to investigate the survival of PC patients focusing on socio-economic circumstances of the individuals and particularly the impact of age and disease grade at diagnosis.
5. To conduct a cohort study to investigate the role of systemic inflammation on the survival of patients with PC

2 Widening deprivation gap in incidence of prostate cancer in the West of Scotland: a population-based study

2.1 Chapter summary

PC is the commonest cancer among men in Scotland. However, the relationship between socio-economic circumstances and histological grade-specific incidence as measured by the Gleason score remains unclear. This study describes trends in overall and grade specific PC incidence by deprivation group over time in the West of Scotland.

Incident cases of PC (ICD-10 C61) from the West of Scotland were extracted from the Scottish Cancer Registry from 1991 to 2007. Socio-economic circumstances were measured using the Carstairs scores. Annual population estimates were obtained from Information Services Division Scotland. Deprivation-specific European age-standardised incidence rates were calculated and disease grade (high versus low) was measured using the Gleason score. Joinpoint regression analysis was carried out to identify significant changes in trends over time and calculate the annual percent change.

15,519 incident cases of PC were diagnosed in the West of Scotland between 1991 and 2007. Overall incidence (age adjusted) increased by 70% from 44 per 100,000 in 1991 to 75 per 100,000 in 2007, an average annual growth of 3.59%. This pattern was driven by significant increases in both low and high grade cancers. Incidence was inversely associated with deprivation with the highest rates among the most affluent group. A widening deprivation gap in incidence was evident from 1997 onwards. From 2003-2007, the deprivation gap in incidence was 40.3 per 100,000 (P for trend < 0.001), with rates 37% lower among the most deprived compared with the affluent. This deprivation gap accounts for an estimated 1,764 over-diagnosed men among the most affluent group during 2003-2007.

The relatively large increase in incidence among the most affluent is mainly due to an increase in diagnosis of low grade disease. Further work is needed to understand whether the detection of low grade disease is associated with survival benefits among affluent men.

2.2 Introduction

This chapter will describe the trends of PC incidence in the West of Scotland. Earlier evidence suggests that socio-economic differences exist in the incidence of PC in England and Wales (Rowan, 2007). In contrast to lung and cervical cancers, incidence rates of PC have been higher among least deprived men and lowest among the most deprived. Significant differences in age-standardised incidence of PC have been reported between different health boards in Scotland during 1994-1996. PSA testing may explain the observed variations in the incidence between health boards (Brewster *et al.*, 2000). However little is known about the recent trends of PC incidence among Scottish men in relation to grade of disease and socio-economic circumstances of patients.

Therefore, the present analysis was conducted to comprehensively describe the overall and grade specific trends of PC incidence by socio-economic status in the West of Scotland for the most recent period.

2.3 Materials and methods

2.3.1 West of Scotland population characteristics

The West of Scotland comprises of approximately half of the population of Scotland, estimated at 2.4 millions. This includes four NHS health boards, Ayrshire and Arran, Forth Valley, Greater Glasgow and Clyde and Lanarkshire. The West of Scotland holds some of the most affluent and most deprived population of the country. Socio-economic differences have been attributed to one of the highest mortality rates and lowest life expectancy of Scottish population compared with the rest of the Western Europe (Scottish Public Health Observatory (ScotPHO)., 2011). Although health care services are free at the point of use for everyone in the UK, significant differences have been observed between health outcomes of Scottish population compared with other constituent countries of the UK (Hanlon *et al.*, 2005).

2.3.2 Incidence data

We extracted incident cases of PC registered in the West of Scotland during 1991 to 2007 using the International Classification of Diseases (ICD) codes, ICD 9 code 185 and ICD 10 code C61 for PC. Cancer Registry uses the Scottish Open Cancer Registration And Tumour Enumeration System (SOCRATES), which receives the electronic notification of cancer from hospital systems - which includes the Scottish Morbidity Records (SMR01), records of treatment offered to patients, prospective audit dataset and death records from General Registrar office for Scotland (GRO(S)) (Information Services Division, 2011). In addition to these, the cancer registry also receives some records from private hospitals (Information Services Division, 2011). Registry data also includes some demographic details including age, post code of residence, date of birth and different measures of socio-economic status. Socio-economic deprivation was inferred for each patient by using the Carstairs score associated with their postcode.

Population estimates were required to calculate the age specific incidence rates of PC. We used age and deprivation specific population estimates 2001 for the West of Scotland, provided by the GRO(S).

2.3.3 Statistical analysis

As the incidence of PC increases sharply with the age and particularly after 50 years, a significant proportion of increase in the crude incidence rates could be due to aging of the population. We used the direct standardisation method to calculate the European age-standardised rates (EASR) to control for the differences in the age structure of the population between different time periods and socio-economic groups. As there were very small number of cases among individuals of less than 60 years so we used following age groups for the calculation of age-standardised rates, ≤ 59 , 60-64, 65-69, 70-74, 75-79 and ≥ 80 years. We also calculated standard errors of EASR's for each age group and their 95% confidence intervals.

Using Carstairs scores, we calculated deprivation specific incidence rates. We observed large variations between groups due to small number of cases in each category. Therefore we combined the deprivation categories 1 and 2 to make most affluent group, categories 3,4 and 5 were combined to create intermediate and categories 6 and 7 were combined to form the most deprived group. We then calculated the age specific rates for each of these three deprivation groups.

We calculated the incidence rates for every year and also by three time periods of 1991-1996, 1997-2002 and 2003-2007. Gleason grade is a pathological score which determines the behaviour and morphology of the tumours. Age-standardised rates were also calculated for low grade (Gleason 2-7) and high grade disease (Gleason 8-10). Cancer registry started recording Gleason scores from 1st January 1997, so grade-specific rates were calculated from year 1997 onwards.

Trend of incidence over time for overall, grade specific and deprivation specific PC incidence were also calculated using joinpoint regression analysis. This analysis detects the point of time at which significant changes occurred in the age-standardised incidence rates. I allowed a maximum of three join points for estimations. Annual percentage changes with their corresponding 95% confidence intervals and p values were also calculated.

I calculated age standardised ratio (ASR) by dividing the EASR of each deprivation category with the least deprived category. For calculation of the number of excess cases based on deprivation categories, I then divided the number of cases in each deprivation category by ASR and subtracting the result from incidence cases in that category (Shack *et al.*, 2008) This gives an estimate of how many extra or fewer cases there would have been had that deprivation category had the same EASR as the least deprived category (Shack *et al.*, 2008).

Weighted ordinary least square linear regression was used to model EASRs for the deprivation categories. The estimate deprivation gap and corresponding confidence intervals were then calculated using the models EASR for the most deprived minus the modelled EASR for least deprived category (National Cancer Intelligence Network, 2008). I calculated the excess cases and deprivation gap for overall as well as grade specific PC incidence.

2.4 Results

A total of 15,519 PC patients were identified who were registered in the West of Scotland from 1991 to 2007. Mean age at incidence was 72.3 years, standard deviation 9.0. Highest incidence rates were observed in the older age groups - 39.1% of cases (n=6,068) occurring in 65-75 years of age men and 41.6% of cases (n=6,455) in men older than 75 years. In the period 1991-2007, 18.8% of patients were in the affluent group, 55.9% in intermediate deprivation group and 25.3% in deprived group. The whole study period of 17 years (1991-2007) was categorised into three categories from 1991-1996, 1997-2002 and 2003 to 2007 (table 2-1). Significant differences in demographic and disease characteristics of patients were observed between these periods (table 2-1).

Age at incidence differed significantly over the study periods, from 73.4 years in 1991-1996 to 71.2 years in 2003-2007 (p value < 0.001). Proportions of patients diagnosed both before the age of 65 years and 65-74 years, increased from the first to the last period, while the proportion of patients older than 75 years at the time of diagnosis reduced during study period (table 2-1).

There was a significant interaction of socio-economic circumstances overtime in relation to incidence of PC. The proportion of patients in the affluent group significantly increased during study periods (17.3% in 1991-1996, 20.3% 2003-2006), while the proportion of men in deprived grouped significantly decreased through these same periods (28.3% in 1991-1996, 22.3% in 2003-2006)(table 2-1).

Both proportions of men with low grade (Gleason \leq 7) and high grade disease (Gleason 8-10) significantly increased during two study periods, as the proportion with unknown grade disease significantly reduced from 16.7 in 1997-2002 to 7.7% in 2003-2007 (table 2-1).

Table 2-1: Baseline characteristics of prostate cancer patients registered in the West of Scotland from 1991-2007

	Period of diagnosis						p-value
	1991-1996		1997-2002		2003-2007		
	All patients, n	%	All patients, n	%	All patients, n	%	
Total registered cases	4,534	29.2	5,506	35.5	5,479	35.3	
Age at incidence (years)							
Age < 65	683	15.1	1,027	18.7	1,286	23.5	
Age 65-74	1,753	38.7	2,106	38.3	2,209	40.3	<0.001
Age ≥ 75	2,098	46.3	2,373	43.1	1,984	36.2	
Gleason grade							
Gleason ≤ 7	–	–	3,033	55.1	3,265	59.6	
Gleason 8-10	–	–	1,556	28.3	1,793	32.7	<0.001
Unknown Gleason	–	–	917	16.7	421	7.7	
Socio-economic circumstances							
Affluent (Depcat 1,2)	785	17.3	1,028	18.7	1,110	20.3	
Intermediate (Depcat 3,4,5)	2,465	54.4	3,052	55.4	3,150	57.5	<0.001
Deprived (Depcat 6,7)	1,284	28.3	1,426	25.9	1,219	22.3	

Period of diagnosis was based on incidence date recorded in cancer registry, p-values calculated by chi square test.

2.4.1 Trend analysis

Generally, EASR of PC increased during the study period from 44 per 100,000 in 1991 to 75 per 100,000 in 2007, an overall increase of 70% with an average annual growth of 3.6% (figure 2-1). Overall increasing trend varied between different time periods. The highest increase seen in 1991-1996 (average annual growth of 8.4%) and in 1999-2004 with a significant average annual growth of 7.7% (table 2-2). Both these periods were followed by a non-significant decline in incidence trends.

Although there was a general increase in age standardised incidence rates during the study period, the increase rates were significantly different between age groups. The incidence rates increased 3 times among men of less than 65 years of age from 7 per 100,000 in 1991 to 21 per 100,000 in 2007, while only 75% and 50% increases in EASR were observed for men of age 65-74 years and ≥ 75 years respectively during the similar periods (figure 2-2).

Figure 2-1: Age-standardised incidence (per 100,000 population) of prostate cancer in the West of Scotland from 1991-2007

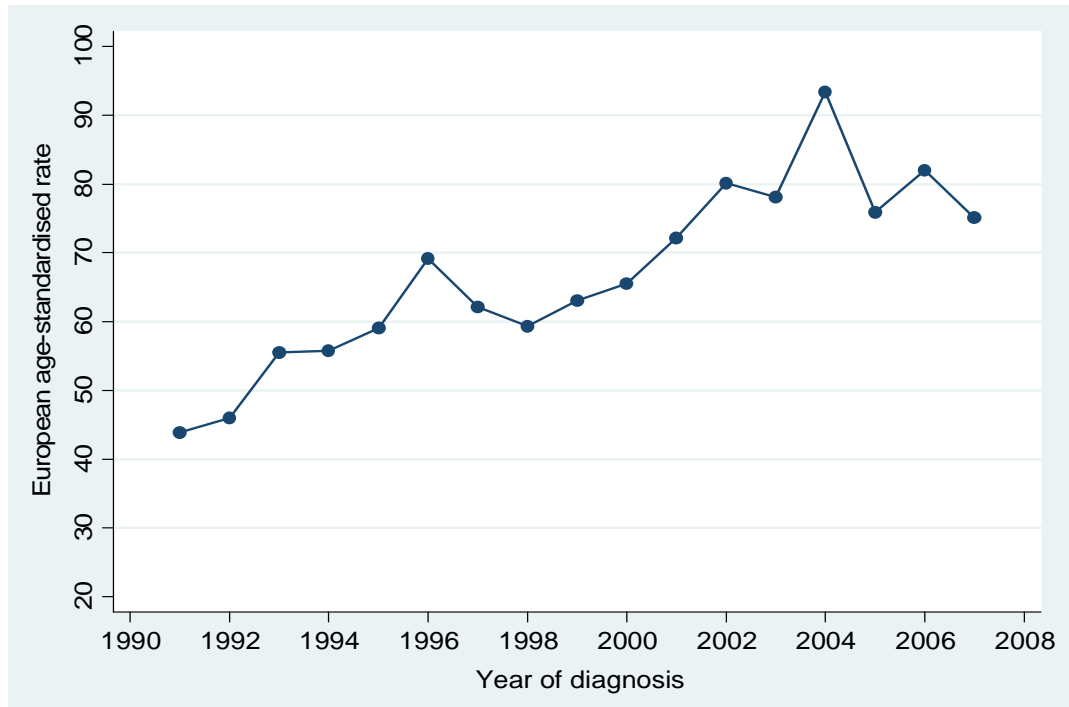


Figure 2-2: Age-standardised incidence (per 100,000 population) of prostate cancer between age groups

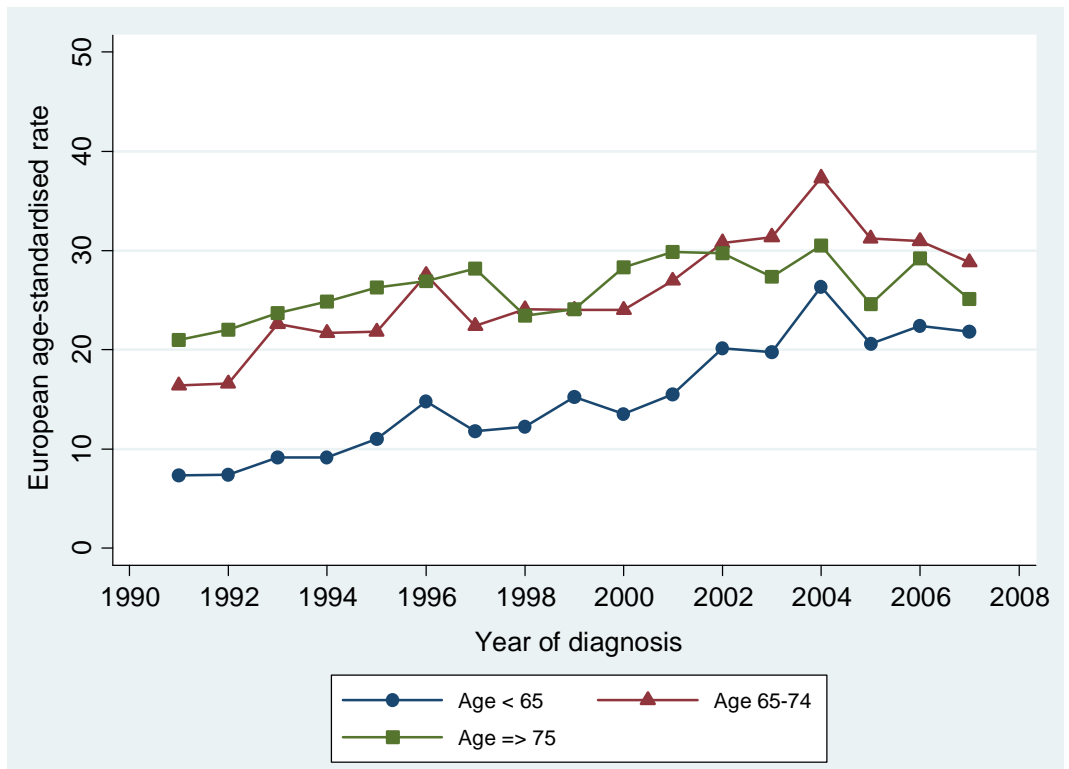


Table 2-2: Trends of prostate cancer incidence by disease grade and socio-economic circumstances from 1991 to 2007: joinpoint analysis

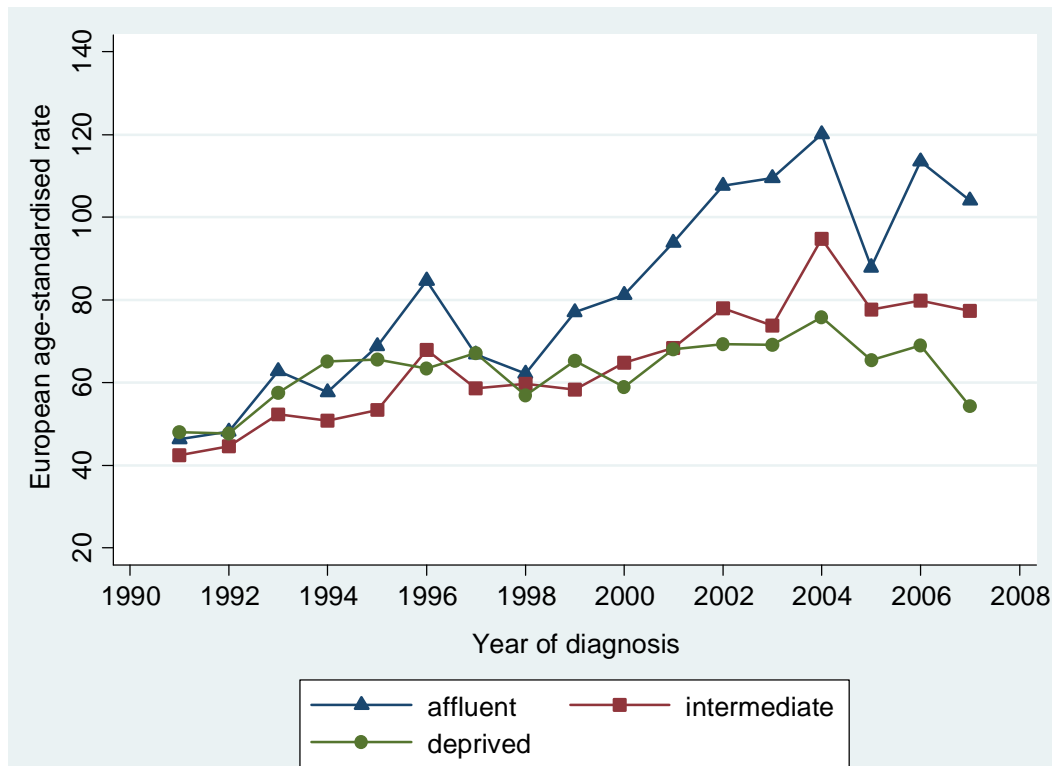
	No. of incident cases (min-max)	EASR rate per 10 ⁶ (min-max)	Annual percentage change (95% CI)		
Overall incidence: 1991-2007					
1991-1996	635-943	43.8-69.2	8.4*	(3.5,	13.5)
1996-1999	815-943	59.3-63.08	-2.5	(-19.3,	17.8)
1999-2004	900-1263	63.08-93.43	7.7*	(1.9,	13.9)
2004-2007	1016-1263	75.16-93.43	-5.6	(-13.4,	2.9)
Deprivation specific overall incidence: 1991-2007					
Affluent (Depcat 1 & 2)	100-250	46.35-120.13	5.28*	(3.8,	6.8)
Intermediate (Depcat 3,4 & 5)	339-736	42.42-96.76	4.05*	(3.0,	5.2)
Deprived (Depcat 6 & 7)	177-277	47.70-75.85	1.33*	(0.1,	2.5)
Grade specific overall incidence: 1997-2007					
Low grade (Gleason ≤ 7)					
1997-2004	435-783	31.16-58.25	7.86*	(4.3,	11.5)
2004-2007	588-783	43.72-47.80	-4.78	(-15.3,	7.1)
High grade (Gleason 8-10)					
1997-2000	248-251	17.57-18.37	0.5	(-18.2,	23.4)
2000-2007	249-433	19.40-31.60	7.6*	(2.6,	12.8)

* The average annual percent change is statistically significantly different from 0

2.4.2 Deprivation gap

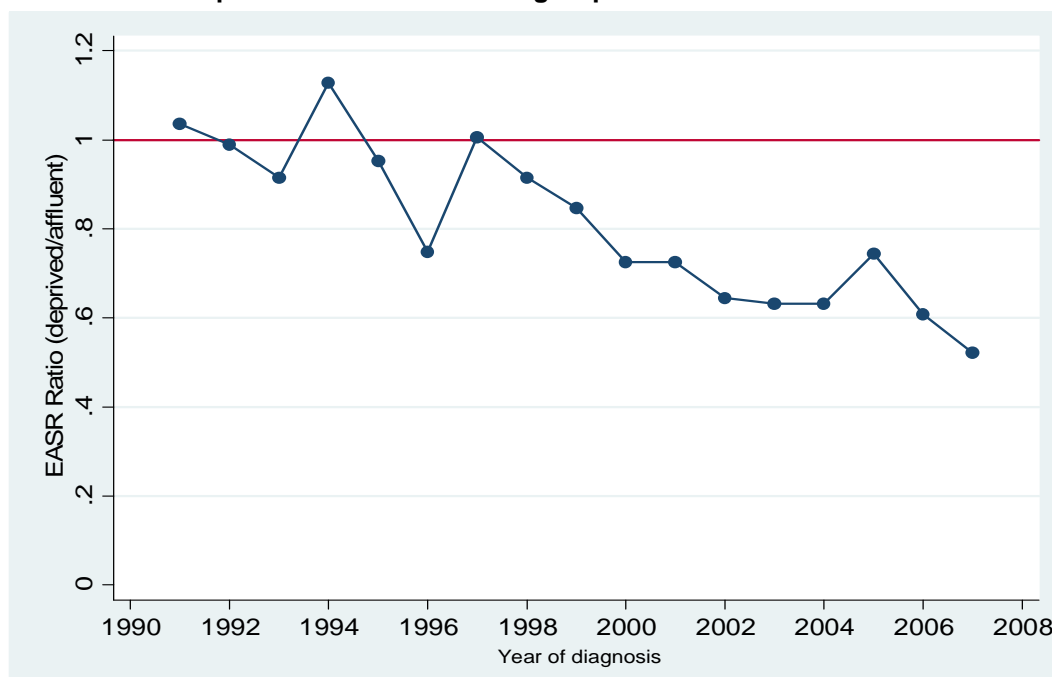
An increasing trend in incidence of PC was observed in all deprivation groups, the largest average annual increase of 5.3% (95% CI 3.8-6.8) was among the most affluent group and the smallest increase of 1.3% (95% CI 0.1-2.5) among the most deprived group (table 2-2). This gap between deprivation groups started appearing after 1997 as trends remained fairly similar in earlier periods of this study (figure 2-3). From 1997 to 2002, the age-standardised incidence among affluent men was 81.46 per 100,000 compared with 64.26 per 100,000 in the most deprived, giving a deprivation gap as an absolute difference of 17.2 per 100,000 ($P = 0.02$, trend) (table 2-3). This gap widened in the most recent period (2003-2007) as the incidence rate among deprived men remained nearly similar compared to previous period, while the incidence rate further increased among affluent men (table 2-3). For the recent period (2002 to 2007), age-standardised incidence among affluent men was 107.01 per 100,000 compared with 66.73 per 100,000 in the most deprived, giving a deprivation gap as an absolute difference of 40.28 per 100,000 ($P < 0.001$, trend) (table 2-3).

Figure 2-3: Age-standardised incidence of prostate cancer between deprivation groups



This can be more clearly interpreted from the ratio of EASRs' (between deprived and affluent). The incidence ratio remained 1 till 1997 and reduced up to 0.5 in year 2007 (figure 2-4).

Figure 2-4: Ratio of European age-standardised incidence rate of prostate cancer between most deprived and most affluent groups



On further analysis of grade specific incidence trends, I observed a significant overall increase in both low grade (Gleason ≤ 7) as well as high grade disease (Gleason 8-10) (table 2-2). However, significant increasing trend of low grade disease was from 1997-2004, while incidence rate of high grade disease increased in recent years 2000-2007 (figure 2-5). The ratio of low to high grade tumours was about 2 for the first part of the study period (figure 2-6). Between 2002 and 2004, there was a slightly higher proportion of low grade tumours but between 2005 and 2007 there was a lower proportion of them. Thus, there was no convincing evidence of a consistent relatively greater increase in incidence of low grade disease over time (figure 2-6).

Figure 2-5: Incidence of grade-specific prostate cancer in the West of Scotland

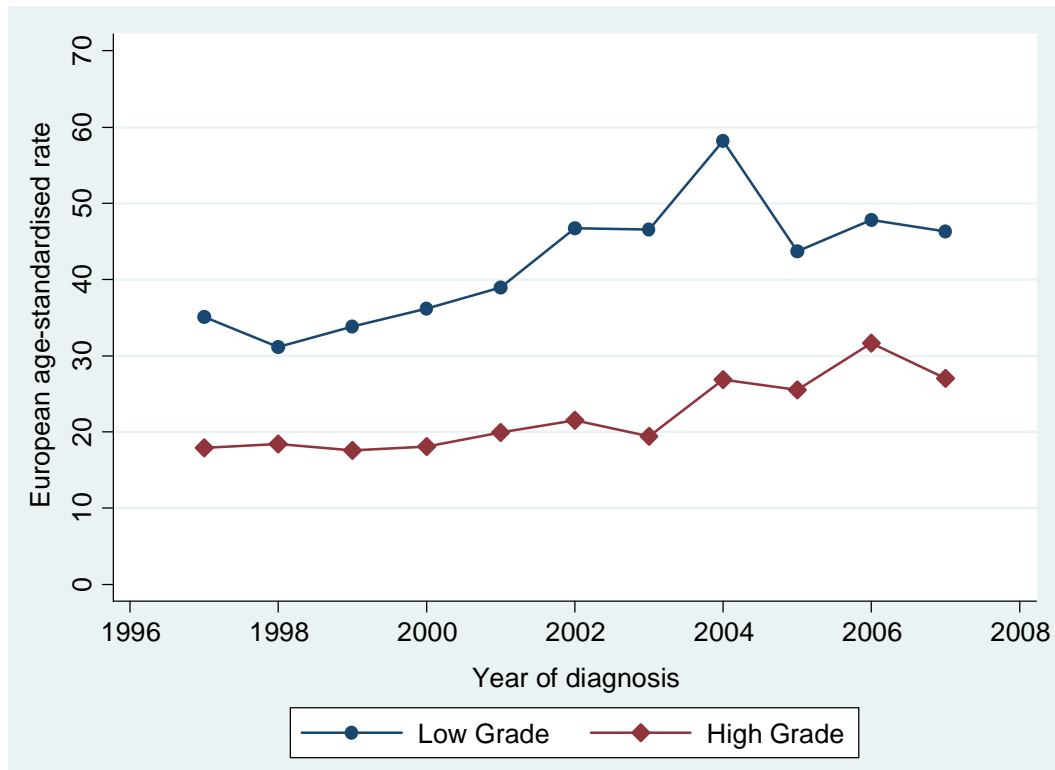


Figure 2-6: Rate ratio of grade-specific age-standardised incidence rates (low grade: high grade) in the West of Scotland: 1997-2007

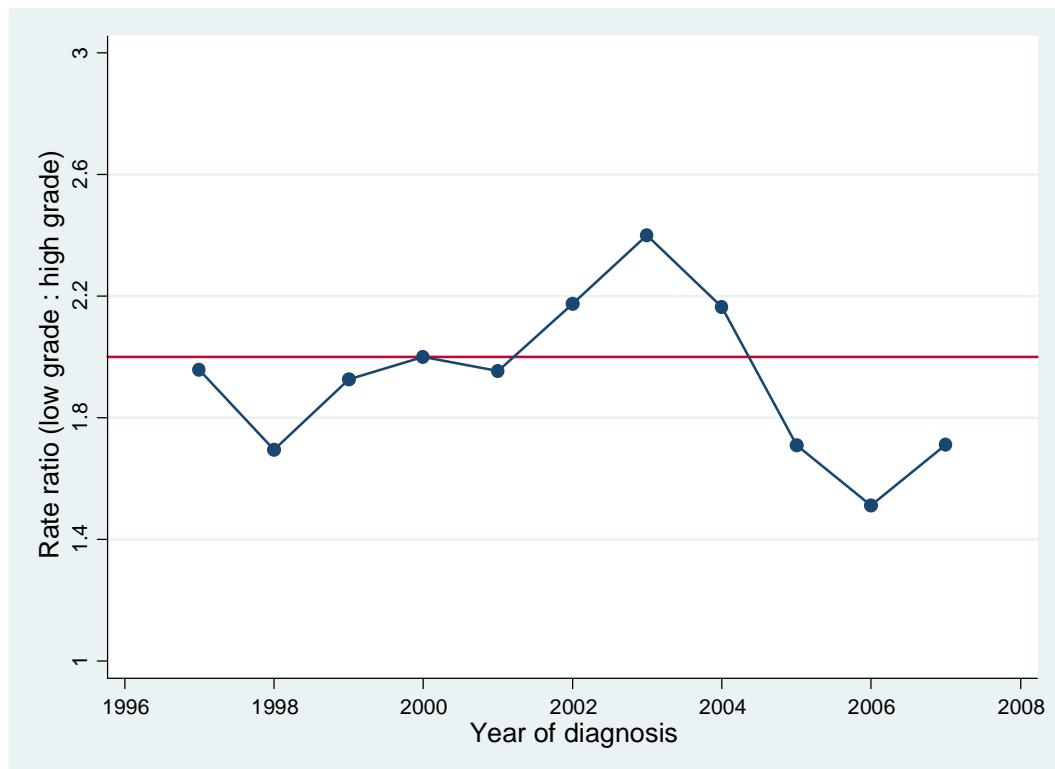


Table 2-3: Prostate cancer incidence by deprivation from 1991 to 2007 in the West of Scotland

Deprivation group	Number of incident cases	European age-standardised rate (EASR) per 100 000	95 % Confidence Intervals		EASR ratio	Estimated excess cases	Annual excess cases/100,000
1991-1996							
Affluent	785	61.44	(48.59,	74.30)	1	0	0
Intermediate	2465	51.92	(39.90,	63.93)	0.84	-452	-75
Deprived	1284	57.91	(39.24,	76.58)	0.94	-78	-13
Overall	4534	57.09	(38.46,	75.72)		-531	-88
P-value for trend		0.76					
1997-2002							
Affluent	1028	81.46	(66.32,	96.59)	1	0	0
Intermediate	3052	64.66	(57.69,	71.62)	0.79	-793	-132
Deprived	1426	64.26	(44.55,	83.98)	0.79	-381	-64
Overall	5506	70.13	(49.12,	91.14)		-1174	-196
P-value for trend		0.02					
2003-2007							
Affluent	1110	107.01	(72.63,	141.38)	1	0	0
Intermediate	3150	80.68	(65.28,	96.08)	0.75	-1028	-206
Deprived	1219	66.73	(46.35,	87.11)	0.62	-736	-147
Overall	5479	84.80	(61.42,	108.19)		-1764	-353
P-value for trend		<0.001					

When I further investigated the disease specific trends in deprivation categories, increasing trend of low grade disease was mainly driven by the higher incidence in affluent men (figure 2-7), while there were no significant differences in high grade disease incidence between deprivation groups (figure 2-8).

From 1997 to 2002, the age-standardised incidence among the most affluent men was 41.79 per 100,000 compared with 34.88 per 100,000 in the most deprived, creating a deprivation gap as an absolute difference of 6.9 per 100,000 ($P = 0.07$, trend) (table 2-4). This gap widened in the most recent period (2003-2007), the age-standardised incidence among the most affluent men was 56.20 per 100,000 compared with 45.73 per 100,000 in the most deprived, giving a deprivation gap as an absolute difference of 10.47 per 100,000 ($P < 0.001$, trend) (table 2-4). An estimated 93 more cases of PC per year would be diagnosed in the West of Scotland if both intermediate and deprived group had the same incidence rate as of affluent group from 2003-2007. We did not observe any significant deprivation gap between high grade diseases for both, earlier or recent periods (table 2-4).

Figure 2-7: Incidence of low grade prostate cancer between deprivation groups

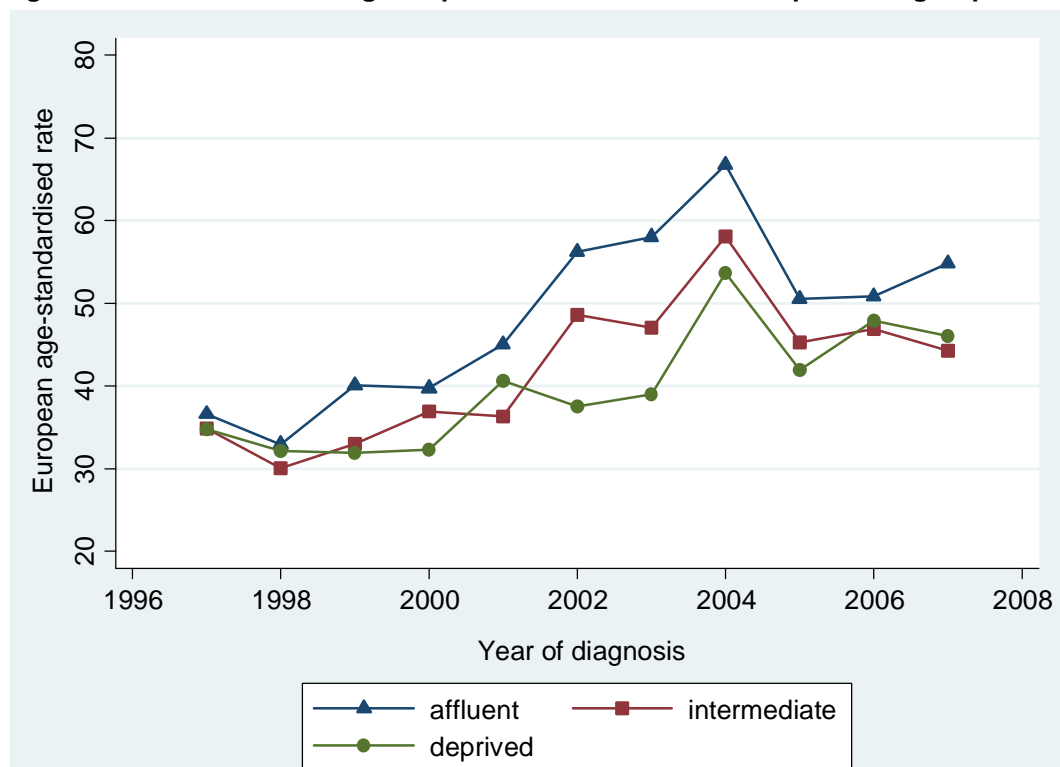


Figure 2-8: Incidence of high grade prostate cancer between deprivation groups

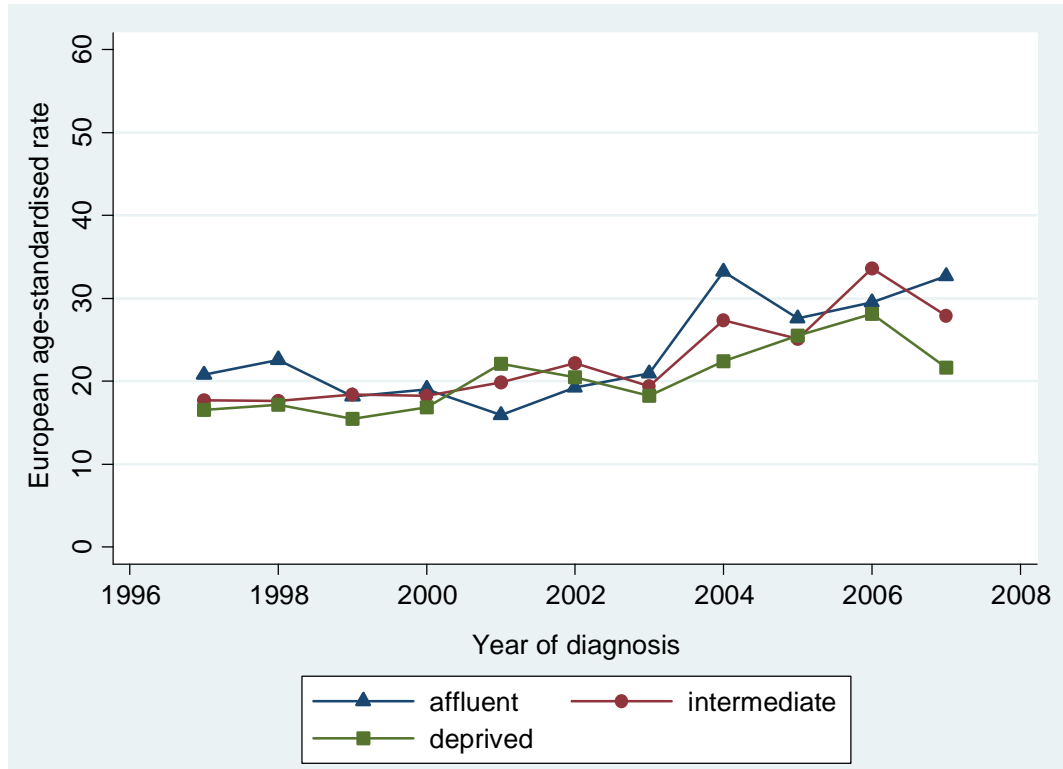


Table 2-4: Grade-specific prostate cancer incidence by deprivation from 1991 to 2007 in the West of Scotland

Deprivation group	Number of incident cases	European age-standardised rate (EASR) per 100 000	95 % Confidence Intervals		EASR ratio	Estimated excess cases	Annual excess cases/100,000
Low Grade Disease							
1997-2002							
Affluent	623	41.79	(20.57,	63.01)	1	0	0
Intermediate	1,709	36.63	(26.32,	46.95)	0.88	-241	-40
Deprived	701	34.88	(20.19,	49.58)	0.83	-139	-23
Overall	3,033	37.77	(22.36,	53.18)		-379	-63
P-value for trend		0.07					
2003-2007							
Affluent	682	56.20	(31.19,	81.21)	1	0	0
Intermediate	1,945	48.33	(36.40,	60.27)	0.86	-317	-63
Deprived	638	45.73	(28.81,	62.65)	0.81	-146	-29
Overall	3,265	50.09	(32.13,	68.04)		-463	-93
P-value for trend		0.02					
High Grade Disease							
1997-2002							
Affluent	258	19.30	(05.33,	33.26)	1	0	0
Intermediate	865	19.02	(11.75,	26.28)	0.99	-13	-2
Deprived	433	18.11	(07.75,	28.46)	0.94	-28	-5
Overall	1,556	18.81	(08.28,	29.34)		-41	-7
P-value for trend		0.36					
2003-2007							
Affluent	359	28.80	(11.29,	46.31)	1	0	0
Intermediate	1,027	26.68	(17.97,	35.38)	0.93	-82	-16
Deprived	407	23.18	(11.35,	35.01)	0.80	-99	-20
Overall	1,793	26.22	(13.54,	38.90)		-180	-36
P-value for trend		0.07					

2.5 Discussion

2.5.1 Main findings of this analysis

I observed a significant rise in incidence of PC in the West of Scotland during 1991 to 2007. The largest increase in incidence occurred in men under the age of 65. Such a pattern has been attributed to PSA testing in England (Moore *et al.*, 2009) but in the absence of any evidence about age-specific use of PSA testing in our study population, I cannot propose that this is likely. PC incidence increased in all socio-economic groups over time but low grade disease increased more in the most affluent group. This produced a socio-economic gradient in incidence from 1997 onwards. While this is consistent with greater diagnostic sensitivity in more affluent populations, it did not produce an overall increase in the proportion of low grade cases as a significant rise in high grade disease was also observed in a most recent period.

2.5.2 Data quality

In present study, the incident data from the Scottish Cancer Registry has been used, and the quality of the available data already discussed. I have a fairly large sample size to estimate the differences between the sub groups of population. Ecological measures of socio-economic status have been widely used in health in general (Carstairs and Morris, 1990) and cancer incidence and survival in particular (National Cancer Intelligence Network, 2008; Shack *et al.*, 2007). Carstairs scores as a measure of deprivation were used in this study. As with all the area-based measures of deprivation using the Carstairs score, it is assumed that all the individuals living in a given geographical area experience the same level of deprivation and associated cancer risk factors. Individual level data like level of education, occupation and income can provide the stronger evidence of socio-economic circumstances but these data are not routinely collected in cancer registries.

2.5.3 Temporal trends in incidence

I observed a significant rise in incidence of PC in the West of Scotland during 1991 to 2007. Age-standardised rates more than doubled from 44 per 100,000 in

1991 to 93 per 100,000 in 2004. Age-standardised incidence on average, increased at a rate of 3.6% annually during the study period. These are age-standardised rates so the rise in incidence observed during the study period is unlikely due to the aging of population. Steep increases in incidence of PC have also been observed in England and Wales from early 1990's to 2004 (Evans and Moller, 2003; Westlake and Cooper, 2008) and in other European countries as well (Bray *et al.*, 2010). Although the testing of older individuals for PSA has been mainly attributed to these large observed increases in PC (Bray *et al.*, 2010), it is still unclear whether the increased incidence since 1991 is completely due to increased detection of cases or a real increase in risk of the disease. The increase in incidence of PC in the West of Scotland between 1991 and 2007 was not accompanied by a strong "grade shift" towards lower grade disease that might have suggested PSA testing was responsible. A true increase in incidence may remain a plausible explanation.

Interestingly, a significantly higher proportion of patients have been diagnosed before the age of 75 years in the recent period (2003-2007) compared with the earlier (1991-2002). Age-standardised rate increased 3-fold for those of age less than 65 years. Studies from UK and USA data showed the similar pattern of increased incidence among younger age groups and that was attributed to the PSA testing among these age groups (Collin *et al.*, 2008; Moore *et al.*, 2009).

2.5.4 Gleason grade-specific temporal trends

Trend of grade specific incidence also showed similar pattern for both low grade (Gleason ≤ 7) and high grade disease (Gleason > 7) of increasing incidence over the study period. Low grade disease increased significantly on an annual average of 7.9% during 1997-2004 followed by a non-significant decline. High grade disease remained fairly stable from 1997 to 2000, while the similar annual growth of 7.6% was observed for high grade disease from 2000 to 2007. There is evidence that PSA testing has led to stage and grade migration of PC in the UK and patients are more likely to be diagnosed at a younger age (<65 years) and with low grade disease (Moore *et al.*, 2009). It is very likely that some of the observed pattern in our study could be because of the increased use of PSA testing in the West of Scotland during that period, which led to an increased

incidence of low grade disease. But increased PSA uptake does not explain the increased incidence of high grade tumours in a later period. The individuals who were diagnosed with high grade disease were significantly older compared with those with low grade disease (73.6 vs 70.6, p-value <0.001). This is an important finding of this study as little is known about the grade specific trends of PC. However, many factors are likely to contribute in the observed trend of aggressive PC. First, variations in the use of different treatment modalities could have an impact on the PC incidence by tumour grades. For example in the US, the surgical removal of prostate gland along with regional lymph nodes was modified in early 1980s to preserve the regional innervation and potency (Quinn and Babb, 2002). This resulted in an increased utilisation of radical prostatectomy through the early 1980s and 1990s, and this could have shifted the disease grade towards high grade because more tissue was available for pathological examination (Quinn and Babb, 2002). In the Surveillance Epidemiology and End Results (SEER) data, it has been observed that patients who were treated surgically had higher grade disease than those who were treated by other modalities. Thus, it is a possibility that during the higher incidence period here in the UK, relatively more tumours were classified as high grade than low grade due to the availability of large amount of tissue as a result of prostatectomy. Unfortunately current data did not have the complete information of treatment provided to the patients so studies from other parts of the UK may provide some evidence on this aspect.

Second, in clinical practice there are more biopsies performed than in the earlier period of study, so the observed increase in the high grade disease could be due to an increase in the number of biopsies performed. In this data I observed a 9% reduction in unknown grade disease in 2003-2007 compared to 1997-2002. This reduction of unknown grade might have artificially inflated the high grades in this period.

Third, the rate of transurethral resection of prostate (TURP), the treatment of benign prostatic hyperplasia, has dramatically declined in recent periods due to availability of other treatments (Evans and Moller, 2003). Transurethral resections were used to lead to the incidental diagnosis of low grade PCs, which

now might not be appearing in earlier age and tumours gained enough time to evolve into high grade at a later age in life.

Finally, if I assume that the increase in high grade disease is not artificially driven by the above mentioned factors, then there might be a real increase in the incidence of high grade disease. Many epidemiological studies have strongly linked obesity with increased risk of high grade PC (Kaaks and Stattin, 2010). Recently, high plasma cholesterol level has also been associated with increased risk of aggressive PC (Platz *et al.*, 2009). If the observed increase of high grade disease in the West of Scotland is genuine, then the increasing obesity and dyslipidemia on population level might explain the observed patterns in our study (Lawder *et al.*, 2010).

2.5.5 Socio-economic patterns in incidence

On further exploration of trend of PCs in the West of Scotland, I observed that age-standardised incidence among the most affluent men increased on average of 5.3% every year, while this remains only 1.3% among the most deprived group. The incidence rate ratio of affluent and deprived remained closer to one in the first half of 1990s, and steeply declined from 1997 onwards. Socio-economic differences in incidence of PC have also been reported in West Midlands, England (Dutta *et al.*, 2005). However, little is known about the factors which influence and drive such changes. Evidence on the causes of PC generally remained inconclusive except for age, genetic predisposition and race. The poorly understood natural history of PC, which in most cases remains a small, slow growing tumour and might not even manifest during lifetime of an individual, makes it a very unpredictable disease.

I further analysed the data to investigate the effect of period of diagnosis on emerging deprivation gap. Overall the increasing trend of incidence appears to be similar in all socio-economic groups till 1997, but a deprivation gap has emerged as result of relative increase in incidence among affluent men. PC incidence rates among the affluent were 17.2% higher than the deprived in 1997-2002. This emerging deprivation accounts for an estimated 1,174 under diagnosed cases of PC (among the deprived and intermediate group) in the West

of Scotland during this period which is approximately 21% of all cases. This gap further widened in most recent period from 2003-2007. The absolute difference of age-standardised rates was 40.3% among the affluent and deprived, with an estimated 1,764 under diagnosed cases among the deprived and intermediate compared with the affluent. This is approximately 32% of total cases diagnosed in this period.

On further analysis of grade-specific disease between socio-economic groups, affluent men were significantly more likely to have low grade disease compared with the most deprived men. This may be explained by differential uptake of PSA uptake between socio-economic groups but in the absence of PSA data it remains unclear yet. Trends of high grade disease did not show any significant difference in incidence between socio-economic groups.

The observed deprivation gap in this analysis is even larger than recently reported gap for the colorectal cancer but in opposite direction (Oliphant *et al.*, 2011). A similar deprivation gap has been reported for PC in England and Wales from 1995-2004, however the size of the gap is even larger in the West of Scotland for both earlier and later periods (National Cancer Intelligence Network, 2008). The incidence of PC has increased among men in higher socio-economic groups both in European countries as well as in the US (Liu *et al.*, 2001; Westlake and Cooper, ; Yin *et al.*, 2010). Even the racial differences in incidence of PC have also been attributed to the socio-economic status of the individuals within their racial group (Yin *et al.*, 2010).

Underlying reasons for this widening deprivation gap are unclear yet. Some differences in prevalent risk factors and lifestyle habits among different socio-economic groups might explain the observed association, but since the aetiology of PC remains poorly understood, definite conclusion about the increased risk of disease among different socio-economic groups could not be established. PSA testing has been widely available and utilised in last two decades (Drummond *et al.*, 2009) and has led to earlier diagnosis of asymptomatic cases. It is very likely that the uptake of PSA testing as a means of diagnosing PC has become relatively much more common among the most affluent groups of population and this has

influenced the association between socio-economic status and incidence over time (National Cancer Intelligence Network, 2008).

2.5.6 Implications for research

The present study suggests socio-economic variations in distribution of PC in the West of Scotland. One important consideration of socio-economic inequalities in the incidence of PC is whether a higher diagnosis among affluent men has any health benefits associated with it or is it just a case of over diagnosis and treatment among affluent men. Previous research indicated that only 16% of asymptomatic men detected by a PSA test would benefit from radical treatments and their disease otherwise would not have compromised their life expectancy and quality of life (Frankel *et al.*, 2003). As early detection of the individuals with PC might not lead to a radical treatment, diagnosis of cancer and living with cancer can have serious psychological influences and impact on quality of life after diagnosis. The upside is that the early detection by PSA testing has provided some evidence that disease grade and stage has been migrated in the UK. In this context individuals living in deprived areas are under diagnosed as suggested by our study and they might present with a higher grade and more advanced stage disease later. Then the question arises whether the early and higher detection among affluent men is associated with survival benefits of these patients. A deprivation gap of -6.9% (minus sign suggests a higher survival among the affluent) in survival of PC patients diagnosed from 1996 to 2000 has been reported previously. As I observed a widening gap in the incidence of PC in the more recent period, it is important to explore whether this higher incidence has influenced the pre-existing deprivation gap in survival of patients during most recent periods or not, while taking into account lag-time bias due to the PSA based diagnoses.

3 Cholesterol and the risk of grade-specific prostate cancer incidence: evidence from two large prospective cohort studies with up to 37 years' follow up.

3.1 Chapter summary

High cholesterol may be a modifiable risk factor for PC but results have been inconsistent and subject to potential “reverse causality” where undetected disease modifies cholesterol prior to diagnosis. I conducted a prospective cohort study of 12,926 men who were enrolled in the Midspan studies between 1970 and 1976 and followed up to 31st December 2007. I used Cox-Proportional Hazards Models to evaluate the association between baseline plasma cholesterol and Gleason grade-specific PC incidence. I excluded cancers detected within at least 5 years of cholesterol assay.

Six hundred and fifty men developed PC in up to 37 years' follow-up. Baseline plasma cholesterol was positively associated with hazard of high grade (Gleason score \geq 8) PC incidence (n=119). The association was greatest among men in the 4th highest quintile for cholesterol, 6.1 to <6.69 mmol/l, Hazard Ratio 2.28, 95% CI 1.27 to 4.10, compared with the baseline of <5.05 mmol/l. This association remained significant after adjustment for body mass index, smoking and height. Men with higher cholesterol are at greater risk of developing high-grade PC but not overall risk of PC. Interventions to minimise metabolic risk factors may have a role in reducing incidence of aggressive PC.

3.2 Introduction

This chapter will investigate the role of cholesterol level in PC risk using the data from two large prospective cohort studies - the Midspan studies. In the earlier chapter 2 (page 95) it has been shown that the incidence of PC has increased over several decades such that it is now frequently diagnosed cancer among men in the UK and also in the West of Scotland.

Three recent reports have suggested that while serum cholesterol has no association with overall incidence of PC, patients with low cholesterol are less likely to have high grade (Gleason score ≥ 8) disease (Mondul et al., 2010; Platz et al., 2008; Platz et al., 2009). In two of these studies, follow-up was short (3.1 and 5.5 years) and none excluded early events (Mondul et al., 2010; Platz et al., 2009) so that “reverse causality” - that is, cholesterol was modified by undiagnosed disease and not a causal factor for it - may have partly explained their observations.

Given that age, genetics and ethnicity are not modifiable risk factors, the potential role of cholesterol on PC risk may be of clinical importance. In the present analysis the association between plasma cholesterol level and both overall and grade-specific PC incidence has been evaluated, using two of the Midspan prospective cohort studies with up to 37 years' follow-up. Individuals diagnosed with PC within 5 years of baseline cholesterol assay were excluded to reduce the potential effects of “reverse causality.”

3.3 Materials and methods

3.3.1 Cohort characteristics

The Midspan studies began in the 1960s and 1970s in Scotland, UK (Hart *et al.*, 2005). These studies are called Midspan because they were centred on the midspan of life. These studies originated in the post war drive to control pulmonary tuberculosis in Scotland using the mass miniature radiography. However, later on these studies were extended to detect and investigate the risk factors of a wide range of chronic diseases. Midspan was the name given to four separate occupational and general population cohort studies based in Scotland (Hart *et al.*, 2005). In the present analysis two Midspan studies were examined. The first, the Collaborative study, was conducted on employed men and women aged from 21 to 75 years from 27 workplaces in Glasgow, Clydebank and Grangemouth between 1970 and 1973 (Davey Smith G. *et al.*, 1998). Further details of this cohort will be described in chapter 4 (Tea and coffee in relation to risk of PC, page 125), as only the Collaborative cohort study's data has been used for that analysis.

The second Midspan study, the Renfrew/Paisley study, was a general population study of residents of the towns of Renfrew and Paisley, conducted between 1972 and 1976. All residents aged 45-64 years were invited to take part and 80% accepted (Hawthorne *et al.*, 1995). Compared to the other population-based studies in the UK of that era, Renfrew/Paisley had a particular advantage of having a large number of female participants in this study. Compared to the other cohorts, men in this study had shorter stature, higher blood pressure, and a higher proportion of smokers continuing to smoke and more had chronic bronchitis (Hart *et al.*, 2005).

Because of the geographical proximity of the study populations, a small number of individuals participated in both cohorts. For individuals with more than one record, only the earliest record was used. Study protocols consisted of a self-administered questionnaire followed by a screening examination at a specially set-up clinic. Questions included demographic details, occupation, lifestyle habits, including smoking, and health (Hawthorne *et al.*, 1995). As part of the screening examination, measurements were made for height, weight and blood

pressure. Body mass index (BMI) was calculated from weight (in kg) divided by height (in metres) squared and categorised according to the World Health Organisation (WHO) classification in which BMI < 18.50 is underweight, 18.50 to 24.99 is the normal range, 25.00 to 29.99 is overweight and ≥ 30.00 is obese. A blood sample was obtained at baseline screening for the measurement of total circulating plasma cholesterol (Hawthorne *et al.*, 1995). Social class was derived from occupation according to the relevant version of the General Register Office Classification of Occupation (General Register Office, 1966) and graded into six categories: I (professional), II (intermediate), III (skilled non-manual), III (skilled manual), IV (partly skilled) and V (unskilled) (Hawthorne *et al.*, 1995).

Ex-smokers were defined as reporting giving up smoking at least a year before screening, otherwise they were defined as current smokers. Cholesterol was categorised by quintiles. Only records for male participants were used for this study.

3.3.2 Follow-up

Follow-up for mortality was carried out by flagging Midspan participants with the National Health Service Central Register. Deaths were then notified to the Midspan team on a monthly basis. Information on cancer registrations and hospital activity was obtained by linkage to the Scottish Morbidity Records (SMR) data and was complete from 1972 onwards (Hart *et al.*, 2010). Follow-up began on the date of screening to the date of cancer incidence, date of death, date of embarkation (leaving the UK) or the censor date of 31st December 2007, whichever came first.

3.3.3 Ethical approval

An application along with a research proposal was submitted to Midspan Steering Committee to access the data of Midspan studies. Following the approval from Midspan Steering Committee, a request along with proposal was sent to the Privacy Advisory Committee at ISD to use the linked data of Midspan with SMR06 and SMR01. The Privacy Advisory Committee of the Information Services Division of NHS Scotland gave permission for the linked data to be used in this study.

3.3.4 Risk factor and outcome definitions

PC was defined as International Classification of Diseases (ICD) revision 9 code 185 and ICD-10 code C61. PC incidence was determined if it was included in any cancer registration (SMR06), any diagnosis position of an acute hospital record (SMR01) or any position on the death record. Where a patient had PC recorded on more than one type of record, the earliest date was taken as time of first diagnosis. The Gleason grading system is a method used to describe the morphology of clinical PC. Data on Gleason score were available from the cancer registry (SMR06). The Scottish Cancer Registry began recording Gleason score from 1st January 1997 and therefore the analysis of grade-specific associations between cholesterol and PC was restricted to the follow-up of the surviving cohort as of 1st of January 1997 and these were just records from SMR06.

3.3.5 Statistical analysis

Cox proportional hazards models were used to estimate hazard ratios (HRs) for PC incidence from screening and for specific histological grades from 1st January 1997. For inclusion in a multivariate model, all those variables which had a p-value of less than 0.20 or were previously well known confounders in such analysis were included in multivariate analysis in a stepwise approach. For grade specific analysis, I excluded men who had died or been diagnosed with PC before 1st January 1997. Separate models were run for each Gleason category, and men with PC and other Gleason scores were censored at their date of diagnosis. Age was taken as the timescale with censoring occurring on 31 December 2007. Using age as timescale is slightly different than the conventional approach of using follow-up time since screening. In age as timescale, the model calculates the hazards based on the age at which individual entered in study and age at which he exited from the study. This approach is more reliable when studying a disease which is strongly associated with age, because for the outcome (incidence of PC in this analysis), I would expect the hazard to change more as a function of age than as a function of time-on-study. The alternative approach of using time since screening as the timescale was also investigated (Korn *et al.*, 1997). There were 100 participants in the underweight category (had BMI less than 18.5) and only one incident case of PC was identified in this group, so this category was

combined with the desirable weight category. Analysis was also carried out after excluding underweight individuals as well.

All analyses were conducted using STATA version 11 (StataCorp, College Station, TX, USA). The following covariates were included in all models: smoking status, BMI and socio-economic status. Height and smoking status were missing for three individuals so they were excluded from multivariate analysis. The lowest category was used as referent for cholesterol and all other categorical covariates.

Adherence to the proportional hazards assumption was investigated by plotting smoothed Schoenfeld residuals against time; no violations of the assumption were identified. All statistical tests were two tailed and statistical significance was taken as $p < 0.05$. The analysis was carried out after excluding individuals diagnosed with PC within five years of screening to minimise confounding due to the possible effects of early disease affecting cholesterol.

3.3.6 Alternative categorisation of cholesterol

Time to event approach was also used, that also did not affect any of the conclusions of this study. The present analysis was also repeated by using the different cut offs for cholesterol, for instance the clinical cut points for cardiovascular diseases (Desirable: <5.17 mmol/l, High: >5.17 mmol/l) and clinical categories ((Desirable: <5.17 mmol/l, Borderline high: >5.1 - <6.21 mmol/l, High: ≥ 6.21 mmol/l). Also, these analyses were carried out separately on each cohort. That did not affect the cholesterol and PC relationship so the final analysis was carried by combining the data of two cohorts. In addition to that, analysis was also carried out after excluding the men who had a diagnosis of diabetes mellitus at the time of screening. Analysis was also stratified based on BMI categories (i.e. desirable, overweight, obese), while number of high grade cases was small in some categories and no clear pattern emerged so analysis was repeated using the median BMI of the sample. Functional form of the association of cholesterol, with the relative hazard of Gleason 8 to 10 PCs estimated in a Cox proportional hazards model using age as the time axis, this was estimated by using a cholesterol level as a continuous variable. The function

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was fitted using restricted cubic splines with three knots (X). The function was standardized such that the HR was 1 at the mean cholesterol level of the lowest quintile.

3.4 Results

Data from 13,071 men were available for analysis, 6022 (46.1%) from the Collaborative Study and 7049 (53.9%) from Renfrew/Paisley. Five Collaborative and nine Renfrew/Paisley participants were lost to follow-up, 42 Collaborative and 55 Renfrew/Paisley participants had missing cholesterol data. Twenty six individuals who participated in both studies were excluded from the Renfrew/Paisley study. This exclusion was on the basis that the longer follow-up of these individuals was available when using their data from Collaborative cohort study. Eight individuals diagnosed with PC in the first five years of screening were also excluded from the analysis. Our final sample therefore comprised 12,926 men followed-up for a total of 293,284 person-years. The median follow-up period was 24 years, maximum 37 years. Median age was 51 years at the time of screening (range, 21-75 years).

Baseline and outcome characteristics of cohort participants are shown in table 3-1. Increasing weight and BMI were positively associated with cholesterol while current smoking and lower social class were inversely associated with cholesterol. Mean plasma cholesterol level did not differ ($p=0.27$) between men who were diagnosed with PC ($5.85 \text{ mmol/l} \pm 0.99$) and those who remained free from it ($5.87 \text{ mmol/l} \pm 0.99$). The mean time between screening (plasma cholesterol measurement) and the PC diagnosis was 22.9 (SD 7.84) years.

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3-1: Baseline characteristics of male Midspan cohorts at screening (1970-76) and prostate cancer outcomes. N=12,926.

	Cholesterol quintiles, level mmol/L									
	<5.05		5.06 – <5.57		5.58 – <6.09		6.1 – < 6.69		≥6.7	
Sample Size	2,727		2,592		2,821		2,286		2,500	
Person-years of follow-up	62,536		59,659		63,340		51,686		56,062	
<i>Number of Deaths % (n)</i>	75.4	(2055)	76.2	(1974)	77.0	(2172)	77.7	(1777)	77.3	(1933)
<i>Number of prostate cancers % (n)</i>	5.1	(138)	4.7	(121)	5.1	(145)	5.5	(125)	4.8	(121)
<i>Gleason grade ≥8</i>	27.9	(17)	37.3	(19)	46.2	(30)	46.5	(33)	33.9	(20)
<i>Gleason grade =7</i>	21.3	(13)	13.7	(7)	12.3	(8)	18.3	(13)	27.1	(16)
<i>Gleason grade <7</i>	24.6	(15)	17.6	(9)	26.2	(17)	16.9	(12)	18.6	(11)
<i>Unknown</i>	26.2	(16)	31.4	(16)	15.4	(10)	18.3	(13)	20.3	(12)
Mean Age, years (s.d.)	50.8	(7.8)	51.0	(7.2)	51.6	(7.1)	51.4	(6.8)	50.9	(6.8)
Mean Height, cm(s.d.)	171.2	(7.1)	171.0	(7.0)	171.0	(7.1)	170.9	(7.1)	171.5	(7.2)
Mean Weight, kg (s.d.)	72.6	(11.5)	74.4	(11.0)	75.0	(11.1)	75.8	(10.7)	76.7	(10.4)
<i>Height (cm), % (n)</i>										
≤165.1	22.7	(618)	22.0	(571)	22.5	(635)	23.2	(531)	21.4	(535)
165.2-170	19.6	(534)	19.9	(517)	22.2	(626)	22.4	(513)	19.5	(487)
170.1-172.72	19.6	(535)	20.3	(526)	18.0	(508)	17.7	(405)	18.7	(468)
172.73-177.8	22.3	(609)	23.6	(611)	21.9	(618)	21.0	(481)	23.6	(591)
≥177.9	15.8	(431)	14.2	(367)	15.3	(433)	15.5	(355)	16.8	(419)
Missing	0	(0)	0	(0)	0.0	(1)	0.0	(1)	0	(0)
Mean BMI (s.d.)	24.7	(3.3)	25.4	(3.3)	25.6	(3.3)	26.0	(3.1)	26.1	(3.0)
<i>BMI (kg m⁻²), % (n)</i>										
18.5 – <25 (Desirable)	55.0	(1501)	48.0	(1243)	43.6	(1231)	38.8	(886)	36.7	(917)
25 – <30 (Overweight)	38.8	(1057)	44.0	(1141)	47.4	(1336)	51.6	(1179)	53.4	(1336)
≥30 (Obese)	6.2	(169)	8.0	(208)	9.0	(253)	9.6	(220)	9.9	(247)
Missing	0.0	(0)	0.0	(0)	0.0	(1)	0.0	(1)	0.0	(0)
<i>Smoking, % (n)</i>										
Never smoker	16.8	(457)	17.9	(463)	17.6	(496)	18.1	(413)	16.5	(413)
Smoker	63.2	(1724)	59.5	(1542)	58.1	(1638)	55.2	(1262)	55.2	(1381)
Ex-smoker	20.0	(546)	22.6	(587)	24.4	(687)	26.7	(610)	28.2	(706)
Missing	0.0	(0)	0.0	(0)	0.0	(0)	0.0	(1)	0.0	(0)
<i>Social Class, % (n)</i>										
I&II	18.1	(493)	21.4	(555)	25.3	(715)	28.3	(646)	34.8	(871)
IIIN	13.4	(365)	14.6	(378)	14.5	(408)	15.0	(343)	17.0	(424)
IIIM	38.4	(1048)	36.7	(952)	34.2	(966)	33.9	(776)	28.5	(713)
IV&V	29.4	(801)	26.4	(684)	25.3	(713)	22.2	(507)	19.5	(487)
Missing	0.7	(20)	0.9	(23)	0.7	(19)	0.6	(14)	0.2	(5)

Six hundred and fifty men with PC were identified. Among 307 cancers that occurred from 1997 onward (when Gleason score was included in cancer registry data), 119 (38.8%) were high grade (Gleason score ≥ 8), 57 (18.6%) were intermediate grade (Gleason=7), 64 (20.8%) low grade (Gleason ≤ 6) and the remaining 67 (21.8%) were of unknown Gleason score. No convincing association was observed between cholesterol and overall hazard of PC, nor any consistent relationship within low and intermediate grade disease (table 3-2). However, the hazard increased consistently from the lowest to the second highest quintile of cholesterol among high grade disease (Gleason score ≥ 8) (table 3-2). On further exploration, a relationship was observed between cholesterol and high grade disease (table 3-3). After adjustment for BMI, smoking and height, a progressive increase in risk of high grade prostate remained between the lowest and second highest quintiles of cholesterol. This is more clearly shown in figure 3-1, in which the smoothed hazard of the most aggressive PCs (Gleason score ≥ 8) increased with increasing cholesterol and then declined. We also noted a progressive increase in risk of all PCs with increasing height (table 3-3).

As no significant association was observed between the highest quintile of cholesterol and risk of high grade disease, I combined the last two quintiles to further investigate the association. I observed significantly higher risk (HR 1.88, 95 CI 1.08-3.27, p-value 0.03) of developing high grade disease among men in the highest cholesterol category (combination of 4th and 5th quintile).

Furthermore, I also investigated the association between cholesterol and the risk of high grade disease using the clinical cut points of desirable, borderline high and high cholesterol groups. Men in the high cholesterol group (≥ 6.21 mmols/l) had significantly increased risk of developing high grade disease (1.75, 95% CI 1.03-2.97, p value 0.036) compared with desirable cholesterol group (<5.1 mmols/l) after adjustment for BMI, smoking and socio-economic status.

I further stratified the analysis based on BMI. The association between cholesterol level and high grade PC differed by BMI, however, no clear relationship emerged when using the desirable, overweight and obese categories, due to smaller number of aggressive PC cases in two highest cholesterol quintiles of obese group (n=7), so analysis was then stratified based on the median BMI of the sample. There was no evidence of an association

between cholesterol level and risk of high grade disease in men with BMIs lower than 25.3. However, among men with high BMI (≥ 25.3 , median of the sample), those in the second highest cholesterol quintile were significantly more likely to develop high grade disease (HR 9.98, 95% CI 2.33-42.78, p value 0.002) after adjustments for socio-economic status and smoking status.

Both in univariate and multivariate models, the relationship between other risk factors including social class, BMI and smoking status with overall and grade specific PC incidence remained inconclusive. These analysis were also repeated using the clinical, cardiovascular cut offs for cholesterol level, however the results remain consistent. Additionally, these analyses were also carried out after excluding men who had BMI less than 18.5 and those who had diabetes mellitus, but no differences in results were observed after these exclusions.

Table 3-2: Unadjusted hazard ratios and 95% CI for overall and Gleason-specific prostate cancer by cholesterol quintiles among Midspan subjects who survived until 1st January 1997. N=6486.

<i>Cholesterol (mmol/L) quintiles</i>	All Prostate cancer			Gleason < 7			Gleason 7			Gleason ≥8			Unknown	
	(n)	Hazard Ratio (95%CI)		(n)	Hazard Ratio (95%CI)		(n)	Hazard Ratio (95%CI)		(n)	Hazard Ratio (95%CI)		[114]	(n)
< 5.05	1,384	1	24.6	(15)	1	21.3	(13)	1	15	(17)	1	26.2	(16)	1
5.06 – <5.57	1,308 (51)	0.87 (0.60, 1.26)	17.6	(9)	0.62 (0.27, 1.41)	13.7	(7)	0.54 (0.22, 1.36)	9	(19)	1.18 (0.61, 2.27)	31.4	(16)	1.04 (0.52, 2.09)
5.58 – <6.09	1,425 (65)	1.03 (0.72, 1.46)	26.2	(17)	1.10 (0.56, 2.27)	12.3	(8)	0.59 (0.24, 1.42)	17	(30)	1.7 (0.93, 3.07)	15.4	(10)	0.59 (0.27, 1.31)
6.1 – < 6.69	1,159 (71)	1.36 (0.97, 1.92)	16.9	(12)	0.96 (0.45, 2.05)	18.3	(13)	1.14 (0.53, 2.47)	12	(33)	2.28 (1.27, 4.10)	18.3	(13)	0.95 (0.46, 1.98)
≥6.7	1,210 (59)	1.09 (0.76, 1.57)	18.6	(11)	0.83 (0.38, 1.81)	27.1	(16)	1.35 (0.65, 2.81)	11	(20)	1.34 (0.70, 2.57)	20.3	(12)	0.85 (0.40, 1.80)

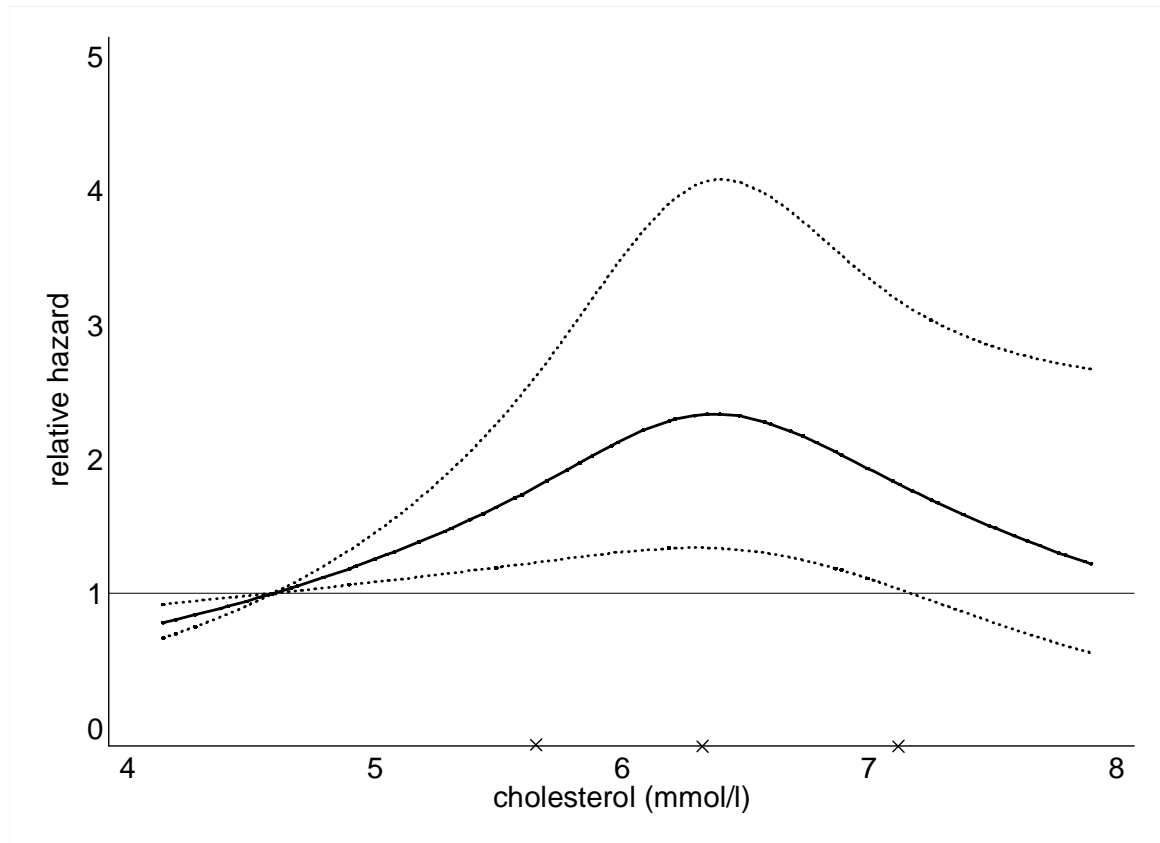
Hazard ratios and 95% CIs were obtained by using age as time-scale.

Table 3-3: Multivariate hazard ratios (HR) for all prostate cancers and those with Gleason grade ≥ 8 by cholesterol quintiles.

	All Prostate Cancers			Prostate cancers Gleason ≥ 8		
	Baseline Sample			From 1st January 1997		
	%	n	Hazard Ratio (95% CI)	%	n	Hazard Ratio (95% CI)
<i>Cholesterol (mmol/L) quintiles</i>						
< 5.05	5.1	(138)	1	1.2	(17)	1
5.06 – <5.57	4.7	(121)	0.89 (0.70, 1.14)	1.5	(19)	1.18 (0.62, 2.28)
5.58 – <6.09	5.1	(145)	0.95 (0.75, 1.21)	2.1	(30)	1.72 (0.95, 3.13)
6.1 – < 6.69	5.5	(125)	1.01 (0.79, 1.29)	2.8	(33)	2.34 (1.30, 4.23)
≥ 6.7	4.8	(121)	0.95 (0.74, 1.22)	1.7	(20)	1.40 (0.73, 2.71)
<i>BMI (kg m⁻²)</i>						
<25 (Under & Desirable weight)	4.8	(279)	1	2.1	(61)	1
25 – <30 (Overweight)	5.3	(320)	1.02 (0.86, 1.20)	1.5	(47)	0.69 (0.47, 1.02)
≥ 30 (Obese)	4.6	(51)	1.03 (0.77, 1.40)	2.3	(11)	1.18 (0.62, 2.27)
<i>Smoking</i>						
Never smoker	6.6	(149)	1	2.1	(31)	1
Smoker	3.9	(294)	0.90 (0.73, 1.09)	1.6	(52)	0.92 (0.59, 1.45)
Ex-smoker	6.6	(207)	1.03 (0.77, 1.40)	2.1	(36)	1.06 (0.65, 1.72)
<i>Social Class</i>						
I&II	5.8	(190)	1	1.9	(38)	1
IIIN	5.6	(108)	1.10 (0.87, 1.40)	2.2	(22)	1.21 (0.71, 2.05)
IIIM	4.7	(217)	1.03 (0.85, 1.26)	1.6	(33)	0.95 (0.59, 1.53)
IV&V	4.2	(135)	0.91 (0.73, 1.14)	1.9	(26)	1.15 (0.69, 1.92)
<i>Height (cm)</i>						
≤ 165.1	4.9	(120)	1	1.8	(17)	1
165.2-170	4.7	(126)	1.05 (0.82, 1.35)	1.8	(23)	1.27 (0.68, 2.37)
170.1-172.72	4.2	(121)	1.11 (0.86, 1.43)	1.4	(22)	1.54 (0.61, 2.19)
172.73-177.8	7.5	(165)	1.27 (1.01, 1.61)	3.2	(36)	1.69 (0.94, 3.05)
≥ 177.9	4.3	(118)	1.35 (1.04, 1.75)	1.3	(21)	1.32 (0.68, 2.55)

Multivariate hazard ratios and 95% CIs were obtained by using age as time-scale; all covariates were included in the model except height. Estimates for height were obtained by replacing the BMI with height.

Figure 3-1: Functional form of the association between cholesterol and high grade prostate cancer (Gleason 8-10)



Relative hazard estimated in a Cox proportional hazards model using age as the time axis. The function was fitted using restricted cubic splines with three knots (X). The function was standardized such that the HR was 1 at the mean cholesterol level of the lowest quintile. Dotted lines indicate the 95% confidence intervals.

3.5 Discussion

3.5.1 Findings of present analysis and potential explanations

I found that plasma cholesterol was positively associated with increased risk of aggressive PC but not with overall risk of developing the disease in this population-based prospective cohort study. Our findings are consistent with other reports on US populations ((Mondul *et al.*, 2010;Platz *et al.*, 2008;Platz *et al.*, 2009). The underlying mechanism by which cholesterol and prostate carcinogenesis may be linked remains unclear. Similarly, data from the Swedish Apolipoprotein Mortality Risk (Van *et al.*, 2010) study reported no evidence of a relationship between hypercholesterolemia and overall PC risk (Van *et al.*, 2010). However, a large study of male Finnish smokers reported a positive association between increasing total cholesterol level and overall risk of PC particularly advanced stage PC (Mondul *et al.*, 2011). The association further strengthened when they restricted the analysis to the cases diagnosed after 10 years from the baseline. However, this study did not find any association between aggressive disease, which may be because Gleason score was only available for 25% of the PC patients (Mondul *et al.*, 2011). Several underlying mechanisms by which cholesterol and prostate carcinogenesis may be linked have been proposed. PC cells tend to over accumulate cholesterol in their cell membrane, forming large lipid rafts which in the cancer cells may facilitate pro-carcinogenic cell signalling (Freeman and Solomon, 2004;Hager *et al.*, 2006;Mondul *et al.*, 2011). Moreover, several other pathways which are considered vital in carcinogenesis, such as sonic hedgehog and Akt pathways, are also cholesterol sensitive (Oh *et al.*, 2007;Zhuang *et al.*, 2002). Thus, having a lower cholesterol level may inhibit these pro-carcinogenic activities in the prostate cells.

Generally, an association has been reported between low cholesterol and increased risk of many cancer types and their associated mortality (Hiatt and Fireman, 1986;Knekt *et al.*, 1988;Davey Smith *et al.*, 1992) which has been ascribed to reverse causality; that is, early undiagnosed cancers lead to behavioural and physiological changes that reduce plasma cholesterol. The longer period between baseline cholesterol assay and diagnosis in our study (about 21 years for grade-specific analyses) compared to others suggests that

reverse causality is unlikely to have been responsible for the observed association. Moreover, any such effect would have been expected to attenuate rather than exaggerate the association.

In this analysis a significant relationship was observed between height and overall risk of PC, while no association with the risk of aggressive disease. Although the pattern of result showed increasing risk of developing high grade with increasing height, results were not significant, possibly due to smaller sample of aggressive PCs in this cohort. Previous evidence suggests that increasing height is associated with a modest increase in the risk of overall PC, with a stronger effect on aggressive PC incidence (Farwell *et al.*, 2011; Ahn *et al.*, 2009; Zuccolo *et al.*, 2008; Sequoia *et al.*, 2006). The findings that height may be linked with PC points toward the early childhood experiences and environmental factors which could lead to the progression of tumours with a worse prognosis. Mechanisms that could underlie the height and its link with PC still need to be studied. However, the dietary programming (particularly in early childhood) of the Insulin like growth factor-1 (IGF-1) plays an important role in the regulation of growth and height in particular (Mucci *et al.*, 2001). There is some evidence also suggest that IGF-1 is linked with the PC, so the height observation of this analysis might be explained by the variation in the level of IGF-1 (Key, 2011).

The mean age at PC diagnosis is high and a large proportion of men are likely to die before diagnosis. The risk estimates I present might therefore have been affected by differential competing mortality risks. However, Cancer Registry data include Death Certificate Only diagnoses - and may have included, PCs detected at post-mortem - that will attenuate such survival biases. The proportion of men who develop PC is higher among those who do not smoke, have a desirable BMI and are taller. The higher proportion of PC among these men results from those factors which confer a survival advantage. They live longer and therefore experience a longer risk time. However, the observation that height is associated with PC does raise the question whether some of those characteristics which promote longevity, are also associated with an increased risk of PC or whether such associations spuriously result from the influence of competing risk. If competing risks influence our data then selection bias could

be large. Cholesterol, height and obesity are related to mortality from cardiovascular disease (Lawlor *et al.*, 2006; Neaton *et al.*, 1984; Strandberg, 1997; Turley *et al.*, 2006) and early death from cardiovascular disease may be an important consideration. One possible scenario is that early cardiovascular disease mortality exhausts the pool of those men who would otherwise be susceptible to PC in later life, consequently systematic selection of more resilient individual may take place (men with low risk of PC but with high levels of traditional cardiovascular risk factors). This potentially could explain the positive association between height and incident PC, but would fail to explain the association between cholesterol and aggressive PC which I report.

The potential clinical implications of our findings are that increasing obesity and associated dyslipidemia may have been responsible for the increasing incidence of PC and that modifying cholesterol may reduce incidence of more aggressive disease. In the present analysis, no association was observed between overall incidence and grade specific risk of PC in relation to BMI. Evidence that obesity is linked with PC risk is generally divergent. Studies on obesity are significantly different from each other, in size, baseline characteristics of cohorts and follow-up times (Gong *et al.*, 2006; Kaaks and Stattin, 2010; Porter and Stanford, 2005; Robinson *et al.*, 2005). It has been suggested that body size can influence the sex hormone profile in the early life of individuals and that interference in sex hormones can play a significant role in development of aggressive PC in later age (Robinson *et al.*, 2005). However, studies mainly focusing the obesity failed to account for the dietary intake of individuals, which has a strong association with body size as well as hormone profiles.

The evidence that statins may reduce PC incidence remains equivocal. Two meta-analyses and a subsequent cohort study did not find any relationship between statin use and PC (Boudreau *et al.*, 2008; Browning and Martin, 2007; Dale *et al.*, 2006). However, Platz and Jacobs found associations between statin use and lower risk of advanced PC only and suggested that plausible biological mechanisms may exist, for example 3-hydroxy-3-methylglutaryl (HMG) coenzyme A reductase inhibition may reduce PC cell survival by interfering with membrane-associated signalling. Preliminary evidence suggests that prostatic inflammation stimulated by either viral infection, bacterial agent

or even because of the chemical damage to the prostatic tissue, is emerging primary aetiological agent in the development of prostatic tumours (Maitland and Collins, 2008). This hypothesis has been further supported by the evidence that the by-products of roasted meat (2-amin-1-methyl-6 phenylimidazo pyridine) were present in the prostate of a mouse model of disease and had the potential to stimulate the inflammatory and tumorigenic activity within the gland (Maitland and Collins, 2008). If inflammation is linked with the development of prostatic tumours, then the anti-inflammatory functions of statins might have some role in lower observed cancers among statin users. Nonetheless, in the absence of more consistent evidence on the effects of statins on PC, the most effective means of reducing incidence of the disease may therefore be through effective weight management.

3.5.2 Strength and weaknesses

This analysis is based on one of the largest population-based prospective studies in the UK and used cancer incidence data for the grade-specific analyses, rather than death records for cancer outcomes. Mortality data are a product of both incidence and case fatality, and do not allow risk factors to be individually differentiated. Furthermore, high cholesterol may increase the risk of death from other causes in PC patients and not necessarily be a causal factor for PC itself. Our study has larger numbers of incident cancers (n=650), longer follow-up and lower losses to follow-up (0.1%) compared with earlier studies (Mondul et al., 2010; Platz et al., 2008). However, our study has some weaknesses. The Midspan questionnaire lacked information on family history of PC, PSA testing and use of statins. The baseline data of this cohort was obtained at a time when all of these factors were not well established in relation to the prostatic cancer. I used plasma total cholesterol level because other measures of cholesterol, such as lipoprotein fractions (high and low density lipoproteins), were not available. PSA and disease stage data were not available which could be used to stratify the analyses based on localised and metastatic PC.

An important consideration is detection bias and whether some population subgroups are more likely to report their symptoms or have frequent medical examinations. There is some evidence that PC is socio-economically patterned

and more common among affluent individual, however in present analysis, social class was used as a measure of socio-economic circumstances and no significant association was observed between the social class and risk of PC. There can be multiple explanations for this. First, this analysis only includes 650 individuals of PC, so the number may be too small to detect any significant difference of risk across socio-economic groups and PC cases of this cohort might not be a true representative of all PCs diagnosed in Scotland. Second, social class was used as a measure of socio-economic circumstances, while the earlier analysis showed in incidence chapter 2 (page 98), used an area-based measure of deprivation, and this difference of measures might have some role in differential findings. Finally, there is a possibility that in real life there may be no association of socio-economic circumstances on overall risk of PC, but the socio-economic status may be just associated with the differential detection rates in sub groups of population.

Further consideration in addition to the socio-economic differences in the detection rate, is the participants who had higher level of plasma cholesterol might be in contact with their GP more frequently to control their hypercholesterolemia than others. So their chances of being diagnosed with PC might be simply higher due to greater utilisation of services.

3.5.3 Implications for public health

This current analysis showed that there is a relationship between cholesterol and aggressive PC risk. In chapter 2 (page 96), analyses showed that high-grade PC has differentially increased in the West of Scotland during recent periods. Taking both these findings together, the observation of increased high grade disease at the population level could be because of increases in metabolic risk factors associated with hypercholesterolaemia and obesity in Scotland. Given that modifiable risk factors are not known for incidence of PC, emerging evidence on hypercholesterolaemia and obesity may be important from a population perspective. Although further evidence is required on the role of obesity and hypercholesterolaemia, in the absence of more consistent evidence effective weight management may be the most useful tool to reduce the burden of aggressive PC.

3.5.4 Implications for future research

Confirmation of recent findings on cholesterol and PC incidence is required in future studies with additional information on PSA and disease stage. In this analysis, the number of men with aggressive PC was small (n=119) so the subgroup analysis may be an artefact due to small number of cases; further investigations on a larger sample may show more clear relationship. An important issue which needs to be considered in further research is to separate the factors which are associated with the detection of cancer rather than the true risk factors of PC. In relation to PC, identification of factors related to detection may be important as PSA testing can cause a diagnosis of cancer but it is not a true risk factor of PC. In the absence of more conclusive evidence on cholesterol and PC, temporal trends of grade and stage-specific incidence from other regions of UK and well developed countries may provide some clue about the role of increases in obesity on population level in incidence of PC.

4 Tea and coffee consumption and the risk of overall and grade-specific prostate cancer: a large prospective cohort study of Scottish men.

4.1 Chapter summary

Tea and coffee may be potentially modifiable and highly prevalent risk factors for the most common cancer in men, PC. However, associations between black tea consumption and PC in epidemiological studies have been inconsistent. Most evidence is limited to a small number of studies with small numbers of cases and short follow-up periods and without grade specific information. Similarly, evidence from large prospective studies and a recent meta-analysis on role of coffee on PC risk remained inconclusive. Coffee intake has been recently linked with reduced risk of aggressive PC incidence. Authors concluded that higher coffee consumption can not be recommended to prevent PC and further epidemiological evidence on the association is required before making any recommendations. I conducted a prospective cohort study of 6016 men who were enrolled in the Collaborative cohort study between 1970 and 1973 and followed up to 31st December 2007. We used Cox Proportional Hazards Models to investigate the association between tea and coffee consumption and overall as well as grade-specific risk of PC incidence.

Three hundred and eighteen men developed PC in up to 37 years' follow-up. I found a positive association between consumption of tea and overall risk of PC incidence ($p=0.02$). The association was greatest among men who drank ≥ 7 cups of tea per day (HR 1.50, 95% CI 1.06 to 2.12) compared with the baseline of 0-3 cups/day. However, I did not find any significant association between tea intake and low (Gleason < 7) or high grade (Gleason 8-10) PC incidence. Men with higher intake of tea are at greater risk of developing PC but there is no association with more aggressive disease. Higher coffee consumption (3 or more cups per day) was inversely associated with risk of high grade (HR 0.46, 95% CI 0.21 to 0.99) but not with overall risk of PC. This association remained significant after adjustment for age, Body Mass Index, smoking, social class, cholesterol level, systolic blood pressure tea intake and alcohol consumption.

4.2 Introduction

Tea and coffee are among the most popular beverages worldwide and have been investigated for their role in PC development. These beverages are also among the few potentially modifiable risk factors for PC but the epidemiological evidence is inconclusive and therefore no recommended guidelines are available for their consumption.

Patients may reduce their fluid intake to ameliorate symptoms of PC, such as polyuria and nocturia, but I could not identify any study that excluded diagnoses made soon after risk factor assessment to minimise apparent “reverse causality.” Also the evidence is very limited specifically with regard to the role of these beverages on the risk of high grade PC, which corresponds to clinically significant disease. A recently published review on comparisons between black tea and green tea in relation to PC also highlighted the need for further epidemiological evidence (Henning *et al.*, 2011), while a recently published study has highlighted the importance of grade-specific risk associated with coffee intake (Wilson *et al.*, 2011).

Therefore the purpose of this analysis was to assess the relationship between tea and coffee consumption with overall as well as grade-specific risk of developing PC among Scottish men in the Collaborative cohort study.

4.3 Material and methods

4.3.1 Cohort characteristics

The Collaborative cohort study was the second of the Midspan studies that began in the 1960s and 1970s in Scotland, UK. Their methods have been described in detail elsewhere (Hart *et al.*, 2005). The Collaborative study was conducted on employed men and women aged from 21 to 75 years from 27 workplaces in Glasgow, Clydebank and Grangemouth between 1970 and 1973 (Davey Smith G. *et al.*, 1998). The response rate was 70% for these workplaces for which response rates were available (87% of the sample).

Study protocols consisted of a self-administered questionnaire followed by a screening examination at a specially set-up clinic. Questions included demographic details, occupation, lifestyle habits including smoking, and health (Davey Smith G. *et al.*, 1998). Daily tea intake reported by the participants was categorised into four groups based on roughly equal number of participants in each group. Daily coffee intake reported by participants was divided into three groups. Weekly reported alcohol consumption was categorised by spirits, beer, and wine. This was converted to units of alcohol by taking one measure of spirits as 1 unit, 1 pint (0.6 litres) of beer as 2 units, and one bottle of wine as 6 units (Hart *et al.*, 1999). Four categories of alcohol consumption were formed (none, 1-10, 11-21, > 21 units of alcohol a week). As parts of the screening examination, measurements were made for height, weight and blood pressure.

A blood sample was obtained at baseline screening for the measurement of total circulating plasma cholesterol. Body mass index (BMI) was calculated from weight (in kg) divided by height (in metres) squared and categorised according to the World Health Organisation classification in which BMI < 18.50 is underweight, 18.50 to < 25 is the normal range, 25 to <30 is overweight and ≥ 30 is obese. I combined the underweight and normal BMI categories because the number of subjects was small in the underweight category and only one subject developed PC. Social class was derived from occupation according to the relevant version of the General Register Office Classification of Occupation (General Register Office, 1966) and graded into six categories:

I (professional), II (intermediate), III non-manual (skilled non-manual), III manual (skilled manual), IV (partly skilled) and V (unskilled) (General Register Office, 1966). Years of full time education was also used as a measure of socio-economic status. The Collaborative cohort study has information on age at leaving full time education. I subtracted five from the age at leaving full time education to calculate years in full time education, assuming that everyone started schooling at five years of age. Ex-smokers were defined as reporting giving up smoking at least a year before screening, otherwise they were defined as current smokers. Only the records for male participants were used for this study.

4.3.2 Follow-up

Follow-up for mortality was carried out by flagging Collaborative study participants with the National Health Service Central Register. Deaths were then notified to the study team on a monthly basis. Information on cancer registrations and hospital activity was obtained by linkage to the Scottish Morbidity Record (SMR) data and was complete from 1972 onwards (Hart *et al.*, 2010). Follow-up began on the date of screening to the date of cancer incidence, date of death, date of embarkation or the censor date of 31st December 2007, whichever came first.

4.3.3 Ethical approval

An application was submitted to Midspan Steering Committee to access the data of Midspan studies. Following the approval from Midspan Steering Committee, a request along with proposed analysis was submitted to Privacy Advisory Committee at ISD to use the linked data of Midspan with SMR06 and SMR01. The Privacy Advisory Committee of the Information Services Division of NHS Scotland gave permission for the linked data to be used in this study.

4.3.4 Outcome definitions

PC was defined as International Classification of Diseases (ICD) revision 9 code 185 and ICD-10 code C61. PC incidence was ascertained if it appeared in any of the records from cancer registration (SMR06), acute hospital record

(SMR01) or death record. Where a patient had PC recorded on more than one type of record, the earliest date was taken as time of first diagnosis. The Gleason grading system is a method used to distinguish the morphology of clinical PC to provide prognostic information. Data on Gleason score were available from the cancer registration data (SMR06). The Scottish Cancer Registry began recording Gleason score from 1st January 1997, thus the analysis of grade-specific associations between tea intake and PC was restricted to follow-up of the surviving cohort as of 1st January 1997.

4.3.5 Statistical analysis

Cox proportional hazards models were used to estimate hazard ratios (HRs) for PC incidence from screening, and for specific histological grade from 1st January 1997. Separate models were run for each Gleason category and men with PC and other Gleason scores were censored at their date of diagnosis. All analyses were conducted using STATA (stcox in STATA v11 StataCorp, College Station, TX, USA). On univariate analysis, variables which had a p-value less than 0.2 or those which are well known confounders in such risk analysis were included in multivariate models. We included smoking status, age, BMI, alcohol intake, coffee consumption, cholesterol level, systolic blood pressure, years of full time education and social class in the multivariate models. Height appeared as a significant factor in previous analysis so height was included in multivariate model when BMI was not in the model as BMI consists of height and weight.

There were missing data for some covariates: 11 in social class; 41 in cholesterol level; 1 in height and weight; 1 in smoking status; and 9 individuals' age at leaving full time education. Total missing data for all covariates was less than 0.01% which did not change any of the associations when I ran the analysis both including those observations after imputations and excluding these individuals. I presented the final results after imputation in which missing information on continuous variables was replaced by the sample mean while for categorical variables missing data were replaced by modal values.

The lowest category was used as referent for the tea and coffee intake covariates and all other categorical covariates. Adherence to the proportional hazards assumption was investigated by plotting smoothed Schoenfeld residuals against time; no violations of the assumption were identified. All statistical tests were two tailed and statistical significance was taken as $p < 0.05$. In total, data for 6022 men were available for analysis, five study participants were lost to follow-up and one individual's tea intake information was missing so they were excluded from the analysis.

4.4 Results

Our final sample comprised 6,016 men followed-up for a total of 155,338 person-years. The median follow-up period was 28 years and maximum 37 years. The median age was 48 years at the time of screening (range, 21-75 years). The mean time between screening and PC diagnosis was 25.8 (SD 10.58) years.

Baseline and outcome characteristics for the study are shown in table 4-1. Three hundred and eighteen men with PC were identified. Individuals who consumed seven or more cups of tea per day were older, more likely to be smokers, non-alcohol drinkers, non-coffee drinkers and had normal BMIs compared with men drinking 0-3 cups per day. However, individuals who drank 7 or more cups of tea per day were less likely to drink alcohol (χ^2 , $p \leq 0.001$). Individuals of middle social class and who had 7-9 years of education were more likely to drink 7 or more cups of tea per day. Individuals who had normal BMI, higher social class and smokers were more likely to consume three or more cups of coffee per day while those taking high amount of alcohol were more likely to be low or non-coffee drinkers (table 4-1).

Table 4-1: Baseline characteristics of male participants of Collaborative Cohort study at screening and prostate cancer outcome. N= 6,016.

	Categories of cups of tea/day								P value*
	0--3		4--5		6		≥7		
Sample Size	1,631		1,770		1,188		1,427		
Person-years of follow-up	43,852		45,744		30,170		35,591		
Men with prostate cancers %(n)	4.6	(75)	5.1	(90)	5.1	(61)	6.4	(92)	0.13
Mean Age (s.d.)	46.4	(7.6)	47.8	(7.2)	48.2	(7.2)	48.3	(6.8)	<0.001
Mean Height (s.d.)	173.6	(7.1)	172.7	(7.1)	172.7	(7.2)	172.6	(6.8)	0.31
Mean Weight (s.d.)	76.8	(10.5)	75.1	(10.5)	75.1	(11.1)	73.9	(10.2)	0.02
Height (cm), %(n)									
≤167.6	24.3	(397)	29.2	(516)	29.0	(344)	29.1	(415)	0.002
167.7-170.2	12.5	(204)	13.7	(243)	12.5	(148)	12.8	(183)	
170.2-175.3	26.3	(429)	26.0	(461)	27.9	(332)	28.7	(409)	
175.3-180.4	24.3	(397)	20.3	(359)	20.0	(238)	20.5	(292)	
≥180.5	12.5	(204)	10.8	(191)	10.6	(126)	9.0	(128)	
Mean BMI (s.d.)	25.5	(3.1)	25.1	(3.0)	25.2	(3.2)	24.8	(3.0)	0.24
BMI (kg m-2), %(n)									
<25 (Under & Desirable)	44.8	(730)	50.6	(895)	47.6	(566)	54.4	(776)	<0.001
25 – <30 (Overweight)	48.3	(788)	43.7	(773)	46.3	(550)	40.6	(579)	
≥30 (Obese)	6.9	(113)	5.8	(102)	6.1	(72)	5.0	(72)	
Alcohol intake (units/week), %(n)									
non drinkers	24.2	(394)	29.7	(525)	36.4	(432)	37.9	(541)	<0.001
1--10	30.7	(500)	31.6	(560)	26.4	(313)	25.7	(366)	
11--21	22.0	(358)	19.8	(351)	20.2	(240)	18.5	(264)	
> 21	23.2	(379)	18.9	(334)	17.1	(203)	17.9	(256)	
Cups of coffee/day									
0	16.8	(274)	38.8	(687)	58.9	(700)	67.9	(966)	<0.001
1--2	34.2	(558)	43.3	(767)	31.7	(377)	25.0	(357)	
≥3	49.0	(799)	17.9	(316)	9.3	(111)	7.3	(104)	
Smoking, %(n)									
Never smoker	19.6	(320)	19.2	(340)	17.0	(202)	16.3	(232)	<0.001
Smoker	55.5	(906)	55.3	(978)	60.1	(714)	62.6	(894)	
Ex-smoker	24.8	(405)	25.5	(452)	22.9	(272)	21.1	(301)	
Social Class, %(n)									
I&II	44.5	(725)	32.6	(577)	27.6	(328)	26.4	(377)	<0.001
IIIN	15.9	(259)	18.0	(318)	18.8	(223)	22.0	(314)	
IIIM	23.3	(380)	29.2	(516)	29.9	(355)	29.8	(425)	
IV&V	16.4	(267)	20.3	(359)	23.7	(282)	21.8	(311)	
Years of full time education									
7--9	38.7	(634)	50.3	(890)	54.0	(642)	55.0	(786)	<0.001
10	17.3	(282)	20.2	(357)	19.1	(227)	20.8	(296)	
11--34	44.0	(715)	29.6	(523)	26.9	(379)	24.2	(345)	

* P value for categorical variables calculated by chi-square test and for continuous variables by linear regression.

I found a convincing association between tea consumption and overall hazard of PC (table 4-2). The hazard increased consistently from the lowest category of tea intake (0-3 cups/day) to the highest category (≥ 7 cups/day).

Individuals taking seven or more cups of tea per day were 65% more likely to develop PC (HR = 1.65, 95 % CI 1.22-2.24, p value = 0.001) compared with those taking 0-3 cups per day. This association remained but was attenuated after adjusting for the effects of age, height, BMI, cholesterol level, systolic blood pressure, smoking status, alcohol intake, coffee consumption, years of full time education and social class. When I included tea as a continuous variable in multivariate analysis the association remained consistent (HR = 1.05, 95% CI 1.01-1.09, p value=0.02) (table 4-2). I also conducted further analyses excluding individuals diagnosed with PC in the first 10 years of screening (n=14), and the association between tea consumption of ≥ 7 cups/day and increased PC risk remained significant (HR = 1.48, 95% CI 1.08-2.04) after accounting for the effects of co-variates.

Among 186 cancers that occurred from 1997 onward (when Gleason score was included in the Scottish Cancer Registry data), 70 (37.6%) were high grade (Gleason score ≥ 8), 38 (20.4%) were intermediate grade (Gleason=7), 41 (22.0%) low grade (Gleason ≤ 6) and the remaining 37 (19.9%) were of unknown Gleason score. I found no convincing evidence of relationship between tea consumption and hazard of grade-specific PC (table 4-3). In univariate analysis, individuals taking high amount of tea were significantly more likely to have high grade PC but this association was no longer significant (HR = 1.44, 95% CI 0.66-3.14, p value 0.36) when accounted for the effects of other covariates.

Table 4-2: Univariate and multivariate hazard ratios (HR) for all prostate cancers by tea categories.

	Total	Univariate analysis				Multivariate analysis *			
		n	Hazard Ratio (95% CI)		p value	Hazard Ratio (95% CI)		p value	
<i>Cups of tea/day</i>									
0-3	1,631	(75)	1			1			
4-5	1,770	(90)	1.21	(0.89, 1.64)	0.23	1.11	(0.79, 1.48)	0.61	
6	1,188	(61)	1.26	(0.90, 1.76)	0.19	1.10	(0.79, 1.57)	0.55	
≥7	1,427	(92)	1.65	(1.22, 2.24)	0.001	1.50	(1.06, 2.12)	0.02	
<i>Cups of tea (continuous)</i>	6,016	(335)	1.06	(1.02, 1.09)	0.002	1.05	(1.01, 1.09)	0.02	
<i>Cups of coffee/day</i>									
0	2,627	(139)	1			1			
1-2	2,059	(114)	0.92	(0.71, 1.17)	0.48	0.94	(0.72, 1.23)	0.66	
≥3	1,330	(65)	0.78	(0.58, 1.05)	0.10	0.91	(0.64, 1.29)	0.59	
<i>Cholesterol level</i>	6,016	(318)	1.06	(0.95, 1.18)	0.29	1.01	(0.90, 1.13)	0.87	
<i>Systolic blood pressure</i>	6,016	(318)	1.00	(0.99, 1.01)	0.14	0.99	(0.99, 1.01)	0.54	
<i>Height (cm)</i>									
≤167.6	1,672	(75)	1			1			
167.7-170.2	778	(31)	0.74	(0.49, 1.12)	0.16	0.79	(0.52, 1.20)	0.27	
170.2-175.3	1,631	(98)	1.11	(0.82, 1.49)	0.51	1.24	(0.91, 1.68)	0.17	
175.3-180.4	1,286	(78)	1.08	(0.79, 1.48)	0.62	1.25	(0.90, 1.74)	0.18	
≥180.5	649	(36)	0.88	(0.59, 1.32)	0.55	1.11	(0.73, 1.68)	0.62	
<i>BMI (kg m⁻²)</i>									
<25 (Under & Desirable)	2,967	(152)	1			1			
25 - <30 (Overweight)	269	(148)	1.12	(0.90, 1.41)	0.31	1.12	(0.89, 1.42)	0.32	
≥30 (Obese)	359	(18)	1.35	(0.83, 2.19)	0.23	1.31	(0.79, 2.16)	0.29	
<i>Alcohol intake (units/week)</i>									
non drinkers	1,892	(115)	1			1			
1-10	1,739	(102)	0.89	(0.68, 1.16)	0.39	0.98	(0.75, 1.29)	0.89	
11-21	1,213	(52)	0.72	(0.52, 1.00)	0.05	0.88	(0.63, 1.23)	0.45	
> 21	1,172	(49)	0.80	(0.57, 1.12)	0.20	0.99	(0.70, 1.41)	0.97	
<i>Smoking</i>									
Never smoker	1,094	(68)	1			1			
Smoker	3,492	(136)	0.95	(0.71, 1.27)	0.71	0.94	(0.69, 1.27)	0.69	
Ex-smoker	1,430	(114)	1.68	(1.25, 2.73)	0.001	1.43	(1.05, 1.94)	0.02	
<i>Social Class</i>									
I&II	2,007	(122)	1			1			
IIIN	1,219	(53)	1.00	(0.72, 1.38)	0.99	1.15	(0.77, 1.72)	0.49	
IIIM	1,114	(68)	1.07	(0.80, 1.44)	0.65	1.23	(0.89, 1.69)	0.21	
IV&V	1,676	(75)	0.96	(0.72, 1.28)	0.80	1.17	(0.82, 1.68)	0.38	
<i>Years of full time education</i>									
7-9	2,952	(130)	1			1			
10	1,162	(68)	0.95	(0.71, 1.27)	0.73	1.34	(0.97, 1.85)	0.07	
11-34	1,902	(120)	1.01	(0.79, 1.30)	0.91	1.34	(0.98, 1.85)	0.07	

*Multivariate model included age and all co-variates presented in the table.

Estimates for height were obtained by replacing the BMI with height.

Table 4-3: Univariate and multivariate analyses for overall and Gleason-specific prostate cancer by tea consumption categories among the Collaborative cohort study subjects who survived until 1st January 1997. N= 3527.

<i>Cups of tea/day</i>	All Prostate cancer				Gleason < 7				Gleason 7				Gleason ≥8				Unknown	
	n	Hazard Ratio (95%CI) ^a		% (n)	Hazard Ratio (95%CI) ^a		% (n)	Hazard Ratio (95%CI) ^a		% (n)	Hazard Ratio (95%CI) ^a		% (n)	Hazard Ratio (95%CI) ^a				
0--3	1,020 (46)	1		26.1 (12)	1		21.7 (10)	1		28.3 (13)	1		23.9 (11)	1				
4--5	1,051 (60)	1.34	(0.91, 1.97)	20.0 (12)	1.02	(0.46, 2.27)	18.3 (11)	1.13	(0.48, 2.67)	40.0 (24)	1.89	(0.96, 3.73)	21.6 (13)	1.19	(0.40, 3.54)			
6	677 (31)	1.10	(0.69, 1.71)	29.0 (9)	1.20	(0.51, 2.85)	22.6 (7)	1.14	(0.43, 2.99)	38.7 (12)	1.49	(0.68, 3.27)	9.6 (3)	0.26	(0.03, 2.20)			
≥7	779 (49)	1.53	(1.02, 2.28)	16.3 (8)	0.95	(0.39, 2.31)	20.4 (10)	1.46	(0.61, 3.51)	42.9 (21)	2.32	(1.16, 4.64)	20.4 (10)	0.93	(0.26, 3.23)			
		Hazard Ratio (95%CI) ^b			Hazard Ratio (95%CI) ^b			Hazard Ratio (95%CI) ^b			Hazard Ratio (95%CI) ^b			Hazard Ratio (95%CI) ^b				
0--3	1,020 (46)	1		26.1 (12)	1		21.7 (10)	1		28.3 (13)	1		23.9 (11)	1				
4--5	1,051 (60)	1.20	(0.80, 1.79)	20.0 (12)	0.81	(0.35, 1.88)	18.3 (11)	1.28	(0.52, 3.13)	40.0 (24)	1.52	(0.75, 3.09)	21.6 (13)	1.41	(0.44, 4.54)			
6	677 (31)	0.90	(0.55, 1.47)	29.0 (9)	0.90	(0.35, 2.32)	22.6 (7)	1.51	(0.53, 4.30)	38.7 (12)	0.97	(0.42, 2.28)	9.6 (3)	0.39	(0.04, 3.51)			
≥7	779 (49)	1.24	(0.79, 1.96)	16.3 (8)	0.70	(0.26, 1.89)	20.4 (10)	1.97	(0.73, 5.37)	42.9 (21)	1.44	(0.66, 3.14)	20.4 (10)	1.27	(0.29, 5.50)			

a = unadjusted hazard ratio, b = hazard ratio estimates adjusted for age at screening, alcohol intake, coffee consumption, smoking status, BMI, cholesterol level, systolic blood pressure, social class and year of full time education

Table 4-4: Univariate and multivariate analyses for overall and Gleason-specific prostate cancer by coffee consumption categories among the Collaborative cohort study subjects who survived until 1st January 1997. N= 3527.

<i>Cups of coffee/day</i>	All Prostate cancer				Gleason < 7			Gleason = 7			Gleason 8-10			Unknown Gleason		
	n	Hazard Ratio (95%CI) ^a		% (n)	Hazard Ratio (95%CI) ^a		(n)	Hazard Ratio (95%CI) ^a		(n)	Hazard Ratio (95%CI) ^a		(n)	Hazard Ratio (95%CI) ^a		
0	1,441	(81)	1	41.5	(17)	1	(12)	1	(39)	1	(13)	1	(13)	1	(13)	
1-2	1,252	(67)	0.89 (0.65, 1.24)	41.5	(17)	1.09 (0.56, 2.14)	(14)	1.25 (0.58, 2.71)	(20)	0.55 (0.32, 0.95)	(16)	1.53 (0.49, 4.83)	(16)	1.53 (0.49, 4.83)	(16)	
≥ 3	834	(38)	0.75 (0.51, 1.11)	17.1	(7)	0.67 (0.28, 1.61)	(12)	1.59 (0.71, 3.53)	(11)	0.45 (0.23, 0.88)	(8)	1.96 (0.60, 6.41)	(8)	1.96 (0.60, 6.41)	(8)	
			Hazard Ratio (95%CI) ^b			Hazard Ratio (95%CI) ^b			Hazard Ratio (95%CI) ^b			Hazard Ratio (95%CI) ^b			Hazard Ratio (95%CI) ^b	
0	1,441	(81)	1	41.5	(17)	1	(12)	1	(39)	1	(13)	1	(13)	1	(13)	
1-2	1,252	(67)	0.84 (0.60, 1.21)	41.5	(17)	1.04 (0.51, 2.17)	(14)	1.23 (0.53, 2.84)	(20)	0.53 (0.29, 0.96)	(16)	1.17 (0.52, 2.64)	(16)	1.17 (0.52, 2.64)	(16)	
≥ 3	834	(38)	0.74 (0.47, 1.16)	17.1	(7)	0.54 (0.19, 1.57)	(12)	1.79 (0.69, 4.62)	(11)	0.46 (0.21, 0.99)	(8)	0.88 (0.31, 2.48)	(8)	0.88 (0.31, 2.48)	(8)	

a = crude hazard ratio, b = hazard ratio estimates adjusted for age at screening, tea consumption, alcohol intake, smoking status, BMI, cholesterol level, systolic blood pressure and social class

No convincing association was found between coffee and overall hazard of PC (table 4-2). We also conducted further analyses excluding individuals diagnosed with PC in the first 10 years of screening (n=14), after multivariate adjustments the inverse association between coffee consumption of ≥ 3 cups/day and reduced PC risk slightly changed (HR = 0.80, 95% CI 0.59-1.10, p value 0.18) although remained non-significant.

On further grade-specific analysis, no association was observed between coffee intake and low grade as well as intermediate grade PC. However, the hazard reduced significantly from the lowest to the highest category of coffee intake (HR 0.46, 95% CI 0.22-0.99) among high grade disease (Gleason score ≥ 8) (table 4-4). These associations did not alter after adjustment for age, height, BMI, smoking, social class, tea consumption, alcohol intake, plasma cholesterol and systolic blood pressure and a progressive reduction in risk of high grade PC remained between the lowest and other two categories of coffee intake (table 4-4). However, the results were borderline significant which could be due to smaller number of cases (n=11) in the highest category of coffee drinkers. We further investigated this association by combining the coffee categories as coffee drinkers and non-drinkers. Men who consumed any amount of coffee had significantly reduced risk of aggressive PC (HR 0.51, 95% CI 0.29-0.87, p = 0.01) compared with non-coffee drinkers after adjustments for age, BMI, smoking, social class, tea consumption, alcohol intake, plasma cholesterol and systolic blood pressure.

4.5 Discussion

4.5.1 Findings and their potential explanations

In this large prospective study, a strong positive association was observed between tea consumption and overall risk of PC, those who drank the most tea, 7 or more cups per day, had 65% higher risk than those taking none to 3 cups of tea per day. But no significant relationship was observed with either low grade (Gleason < 7), intermediate grade (Gleason = 7) or high grade disease (Gleason 8-10). This could be because of the small number of PC cases in these categories. Furthermore, coffee intake was associated with reduced risk of high grade PC but not with overall risk of developing the disease in this population-based prospective cohort study. These findings did not alter after adjustments for co-variates.

Many in-vitro and in-vivo studies have demonstrated the role of anti-carcinogenic activity of tea extracts and polyphenols for many cancers including lung, oral cavity oesophagus, small intestine, colon, bladder, liver, pancreas, prostate and mammary glands (Peng *et al.*, 2010; Sukhthankar *et al.*, 2008; Yang *et al.*, 2011). However, epidemiological evidence on the role of tea remains equivocal for all cancers including prostate (Lee *et al.*, 2009; Sun *et al.*, 2006; Tang *et al.*, 2009). This discrepancy might be due to several factors, including lifestyle, correlation between animal models and human and the differences in metabolism among individuals.

The positive association of tea consumption and increased risk of PC that I observed was consistent with one recent study (Sharpe and Siemiatycki, 2002) and differed from previous studies which showed either no association (Ellison, 2000; La *et al.*, 1992) or a protective effect against PC (Jain *et al.*, 1998; Severson *et al.*, 1989). Data on type of tea, socio-economic circumstances and lifestyle factors were limited in these studies. Inconsistent results between these studies which were conducted in different countries might be due to confounding effects of socio-economic and lifestyle factors associated with the tea drinkers. Furthermore, either these studies were retrospective in design (Ellison, 2000; Jain *et al.*, 1998) or they had short follow-ups and small number of cases with PC (Heilbrun *et al.*, 1986; Kinlen *et al.*, 1988).

Several biological mechanisms have been proposed which may explain the inverse association between high coffee consumption and aggressive PC. Coffee consumption can lower the insulin-like growth factor-1 (IGF-1) (Key, 2011) which is associated with increased incidence of PC particularly high grade and advanced stage disease (Mucci *et al.*, 2001; Roddam *et al.*, 2008). Additionally, coffee is considered as a major source of antioxidants and many observational studies suggested that coffee consumption lowers the inflammation (Cardenas *et al.*, 2011; Kempf *et al.*, 2010). There is growing evidence which suggests that inflammation plays a vital role in the development of PC through the generation of proliferative inflammatory lesions (Maitland and Collins, 2008). Therefore, higher consumption of coffee may have a protective role in aggressive PC by reducing the inflammatory activity in tumour.

4.5.1.1 True or artefactual effects

This positive association of tea with the risk of PC was consistent with increased number of cups per day. Heavy tea drinkers were more likely to have a normal BMI, be non-drinkers and have desirable cholesterol levels. These associations raise the question of whether characteristics that promote longevity are truly causally associated with an increased risk of PC or whether they reduce deaths from competing risks and thereby increase risk time for the development of PC.

It might also be hypothesised that reverse causality might explain the protective effect of tea or coffee on PC reported elsewhere. That is, men with undiagnosed PC may reduce their fluid intake, including tea and coffee, to reduce symptoms of polyuria. Thus, PC would be less frequent among men who drank more tea or coffee. However, PC often produces no urinary symptoms because most of the tumours arise in the peripheral zone of the prostate gland (Simmons *et al.*, 2011). In addition, I conducted analyses to assess possible reverse causation by excluding individuals who were diagnosed in the first 10 years of screening, but it did not significantly alter the positive (harmful) association between tea and PC risk and inverse association between coffee and PC.

Another important consideration for epidemiological studies is, in cultures where coffee, tea, alcohol intake constitute a major proportion of daily fluid intake the mutual confounding effect of total fluid intake and tea/coffee consumption

might have significant impact on any observed effect. Further evidence from large prospective studies with careful investigation of effect modification and confounding might provide piece of evidence which would be of interest for biological studies.

An important consideration is the types of tea and coffee consumed among the participants of different studies. For example, green tea has been shown strong preventive effect compared to black tea both in animal and epidemiological studies (Henning *et al.*, 2011). Participants of the Collaborative cohort study probably drank black tea almost exclusively as it has been commonly used in the English speaking countries and the UK had the highest tea consumption in that era when the participants were screened for this study (Bokuchava and Skobeleva, 1980; Stocks, 1970). The brand of tea and coffee may influence its carcinogenicity, as the composition of these products is highly dependent on their processing, large variations in the flavanol and catechin and contents and their antioxidant capacity having been observed in different studies (Graf *et al.*, 2005; Henning *et al.*, 2003). The inconsistency between epidemiological studies might be explained by the differences of chemical contents of different tea and coffee brands.

During the 1970s, coffee was more frequently consumed by middle class individuals, whereas tea was consumed more by the working class population, its consumption being particularly associated with breaks during the day and with evening meals. I observed a strong pattern between tea intake and social class (table 4-1), however, I did not observe any association between social class and PC risk. I also used years of full time education as a measure of socio-economic status; this also did not alter the association of tea intake and PC risk.

4.5.2 Strengths and weaknesses

These findings are based on one of the largest prospective cohorts in the UK, with long follow-up, lower losses to follow-up, adjustment for other lifestyle habits and information on Gleason grades of the diagnosed cases. This study has several limitations. First, the Midspan questionnaire did not have information on family history of PC and other dietary intake history including lycopene, multivitamins, processed meat and calcium which have been linked with the risk

of PC in many studies (Key *et al.*, 2007; Park *et al.*, 2007; Rodriguez *et al.*, 2006). Second, data on tea and coffee intake was self reported at the time of screening which may suffer from information bias. Third, although reverse causation did not appear to explain the results, it cannot be ruled out as a possible source of bias. Finally, any misclassification in tea and coffee intake due to differences in cup size or type of tea and coffee might bias these results. However, such misclassification would be expected to bias these results toward the null rather than the positive association (tea & PC) which was observed in this analysis.

4.5.3 Implications of this research

There has been much interest in the preventive effects of tea on PC risk. I found a harmful effect of tea on PC risk and some preventive effect of coffee on high grade disease. This questions the preventive effect of tea observed in previous studies and further supports current recommendations that tea should not be considered a preventive factor for PC. The association between tea and coffee intake and PC should be investigated in prospective epidemiological studies in relation to different compositions of tea and coffee.

In conclusion, men who consumed high amounts of tea experienced the highest risk of PC, however no association was observed for high or low grade disease. I also observed a significant association between coffee and risk of high grade PC but not with overall risk. Our findings are important, given the poorly understood natural history and lack of known modifiable risk factors of PC.

5 Widening deprivation gap in survival of prostate cancer patients: impact of age and Gleason grade at diagnosis

5.1 Chapter summary

In the UK (UK), survival of PC patients has improved in the last two decades, however, socio-economic inequalities in survival have also been reported from regional studies. This may be attributed to differential detection of localised disease between groups, differential existence of comorbidities between groups and disparities in treatments between groups. A deprivation gap in survival (better survival for least deprived compared with the most deprived) has been reported previously in studies carried out in England, Wales and Scotland. The present analysis was carried out to describe and compare the trends in relative survival between different socio-economic groups of PC patients from 1991-2007 using the most up to date data available in this region. Furthermore the aim of present analysis was to investigate the impact of age at diagnosis and Gleason grade on deprivation gap of survival.

Incident cases of PC (ICD-10 C61) from the West of Scotland were extracted from the Scottish Cancer Registry from 1991 to 2007. Socio-economic circumstances were measured using the Scottish Index for Multiple Deprivation (2004). Age and deprivation specific mortality rates were obtained from General Registrar Office for Scotland (GRO(S)). One, three and five year relative survival was estimated by using the complete approach. The survival gradient across the five deprivation categories based on the SIMD score were estimated with linear regression, weighted by the variance of the relative survival estimate, using STATA software (StataCorp, version 11)

The rate of five year-survival increased from 58.2 to 78.6% in men between 1991 and 2007 (an average deprivation adjusted increase of 10.2% between six years periods). Despite substantial improvements in survival of PC patients, there was a deprivation gap between the three periods of diagnoses. The deprivation gap in five year relative survival widened from -4.76 in 1991-1996 to -10.08 in 2003-2007. On age and grade specific analyses, a significant deprivation gap in five year survival existed between all age groups except among patients' age ≥ 75 and both low and high grade disease. On multivariate analyses, deprivation was significantly associated with increased excess risk of death independent of age, Gleason grade and period of diagnosis.

5.2 Introduction

This chapter will describe the trends in survival of PC patients in the West of Scotland from 1991 to 2007. It will discuss the existence of, and widening gap in, survival among different socio-economic groups of population and the impact of age and Gleason grade at diagnosis on socio-economic inequalities in survival.

Population-based survival rates are influenced by the quality and effectiveness of health care systems. Generally, survival of PC patients has improved in the last two decades worldwide, particularly in western countries. However, these improvements are not consistent among countries, races and socio-economic groups. A deprivation gap of -6.9% was observed among PC patients diagnosed during 1996-2000 in Scotland (Shack *et al.*, 2007). These differences in survival may have been influenced by differences in health education programs, availability and quality of services for early detection and treatment of cancer and then post-treatment care and support. In an earlier chapter 2 (page 98), analyses showed that a deprivation gap appeared in the incidence of low grade disease which might be due to higher uptake of PSA testing among this group. In this scenario, it could be expected that the pre-existing gap in survival will further widen in Scotland due to higher detection of low grade disease among affluent men.

Therefore the objective of this analysis was to describe and compare the trends in relative survival between different socio-economic groups of PC patients from 1991-2007. A further aim was to investigate the impact of age and Gleason grade at diagnosis on deprivation gap of survival. In addition, a modelling analysis was also carried out to examine the major determinants associated with survival of PC patients in the West of Scotland.

5.3 Material and methods

5.3.1 Incidence data

I examined the data of adults (aged 15-100 years) diagnosed with a first, primary malignant neoplasm of prostate (excluding non-melanoma skin cancer) during 1991-2007 in the West of Scotland, using the International Classification of Diseases (ICD) codes, ICD 9 code 185 and ICD 10 code C61 for PC. I used the incidence data through 31st December 2007 and follow-up data till 31st December 2008, as this was the most recent year of complete data available at the time of this analysis. The cancer registry receives the notification of cancer diagnosis from different sources, described in chapter 1 (page 30). Incidence data were linked to death records provided by the General Registrar Office for Scotland (GRO(S)). The vital status of all patients was considered to be known up to 31st December 2008. Patients identified from death certificate records only were excluded (n=225, 0.01% of all registered records) from this analysis. This is because they had zero survival due to the same incidence and death dates. Thirty patients belonging to areas other than the West of Scotland and one patient older than 100 years were also excluded from this analysis.

Socio-economic status of individuals was assigned by matching their postcode of residence at diagnosis using the Scottish Index of Multiple deprivation (SIMD) 2004 score. In the incidence chapter (page 79) of this thesis, Carstairs score was used as a measure of socio-economic circumstances; the particular reason for using the SIMD in this analysis was that the age, sex, year and deprivation specific population mortality rates were only available based on SIMD groupings. So SIMD as was used as measure of socio-economic circumstances for the estimation of relative survival as the background mortality is vital in such estimations.

5.3.2 Statistical analysis

For survival analysis, complete life tables of single year of age (up to 100 years) and deprivation category were derived from the number of deaths in each deprivation category in Scotland from 1991-2008. These life tables were derived from number of deaths for years 1991 to 2008. Corresponding population

denominators were drawn from the 1991 and 2001 census population from General Registrar office for Scotland. I used the mortality rates of 2007 for the year 2008, assuming that there would not be significant differences in rates between two years.

Age at diagnosis was categorised in three groups as ≤ 65 , 65-74 and ≥ 75 years. To explore the time trends in survival, year of diagnosis was categorised into three categories as 1991-1996, 1997-2002 and 2003-2007. The rationale behind using these categories of year of diagnosis was that Scottish Cancer Registry started the recording of Gleason-grade from 1st January 1997. Therefore, by making these categories, grade specific analysis was carried out in two later periods. Gleason grade was categorised as low (Gleason 2-6), intermediate (Gleason = 7) and high grades (Gleason 8-10).

Cumulative survival following the diagnosis was estimated using the Kaplan-Meier method and the logrank used to test the independence between groups. Cumulative survival was calculated for five years and groupings of variable were done by using the above mentioned thresholds. For cancer specific survival, I estimated one, three and five year relative survival rates for PC patients diagnosed in the West of Scotland by age, deprivation category, Gleason grade and calendar period of diagnosis. Relative survival is the ratio of the observed (absolute) survival of PC patients and the survival that would have been expected if the patient had had the same age and deprivation specific mortality in each period (background population mortality); a technique which has been used earlier in the estimation of deprivation gap in Scotland (Shack *et al.*, 2007). Survival probabilities for cancer patients were estimated at 6 month intervals from diagnosis to 5 years. Cumulative relative survival up to 5 years after diagnosis was estimated for patients diagnosed in calendar periods 1991-1996, 1997-2002 and 2003-2007.

Both cohort and complete approaches were used to estimate the observed survival. There is a main difference between two techniques in estimation of observed survival. In estimation of five year survival using cohort approach, all patients must have a potential follow-up of at least five years. Using complete approach, to estimate five year survival some patients must have been

diagnosed five years before and the recently diagnosed patients (follow-up less than 5 years) can be included in the analysis, even though they cannot be followed for five years. Both techniques provided similar results so the results of complete approach are presented in this chapter.

Survival gradients across the five deprivation categories based on SIMD score were estimated with linear regression, weighted by the variance of the relative survival estimate (Coleman *et al.*, 2004) using STATA software (StataCorp, version 11). The difference between the relative survival rates fitted by the linear regression model for the least deprived and the most deprived categories is presented as “deprivation gap” in survival. The deprivation gap is reported as negative (-) if the most deprived group has lower survival than the least deprived. Average changes in the deprivation gap between the three periods have also been reported, taking into account the shorter duration of the final period (1 year shorter than the two earlier periods).

To investigate the impact of age at incidence and Gleason grade of tumour on deprivation gap, the deprivation gap was estimated stratifying by age and Gleason grade categories. The deprivation gap was estimated by least-squares linear regression, weighted by the variance of each of the relative survival estimate stratified by age and Gleason grade. The significance was evaluated with a likelihood ratio test at the 5% level.

To investigate the major determinants associated with mortality, a full likelihood approach was used to model the excess mortality (Esteve *et al.*, 1990). This method estimates the excess risk of mortality associated with PC as mortality of PC patients is compared with a matched cohort using the background population mortality. Age at diagnosis, Gleason grade, deprivation and period of diagnosis were used as independent variables in modelling excess risk of death.

As in all statistical methods, there are certain assumptions associated with relative survival analysis and modelling excess risk of death. The key assumption associated with this analysis is the “proportional hazards”, i.e. the hazard for any two patient subgroups, are proportional over the follow-up time. Scaled

Schoenfeld residuals were plotted and proportional hazards were tested for each covariate included in the model. The principle is to test whether a regression line through residuals differs significantly from $y=0$ over time (Schoenfeld D, 1982). In other words, these residuals are used to test the null hypothesis that the log hazard-ratio function is constant over time, that is, the ratio of hazard between different groups (for example, between patients aged <65 and 65 and over) is constant over time. No violation of this assumption was noted.

5.4 Results

A total of 15,519 men were identified who were registered with a diagnosis of PC in the West of Scotland from 1991-2007. Men who had zero survival ($n=226$) and were older than 100 years at the date of diagnosis ($n=1$) were excluded from this analysis. A total of 15,292 patients diagnosed in the West of Scotland were included in the final analysis. The proportion of men aged 65 and younger at diagnosis increased over the study period, from 15.4% between the years 1991-1996 to 23.6% between the years 2003-2007 (χ^2 , $p < 0.001$). Mean age at incidence decreased during the same periods from 73.2 ± 8.74 to 71.1 ± 9.08 . The highest proportion of cases were observed in older age groups, 39.4% of cases ($n=6,023$) occurred in 65-75 years of age and 41.1% of cases ($n=6,285$) in men older than 75 years. Overall, 17.2% of patients were in the least deprived group while 27.5% in most deprived group. The study period (1991-2007) was categorised into three groups from 1991-1996, 1997-2002 and 2003 to 2007 (table 5-1). Baseline characteristics of study population are described in table 5-1.

Regarding disease grade, more than half of the men (57.6%) had either low grade (Gleason ≤ 7) or intermediate grade disease (Gleason = 7). Proportions of low grade disease significantly increased during the study period while the proportion of unknown grade patients significantly reduced from 16.7 in 1997-2002 to 7.7% in 2003-2007 (χ^2 , $p < 0.01$).

Table 5-1: Baseline characteristics of prostate cancer patients registered in the West of Scotland from 1991-2007

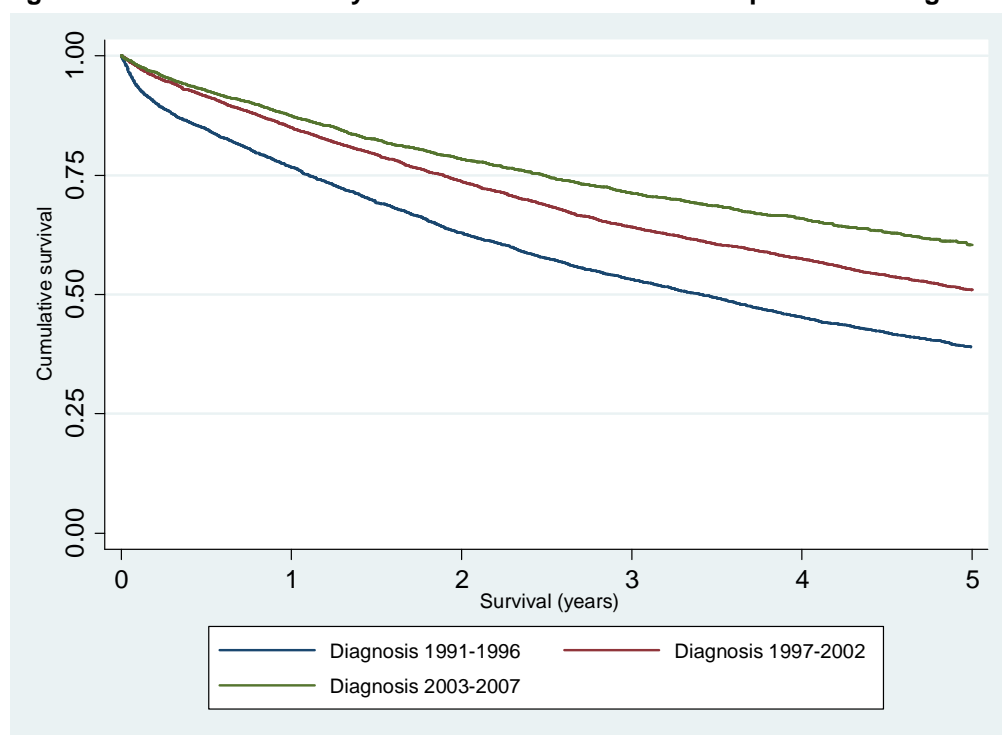
	Total patients		All deaths	
	n	%	n	%
Total registered cases	15,549	–	9,355	60.2
Patients not residing in the West of Scotland	30	–	19	63.3
Zero survival or death certificate only (DCO)	226	–	–	–
Age more than 100 years at diagnosis	1	–	1	100.0
Patients included in final analysis	15,292		9,109	59.7
Age at incidence (years)				
Age < 65	2,984	19.5	1,086	11.9
Age 65-74	6,023	39.4	3,232	35.5
Age ≥ 75	6,285	41.1	4,791	52.6
Gleason Grade				
Gleason < 7	4,065	37.2	1,421	27.1
Gleason = 7	2,231	20.4	756	14.4
Gleason 8-10	3,311	30.3	2,051	39.0
Unknown Gleason	1,316	12.1	1,026	19.5
SIMD 2004, Quintiles				
1 (least deprived)	2,623	17.2	1,295	14.2
2	2,278	14.9	1,219	13.4
3	2,450	16.0	1,444	15.9
4	3,737	24.4	2,365	26.0
5 (most deprived)	4,202	27.5	2,786	30.6
Period of Diagnosis				
1991-1996	4,369	28.6	3,855	42.3
1997-2002	5,474	35.8	3,580	39.3
2003-2007	5,449	35.6	1,674	18.4

Period of diagnosis was based on incidence date recorded in cancer registry.

5.4.1 Cumulative survival

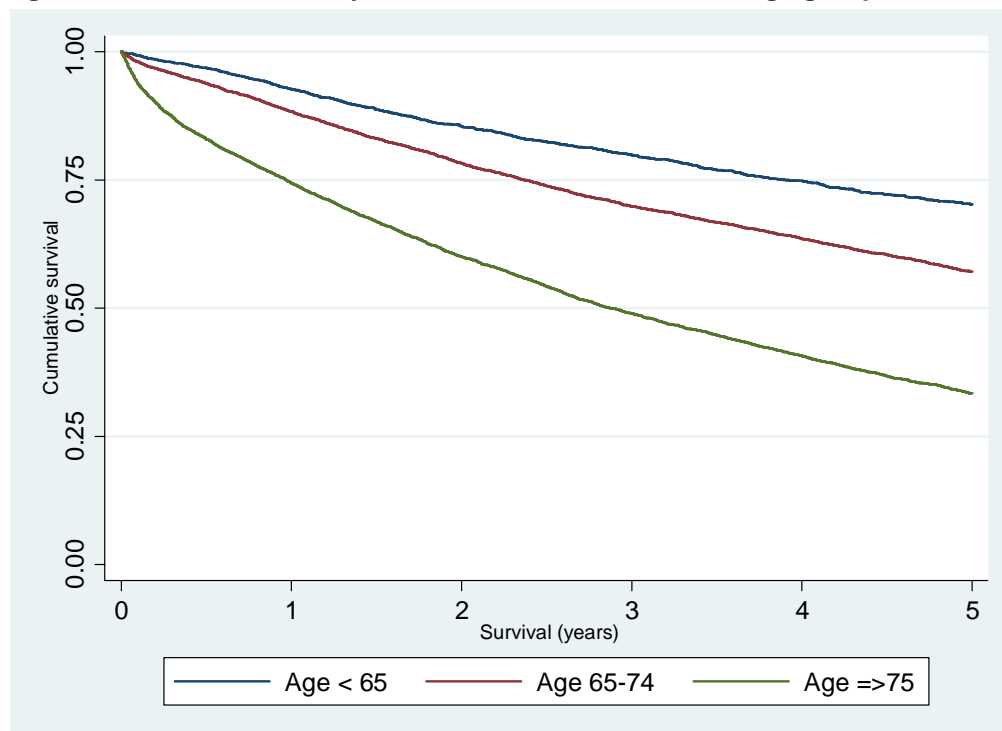
A total of 9,109 (59.6%) patients diagnosed with PC died during the study period. Overall, cumulative survival at one year and five year after diagnosis were 82.9% and 48.4%, respectively. In general, there was a trend towards improved survival in most recent periods, with a cumulative five year survival of 38.3% in 1991-1996 and 56.8% in the most recent period of 2003-2007. Figure 5-1 shows a significant difference in five year survival between three periods of diagnosis (logrank $p = <0.001$).

Figure 5-1: Cumulative five year survival between different periods of diagnosis



Similarly, significant differences in survival were also observed between different age groups. Five year survival was significantly better (logrank $p = <0.001$) for younger age group men (<65 years) compared with older age group (≥ 75 years).

Figure 5-2: Cumulative five year survival between different age groups



Significant disparities in survival were also observed between socioeconomic groups, with better survival for the least deprived and poorer for the most deprived group. Cumulative five year survival was 56.1% and 42.7% for least deprived and most deprived groups (logrank $p = <0.001$), respectively (figure 5-3). Furthermore, significant differences in survival were also seen between Gleason categories (figure 5-4). Men in the low Gleason grade category had 41.0% higher five year survival compared with the high Gleason grade group (70.8% vs 29.8%, logrank $p = <0.001$) while men with unknown Gleason had even poorer survival compared with the high Gleason grade group (figure 5-4).

Figure 5-3: Cumulative five year survival of prostate cancer patients between different socio-economic groups

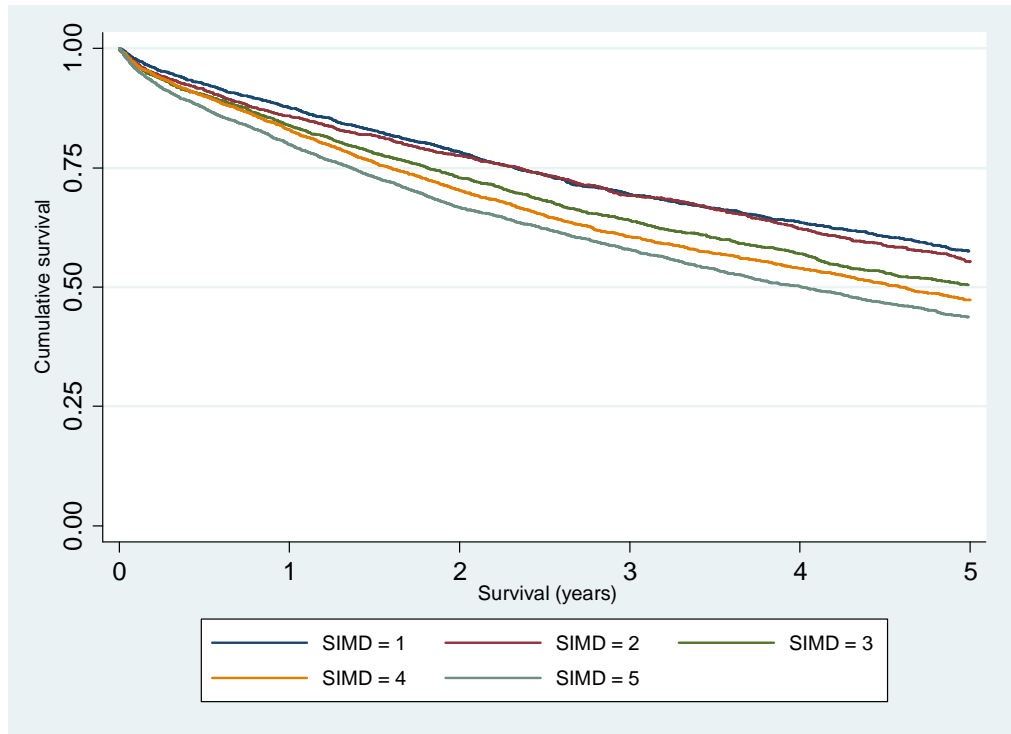
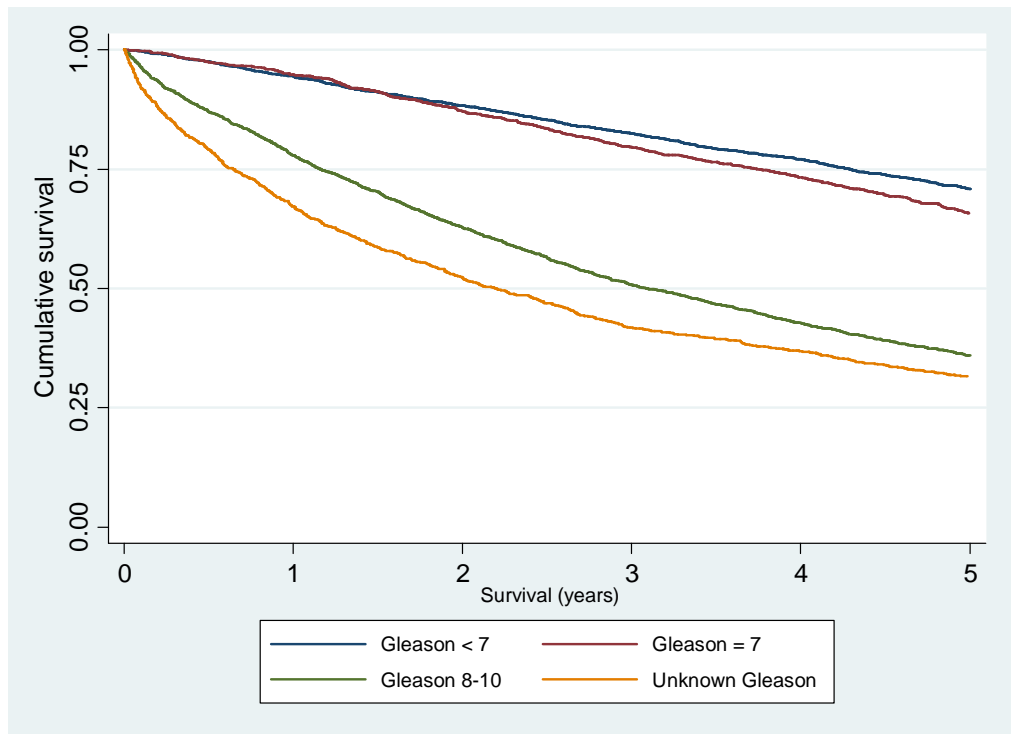


Figure 5-4: Grade specific five year cumulative survival of prostate cancer patients



5.4.2 Relative survival analysis

Relative survival was calculated stratified by age, disease grade, socio-economic circumstances and period of diagnosis using complete approach. Five year relative survival was better for men younger than 65 years (77.4%), having low Gleason grade (92.8%) and those from least deprived areas (73.2%). Men in the oldest age group (age ≥ 75) had poorer five year survival compared with younger age groups (figure 5-5). Grade-specific analysis showed that both low Gleason grade (Gleason < 7) and intermediate Gleason grade categories (Gleason = 7) had better five year survival than high Gleason grade category with an average difference of 40.0% better five year relative survival in low grade category (figure 5-6).

Figure 5-5: Five year relative survival by age groups (age at diagnosis)

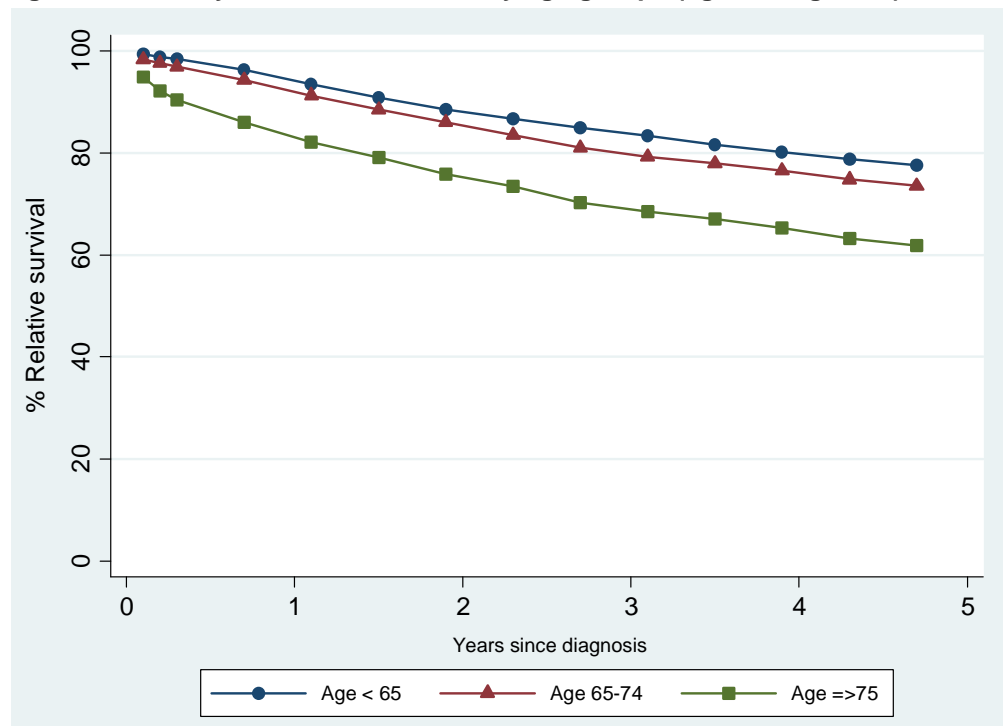
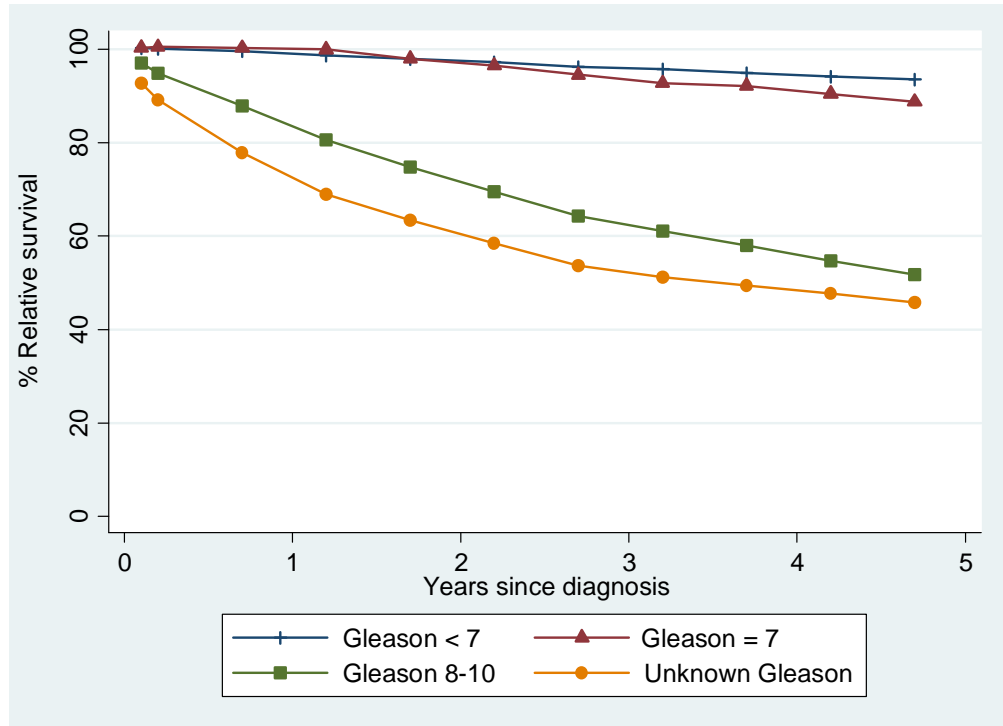


Figure 5-6: Five year relative survival by Gleason grade categories.

Further analysis to explore whether the difference in survival between deprivation groups (figure 5-7) could be because of differential distribution of high grade disease was carried out. Differences in relative survival of deprivation groups (higher survival for least deprived and lower for most deprived) for both in low as well as high grade disease (figure 5-8) were observed.

Figure 5-7: Five year relative survival by socio-economic groups

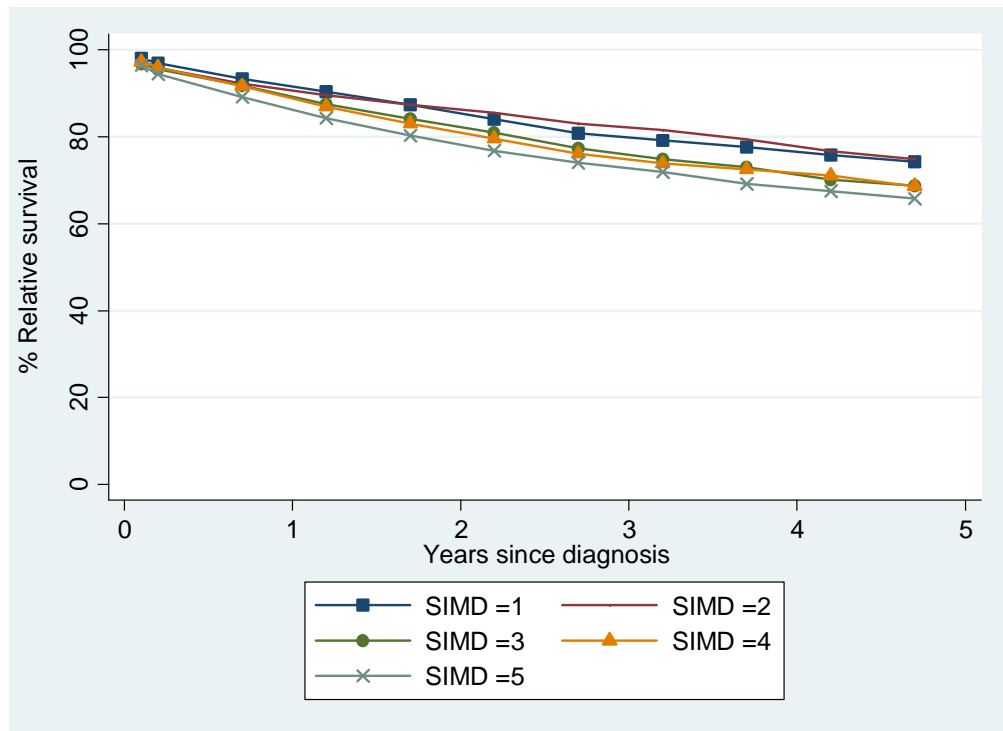
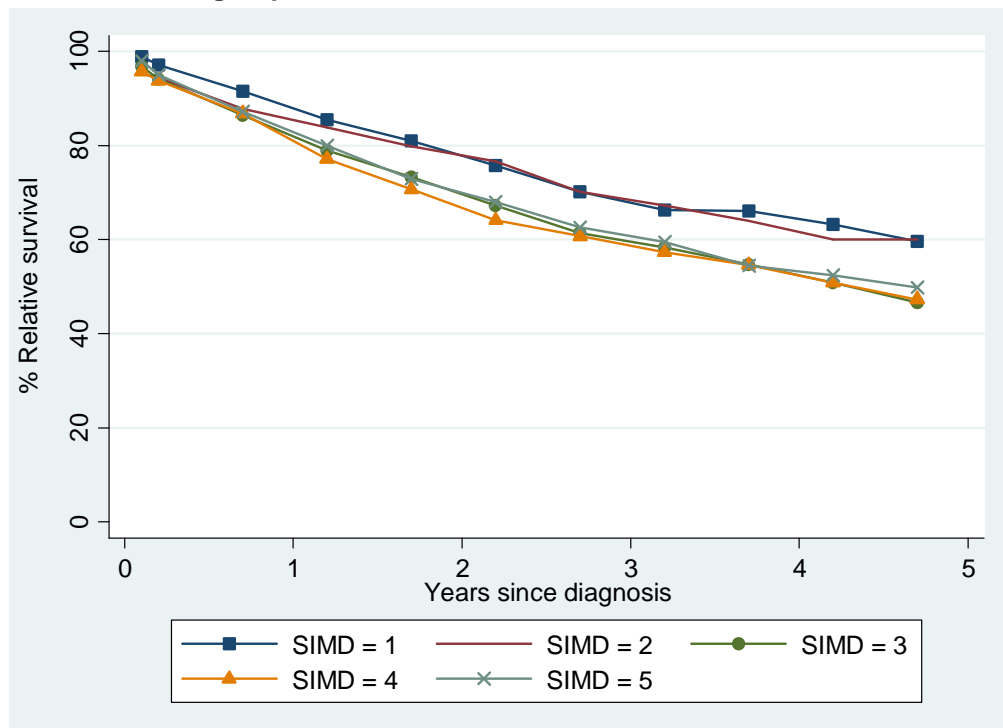


Figure 5-8: Five year relative survival of high Gleason grade disease between socio-economic groups



Chapter 5

Both short and long term survival of PC patients have improved since 1991 (table 5-2). Relative survival at 1 year increased significantly from 83.2% in 1991-1996 to 92.1% in 2003-2007 (fitted, deprivation adjusted increase of 4.5% between periods). Five year survival increased from 58.2% to 78.6% in men over the same period, an average deprivation adjusted increase of 10.2% between six years periods. Five year survival increased in both period, with a larger increase in the first periods from 1991-1996 to 1997-2002 (11.8%) while relatively smaller increase (7.6%) in survival was seen in later period (Table 5-2).

Figure 5-9: Five year relative survival between different periods of diagnosis in the West of Scotland.

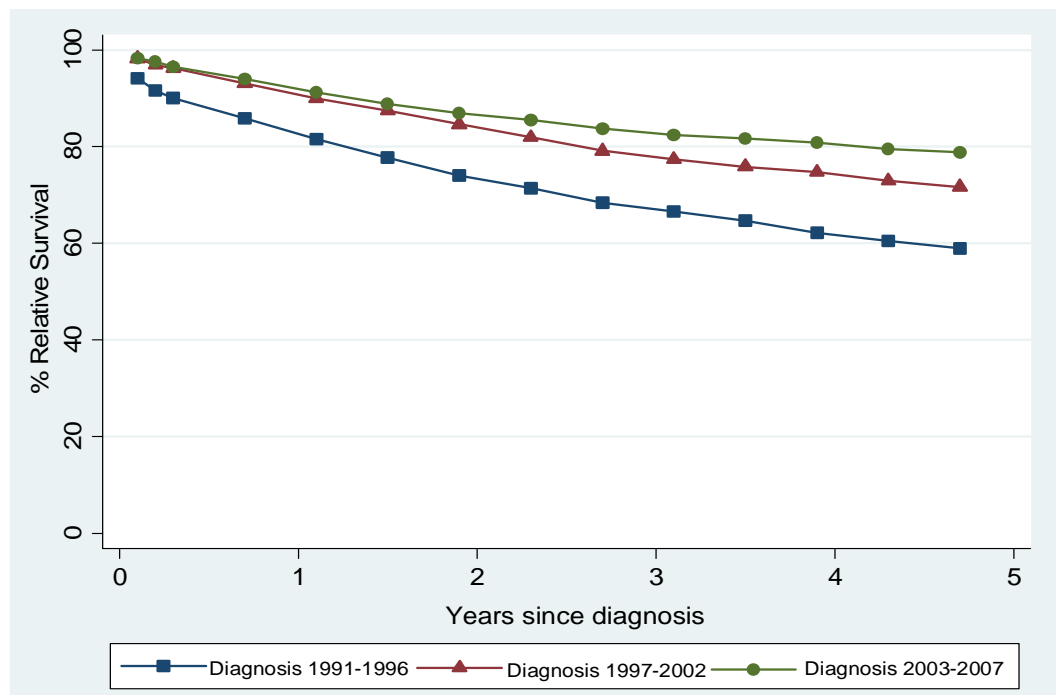


Table 5-2: Trends in survival (%) of prostate cancer patients by period of diagnosis in the West of Scotland: 1991 to 2007

Time since diagnosis	Calendar period of diagnosis						Average change (%) between periods ^a	
	1991-1996		1997-2002		2003-2007		(95% CI)	
	Survival, %	(95% CI)	Survival, %	(95% CI)	Survival, %	(95% CI)		
1 year	83.2	(81.7, 84.5)	90.9	(89.9, 91.9)	92.1	(91.2, 93.0)	4.5	(-19.4, 28.3)
3 years	67.4	(65.5, 69.2)	78.1	(76.5, 79.6)	83.1	(81.6, 84.6)	7.8	(-13.1, 28.8)
5 years	58.2	(56.0, 60.3)	71.0	(69.1, 72.8)	78.6	(76.4, 80.8)	10.2	(-8.9, 29.3)

a= Mean absolute change in relative survival between periods adjusted for deprivation

5.4.3 Deprivation gap in overall relative survival

Despite substantial improvements in survival of PC patients, there was a deprivation gap in each of the three periods of diagnoses (figure 5-10). Large improvements in survival were seen in the time from earlier to middle periods in all socio-economic groups. The deprivation gap was smaller in 1991-1996 and widened during later periods, due to large improvements in survival among the least deprived group. One year survival for men in the most deprived group, diagnosed during 1991-1996 was 4.7% lower than men in the least deprived group (deprivation gap -4.68, 95% CI -7.17, 2.19, - sign suggests lower survival among most deprived men compared with the least deprived). This deprivation gap slightly shrunk during the study period (table 5-3). A similar pattern of deprivation gap was observed in 3 year survival between the study periods. The deprivation gap widened in five year survival from -4.76 in 1991-1996 to -9.08 in 1996-2002, with a relatively small change in most recent period (table 5-3).

Figure 5-10: Deprivation gap in 5-year relative survival from 1991-2007 in the West of Scotland.

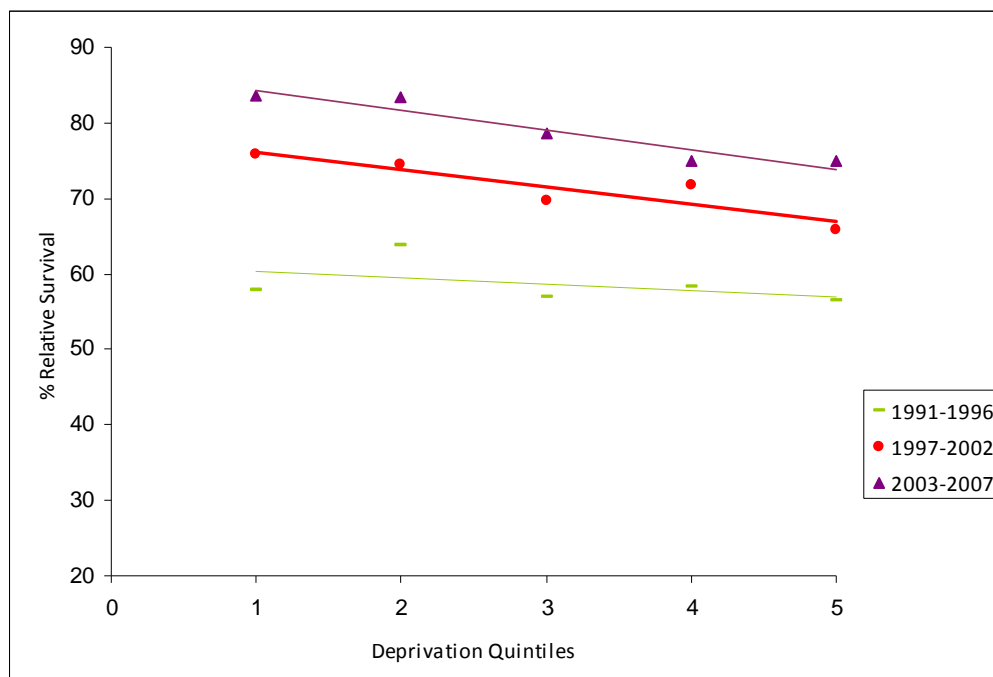


Table 5-3: Trends in the deprivation gap in relative survival of prostate cancer patients by time since diagnosis and calendar period in the West of Scotland during 1991-2007

Time since diagnosis	Calendar period of diagnosis ^a						Average change (%) between periods ^b	
	1991-1996		1997-2002		2003-2007		Deprivation	
	Deprivation gap (%)	(95% CI)	Deprivation gap (%)	(95% CI)	Deprivation gap (%)	(95% CI)	gap (%)	(95% CI)
1 year	-4.68	(-7.17, -2.19)	-4.52	(-6.02,-3.02)	-3.96	(-5.7, -2.18)	0.19	(-0.30,0.41)
3 years	-6.72	(-13.21, -0.23)	-8.08	(-12.65, -3.50)	-7.56	(-10.05, -5.07)	-0.42	(-7.31, 6.47)
5 years	-4.76	(-10.55, 1.03)	-9.08	(-12.37, -5.78)	-10.08	(-13.05, -7.11)	-2.65	(-14.83, 23.65)

a = Relative Survival estimated by complete approach, b= Mean absolute change in survival in between periods adjusted for deprivation.

5.4.4 Impact of age at incidence and Gleason grade on deprivation gap

Further analysis was carried out to investigate the impact of age and Gleason grade at diagnosis on the deprivation gap in survival. The deprivation gap persisted between age groups in all three periods of diagnosis, except for age group ≥ 75 years. In this age group, there was only a significant deprivation gap (-7.4%) in the most recent period of 2003-2007 (table 5-4).

Grade specific analysis showed a significant gap of -7% in five year survival between the most deprived and least deprived (higher survival among least deprived) existed for low grade disease between both study periods, while no significant difference in survival was observed for intermediate grade disease (Gleason = 7). A deprivation gap of approximately -10% remained stable for high grade disease between the two study periods (table 5-4), while the deprivation gap of unknown Gleason grade patients, widened from -1.8% for those diagnosed during 1997-2002 to -8.8% for those diagnosed during 2003-2007 (table 5-4).

Table 5-4: Deprivation gap in 5-year relative survival of prostate cancer patients by age, Gleason grade and calendar period in the West of Scotland during 1991-2007

Characteristics	Calendar period of diagnosis ^a					
	1991-1996		1997-2002		2003-2007	
	Deprivation gap (%)	(95% CI)	Deprivation gap (%)	(95% CI)	Deprivation gap (%)	(95% CI)
Age < 65	-13.6	(-23.24, -3.95)	-13.32	(-16.23,-10.41)	-7.72	(-24.49, 9.05)
Age 65-74	-5.36	(-16.28, 5.56)	-11.48	(-13.20, 9.76)	-9.92	(-12.11, -7.73)
Age ≥ 75	2.00	(-1.65, 5.66)	-1.44	(-12.22, 9.34)	-7.36	(-12.32, -2.40)
Gleason < 7	–	–	-6.64	(-11.82,-1.46)	-6.88	(-12.95, -0.80)
Gleason = 7	–	–	-0.4	(-7.16, 6.36)	3.92	(-6.47, 14.31)
Gleason 8-10	–	–	-10.12	(-16.63, -3.61)	-8.76	(-20.37,2.85)
Unknown Gleason	–	–	-1.8	(-14.75,11.14)	-8.76	(-13.72,-3.80)

a = Relative Survival estimated by complete approach

5.4.5 Determinants of survival

On both univariate and multivariate analyses, patient demographics (including age at incidence and socio-economic circumstances), Gleason grade and period of diagnosis were significantly associated with excess risk of death due to cancer (table 5-5). Being age 75 years or older conferred more than double the risk of death in 5 years ($p < 0.001$) adjusting for Gleason grade, period of diagnosis and deprivation. The middle age group (age 65-74 years) also showed significantly higher risk of death at five year compared with youngest age group. Increase in Gleason grade showed a dose-response effect on excess risk of death after adjustments for age and socio-economic circumstances. Gleason > 7 and unknown Gleason had four and five times higher risk of death ($p < 0.001$) in five years, respectively, after adjusting for age, socio-economic circumstances and period of diagnosis (table 5-5).

5.4.6 Period of diagnosis and deprivation

As survival has improved over time, the period of diagnosis was significantly associated with better survival (lower risk of death). Individuals diagnosed during 2001-2007 had 14% lower risk of death compared to those diagnosed in 1991-2000 after adjusting for age, Gleason grade, deprivation and background survival improvements in the general population. Socio-economic circumstances were independently associated with excess risk of death due to cancer. Excess risk of death gradually increased with increasing deprivation. Patients from the most deprived group had a 48% higher risk of death (RER 1.48, 95% CI 1.31-1.68) compared to those in the least deprived group (table 5-5).

Table 5-5: Five-year relative survival of prostate cancer patients modelled using the full likelihood approach

	Univariate analysis		Multivariate analysis	
	Relative Excess Risk (95% CI)	p value	Relative Excess Risk (95% CI)	p value
Age at incidence				
Age ≤ 65	1		1	
Age 65-74	1.43 (1.26, 1.62)	<0.001	1.31 (1.15, 1.48)	<0.001
Age ≥ 75	2.88 (2.56, 3.24)	<0.001	2.31 (2.06, 2.60)	<0.001
Gleason Grade				
Gleason < 7	1		1	
Gleason = 7	1.34 (1.12, 1.61)	0.001	1.26 (1.06, 1.49)	0.007
Gleason 8-10	5.22 (4.57, 5.95)	<0.001	4.33 (3.83, 4.89)	<0.001
Unknown Gleason	6.68 (5.78, 7.71)	<0.001	5.27 (4.61, 6.03)	<0.001
SIMD 2004, Quintiles				
1 (least deprived)	1		1	
2	1.05 (0.90, 1.24)	0.35	1.11 (0.96, 1.29)	0.16
3	1.33 (1.14, 1.55)	<0.001	1.29 (1.13, 1.49)	<0.001
4	1.47 (1.28, 1.69)	<0.001	1.36 (1.19, 1.54)	<0.001
5 (most deprived)	1.71 (1.50, 1.96)	<0.001	1.48 (1.31, 1.68)	<0.001
Period of diagnosis				
1991-2000	1		1	
2001-2007	0.69 (0.64, 0.76)	<0.001	0.86 (0.79, 0.93)	<0.001

Multivariate model included all co-variables presented in the table.

5.4.7 Impact of period of diagnosis and deprivation on grade specific survival

Deprivation was associated with increased risk of death, independent of age at incidence and period of diagnosis for both low grade and high grade disease groups. This was not true for the intermediate grade (Gleason = 7). Risk of death reduced for all grades during the later period (2003-2007), with 81% reduction in low grade disease group, 61% among intermediate group and 22% risk reduction in high grade disease group (table 5-6). The risk of death increased among those with unknown grade in the later period compared to the earlier one.

As the biggest reduction in risk was observed in low grade disease during the study period, the biggest deprivation effect was observed in the same disease group. A risk reduction of 81% in excess risk of death was seen among low grade category in 2003-2007 compared with 1997-2002. This may be because due to change in biological spectrum of disease over time. Socio-economic gradient persisted even in this disease group and men from the most deprived group with low grade disease group had more than doubled the risk of death compared with the least deprived group in first five years of diagnosis (table 5-6).

Table 5-6: Grade specific 5-year relative survival of prostate cancer patients modelled using the full likelihood approach

	Gleason < 7			Gleason = 7			Gleason 8-10			Unknown Gleason		
	Relative Excess Risk (95% CI)	p value		Relative Excess Risk (95% CI)	p value		Relative Excess Risk (95% CI)	p value		Relative Excess Risk (95% CI)	p value	
<i>SIMD 2004, Quintiles</i>												
1 (least deprived)	1			1			1			1		
2	1.20 (0.41, 3.52)	0.742		0.94 (0.44, 1.99)	0.871		1.05 (0.81, 1.36)	0.702		1.25 (0.90, 1.73)	0.192	
3	1.69 (0.62, 4.64)	0.309		1.01 (0.48, 2.12)	0.981		1.42 (1.13, 1.79)	0.003		1.02 (0.73, 1.46)	0.875	
4	1.61 (0.61, 4.26)	0.005		1.36 (0.73, 2.55)	0.331		1.48 (1.19, 1.84)	<0.001		1.06 (0.78, 1.43)	0.722	
5 (most deprived)	2.61 (1.09, 6.26)	0.031		0.84 (0.39, 1.82)	0.657		1.36 (1.10, 1.69)	0.005		1.47 (1.13, 1.92)	0.004	
<i>Period of diagnosis</i>												
1997-2002	1			1			1			1		
2003-2007	0.19 (0.05, 0.74)	0.017		0.39 (0.27, 0.68)	<0.001		0.78 (0.68, 0.90)	<0.001		1.87 (1.55, 2.40)	<0.001	

All estimates were adjusted for age at incidence

5.5 Discussion

5.5.1 Main findings

Present analysis suggests that survival of patients with PC has significantly improved in the West of Scotland during the study period. Despite this, socio-economic inequalities in survival of PC patients existed and widened in most recent periods. Furthermore, largest improvements have been observed in low grade disease (Gleason < 7) but socio-economic inequalities in survival persisted even if men are diagnosed at a relatively younger and with low grade disease. Socio-economic circumstances of individuals appeared as a significant determinant in the survival of PC patients independent of their age at diagnosis, Gleason grade and calendar period of diagnosis.

5.5.2 Data quality

Scotland Cancer Registry data for the West of Scotland was used for this analysis providing a fairly large sample with long follow-up of patients to carry out this analysis. Different techniques were used to estimate the relative survival, i.e. cohort and complete approach, both produced identical results. Those who were diagnosed with PC from death certificate only or with zero survival time were excluded from this analysis - this comprised a small proportion though (n=226, 0.01%). Exclusion of these cases from the analysis does not explain the existing and widening deprivation gap in relative survival for multiple reasons. First, there was no significant difference in distribution of these cases between socio-economic groups. Secondly, the proportion of patients excluded from the analysis is very small to have any significant impact on the estimates provided in this analysis.

5.5.3 Temporal trends in survival

Present analyses suggest that the recent trends in survival of PC patients are encouraging. Improvements have been observed in both short term (1-year) and long term survival (5-year) in the West of Scotland. One year survival improved by approximately 4.5% every six years between 1991-1996 and 2003-2007, while five year survival increased by 10% during the same period. Overall,

improvement in survival seems consistent with reports from England and Wales (Rowan *et al.*, 2008). Survival of patients with PC has improved during corresponding periods in many European countries. Denmark for example, observed approximately 7% improvement in five year survival between 1985-2004 (Lund *et al.*, 2007). Another recent report from Denmark also suggested similar findings (Borre *et al.*, 2011). In the Netherlands, survival improved by approximately 1.8% annually from 1989 to 2006 (Cremers *et al.*, 2010).

The pattern and trends in PC survival in the West of Scotland are not artefacts - there seems a genuine increase of both incidence and survival. There are many contributing factors (including patients' demographics and disease characteristics) which can explain these trends. Men in younger age group and those from relatively least deprived groups experienced better survival compared with older and most deprived groups, respectively. These factors are discussed in detail in a following section of this chapter.

Disease related factors are affected by PSA testing, which can partly explain both the increase in incidence and survival. The introduction of PSA testing has led to stage and grade migration of PC (Moore *et al.*, 2009). This has resulted in a rapid shift in the biological spectrum of the disease and at a population level PC is no longer a fatal and incurable disease now as it was in 1980s. Nowadays, a higher proportion of individuals are diagnosed with localized, small volume and low grade prostate tumours, which are registered and treated aggressively and, ultimately, lead to better survival of patients.

There are some potential problems associated with PSA testing and its impact on survival of patients. PSA testing increases the average survival time by diagnosing some tumours years before the tumour would have been detectable by clinical examination or symptoms. This may result in a lead time bias, meaning that men who are identified by PSA testing appear to survive longer than men who are identified by other methods. In this case, PSA detected individuals show to have longer survival when in reality there would be no real difference in time to death between PSA tested or untested men (van Leeuwen *et al.*, 2010). The other problem with PSA testing and survival is the length time bias. PSA testing is more likely to diagnose slower growing tumours which may

remain asymptomatic for longer time prior to their development as symptomatic disease compared to fast growing or aggressive tumours. Thus, the men diagnosed with PSA testing tend to live longer because they had slow growing tumours. These issues associated with PSA testing must be considered while interpreting the survival trends (van Leeuwen *et al.*, 2010). Early detection is not only associated with PSA testing, evidence suggests that increasing incidence trends in Northern Ireland and Republic of Ireland are also due to increasing rates of prostatic biopsy and not only because of the PSA (Carsin *et al.*, 2010). That study also argued that a reduction in mortality in both countries was not fully explained by PSA testing and mortality rates started falling even before the expected beneficial effects of widespread PSA testing (Carsin *et al.*, 2010).

In recent years, greater awareness among public health professionals is another factor that might have contributed to better management of patients. For instance, greater awareness of PC and its symptoms might have increased demands of PSA testing by older men or family members leading to higher detection (Drummond *et al.*, 2009). This may ultimately have lead to more intensive monitoring of patients after diagnosis and thus could also have played a role in better survival and lower mortality. Besides the possible benefits associated with PSA testing, there is also a risk of over diagnosis and treatment of asymptomatic cases of PC which might have never manifested as clinically symptomatic disease during their life time (Moore *et al.*, 2009).

Treatment may have influence on survival of cancer patients following diagnosis but evidence on the effectiveness of treatment modalities and their role in improving the survival remains equivocal. Large randomised trial on men with early stage PC detected in PSA-era suggests some benefit of radical treatment over watchful-waiting (Bill-Axelson *et al.*, 2011b) but subsequent trial in a different setting failed to show such benefit (Wilt *et al.*, 2012). In the absence of population-based treatment data of PC patients, it is difficult to conclude that treatment has contributed in observed survival trends during the studied period. Lead time and length time biases, discussed earlier may remain the plausible explanations of observed survival trends in the West of Scotland.

5.5.4 Socio-economic inequalities in survival

Despite the overall improvement in survival of PC patients, socio-economic inequalities in survival of PC patients widened further over the periods 1997-2002 and 2003-2007. Estimates of one, three and five year deprivation gaps in survival have been presented along with the trends of these gaps over time. The concurrent increase in survival differences between the least deprived and most deprived men, taken with the more rapid increase in incidence of low grade disease among least deprived men, may suggest that individuals from higher socio-economic groups had greater access to PSA testing during these recent periods. The deprivation gap in survival for PC patients has been widening as reported earlier from Scottish National dataset (Shack *et al.*, 2007).

Socio-economic differences in survival have been observed in many countries including Australia (Hall *et al.*, 2005), New Zealand (Haynes *et al.*, 2008), England and Wales (Rowan *et al.*, 2008) and the US (Dayal *et al.*, 1985). In England and Wales, recent improvement in survival of many adult cancers including prostate has been more marked for least deprived groups compared with most deprived (Coleman *et al.*, 2004). The NHS Cancer Plan was implemented in 2000 in England and Wales and one of the major aims of that was to tackle the inequalities in cancer survival. However, a recent study examined the survival differences among affluent and deprived cancer patients before and after the plan and reported that there is very little variation in deprivation gap in survival even 10 years after the implementation of the NHS Cancer Plan (Rachet *et al.*, 2010).

Deprivation specific survival cannot be directly compared to other Western countries or even with the constituent countries of UK because the measures of deprivation used in different studies are not identical and size of effect could vary simply because of different measures. However, the relative changes and differences can be evaluated. In Scotland, the deprivation gap in survival of many adult cancers has been larger for Scottish population as compared to England and Wales during a 15 year period between 1986 to 2000 (Shack *et al.*, 2007). Nonetheless, the overall pattern remained quite consistent, i.e. the

deprivation gap in survival of most cancers is widening in both countries (Shack *et al.*, 2007).

Several factors can contribute towards lower survival among more deprived men including older age, advanced stage and aggressive disease at presentation, higher prevalence of comorbidities and unhealthy lifestyle habits. PSA testing seems to play its role in PC; some evidence suggested that deprived population might have lower uptake of PSA and thus had a late diagnosis with extended disease. This has born out by evidence that presentation of deprived men with PC has not changed over the years (Mokete *et al.*, 2006). Whether the lower testing rate is due to the lack of availability of the test from the General Practitioners or whether the men in more deprived groups do not simply come forward for testing is largely unknown.

Some studies have attributed the socio-economic inequalities in survival to higher levels of comorbidity among the more deprived patients (Clarke, 2008). Along with comorbidity, there are numerous other factors that can contribute to socio-economic inequalities in survival. For example, risk behaviours such as heavy smoking or alcohol intake, which are more prevalent among the most deprived socio-economic group could explain some of the differences in survival from patients from most deprived men (Jeffreys *et al.*, 2009; Lawder *et al.*, 2010).

These views are fairly straightforward and inherently plausible as these are derived from the clinical experience. However, they can be challenged by some of the results of this analysis, keeping in view the design and statistical methods used here. As age and deprivation specific background population mortality rates were used for the estimation of relative survival in this section, differential comorbidity between socio-economic groups can not directly account for the excess risk of death associated with cancers. Presence of comorbidity can increase the risk of death due to non-cancer causes. The present analyses compensated for background population mortality difference between socio-economic groups. Therefore, these non-cancer deaths will not affect the survival estimates presented in this section. Differential co-morbidity can only contribute to socio-economic inequalities in relative survival if there is an interaction

between the presence of co-morbidity and the actual treatment received for the cancer (Rachet *et al.*, 2008). There is some evidence from England that non-metastatic PC patients from low socio-economic backgrounds are less likely to receive aggressive surgical or radiological treatment compared with the least deprived population groups (Fairley *et al.*, 2009) possibly due to the presence of co-morbidities.

Generally, survival appears to be improved for both least and most deprived groups but it improved more rapidly for the least deprived compared with the most deprived or in some cases at a same rate without closing the deprivation gap in survival. If differential comorbidity between most deprived and least deprived PC patients explains the persistent or widening deprivation gap in survival, it would imply that the impact of comorbidity on choice of treatment (or outcome) had actually been increasing more among the most deprived than the least deprived (Rachet *et al.*, 2008). This seems implausible, rather socio-economic differences in the diagnosis of PC and/or treatment of this disease should be seen as a potential explanation of survival difference between social groups.

5.5.5 Age and grade-specific patterns in survival

Age and Gleason grade are considered to be strong predictors of prognosis of PC patients. Large improvements in survival were observed among those diagnosed with low grade disease (Gleason < 7). The risk of death significantly reduced among men with low grade disease in the most recent period (2003-2007) compared with earlier period (1997-2002). A reduction of 80% in the excess risk of death in the most recent period, suggests that the biological spectrum of PC has changed over time and in more recent years, we are treating an entirely new disease which is perhaps a very low risk cancer. Despite the largest improvement in survival in this disease group, more than double the risk of death was observed for the most deprived group compared with the least deprived.

In this dataset, least deprived were more likely to be diagnosed at a younger age and with lower grade. Age and Gleason grade-specific analysis did not show any consistent pattern or impact on deprivation gap in this analysis. A deprivation gap was seen in all age groups and within both low and high grade

disease groups. This suggests that there may be disparities among different socio-economic groups other than the difference in age and disease grade at presentation.

Disease stage at diagnosis is also an important factor associated with the survival of PC patients (Jeffreys *et al.*, 2009). For example in the US, Black men have poorer survival compared to Whites and one of the explanations for that is the relatively late presentation by Black men with advanced and metastatic disease at diagnosis. Delayed presentation by low socio-economic groups is also considered a contributory factor in socio-economic inequalities in cancer survival in the UK. However, the hard evidence on this for PC in the UK is still sparse. There is some evidence from recent studies investigating the impact of race in clinical presentation of PC in UK, but no significant differences were observed between White and Black men's age, disease grade and stage at presentation (Evans *et al.*, 2010; Jack *et al.*, 2010). Unfortunately, disease stage information was not present in the Scottish Cancer Registry data, so the role of disease stage in the existing deprivation gap in survival could not be investigated.

5.5.6 Implications of this research

Present analysis highlights a significant socio-economic gap in survival of PC patients. Interestingly, clinical commentators mainly attribute this difference in survival to the co-morbidities while most epidemiologists emphasise the late diagnosis in deprived groups as a key determinant of poorer survival. This difference in survival is perhaps combination of different factors rather than the co-morbidity or disease stage alone, and highlights the need for further research to understand the main determinants of socio-economic inequalities.

Furthermore, high quality information on staging and comorbidities need to be collected to understand the survival differences between socio-economic groups. England has already given it a high priority through the Cancer Reform Strategy. This is perhaps urgently needed in Scotland as well that clinical team collect the staging and co-morbidity information and linking the clinical audit data with Cancer Registry may provide further understanding about the reasons of socio-economic differences.

5.5.7 Limitations of this research

There are some limitations to this analysis which need to be mentioned. The SIMD was used as a proxy measure of socio-economic circumstances of PC patients in the present analysis. As with all the area-based measures of deprivation, using SIMD score assumes that all the individuals living in a given geographical area experience the same level of deprivation and other associated factors. Individual level data such as level of education, occupation and income can provide stronger evidence of socio-economic circumstances; however, these data are not routinely collected in cancer registries. Earlier studies carried out in different regions of the UK, despite the use of different area-based measures, also provided similar results which suggest that the least deprived have better survival compared with the most deprived, which suggests that these findings are not just due to the measurement index. In addition, race has been widely used as a measure of socio-economic circumstances in the US and provided quite similar results suggesting that individuals from poorer background experience worse survival. Another important limitation is the unavailability of information on the stage of the cancer and comorbidity which is well known prognostic factors in survival of patients.

Despite these limitations, the present analyses indicate that overall survival has improved in the West of Scotland with the largest risk reduction of death in low grade disease in more recent period, which suggests that spectrum of disease has changed over time. Improvement in survival among least deprived group was at a greater rate than the most deprived, likely to be more important than age and grade at diagnosis in maintaining the deprivation gap in survival. Further research is needed to better understand the causal factors associated with socio-economic disparities in survival.

6 Systemic inflammation and survival of patients with prostate cancer: evidence from the Glasgow Inflammation Outcome Study.

6.1 Chapter summary

There is some evidence that systemic inflammation may be associated with survival in patients with PC. However, it is unclear whether this is independent of grade. I therefore investigated the role of inflammation-based prognostic scores, the modified Glasgow Prognostic Score and Neutrophil Lymphocyte Ratio (NLR), and their associations with Gleason grade in patients with PC. Patients from a cohort, the Glasgow Inflammation Outcome Study, who had diagnosis of PC, were included in this study. The mGPS was constructed by combining C-reactive protein and albumin while NLR by calculating the ratio of neutrophils to lymphocytes. I estimated five-year relative survival and relative excess risk of death by mGPS and NLR categories after adjusting for age, socio-economic circumstances and Gleason grade.

Eight hundred and ninety seven PC patients were identified. Of those 422 (47%) died during a maximum follow-up of 6.2 years. Systemic inflammation appeared to have significant prognostic value. The mGPS predicted poorer 5-year overall and relative survival independent of age, socio-economic circumstances, disease grade and NLR. Raised mGPS also had a significant association with excess risk of death (mGPS 2: Relative Excess Risk = 2.41, 95% CI 1.37-4.23) among aggressive, clinically significant PC (Gleason grades 8-10). The mGPS is a strong measure of systemic inflammation, when compared to NLR. PC patients with a raised mGPS had significantly higher risk of death for overall as well high grade disease. Inflammation-based prognostic scores showed some prognostic value for patients with PC, however, further evidence is required to determine their utility in routine clinical practice.

6.2 Introduction

The aim of this chapter was to investigate the role systemic inflammation in survival of patients with PC. Different markers of systemic inflammation have been discovered, however, in this chapter only include neutrophil lymphocyte ratio (NLR) and modified Glasgow prognostic scores (mGPS). I have used the relative survival and model that to estimate the excess risk of death with PC in this chapter.

The natural history and progression of PC is poorly understood, however some evidence suggests an association between the activation of the systemic inflammatory response, as evidenced by raised C-reactive protein concentrations, and survival in patients with PC (McArdle *et al.*, 2006; McArdle *et al.*, 2010). However, these studies were small and it is unclear if these relationships remain in a large cohort, independent of Gleason grade, socio-economic status and time of sampling. Therefore, the aim of the present analysis was to investigate the associations between inflammation-based prognostic scores (mGPS and NLR) and survival in a large cohort of patients with PC.

6.3 Materials and methods

From a cohort previously described, cancer patients in north Glasgow, UK, (Proctor *et al.*, 2010) who had a single blood sample taken between 1st January 2000 and 31st December 2007 for C-reactive protein, albumin, calcium as well as liver function tests, where available, were included in this analysis. The limit of detection of C-reactive protein was a concentration of less than 5 mg l⁻¹ (Proctor *et al.*, 2010). If more than one record was available for a patient then only the initial record was used. Patients were excluded if they did not have a complete set of identifying details (name, sex, date of birth and hospital number) (Proctor *et al.*, 2010).

PC diagnosis was established by linkage of the above biochemistry data and the Scottish Cancer Registry, also known as Scottish Morbidity Record number six (SMR06). Linkage was by exact matching of patients' forename, surname and date of birth, followed by Soundex phonetic matching algorithm if initial exact matching was unsuccessful. PC was defined as International Classification of Diseases (ICD), ICD-10 code C61. Only those patients who had a blood sample taken within a period of two years, before or after diagnosis of PC, were included in the analysis.

Socio-economic status of individuals was assigned matching their postcode of residence at diagnosis using the Scottish Index of Multiple deprivation (SIMD) 2004 score.

The Gleason grading system is known to be associated with prostatic cancer prognosis (Sogani *et al.*, 1985) and was used to describe tumour morphology. Gleason grade was extracted from the Scottish Cancer Registry where available. Date and cause of death was extracted through cancer registration patient based-linkage with General Register Office for Scotland (GRO(S)) death records. This study was approved by the Research Ethics Committee, North Glasgow NHS Trust.

The mGPS and NLR were constructed as described in previous studies (Aliustaoglu et al., 2010; Gomez et al., 2008; Proctor et al., 2011b) (Table 6-1).

Table 6-1: Systemic inflammation-based prognostic scores

Prognostic Scores	Score
The modified Glasgow Prognostic Score	
C-reactive protein \leq 10 mg/l	0
C-reactive protein > 10 mg/l and albumin \geq 35 g/l	1
C-reactive protein > 10 mg/l and albumin < 35 g/l	2
Neutrophil Lymphocyte Ratio	
Neutrophil count:lymphocyte count < 5:1	0
Neutrophil count:lymphocyte count \geq 5:1	1

Follow-up was from date of incidence of cancer to the date of death or censor date (31st December 2008), whichever came first. Relative survival was used as a measure of cancer patients' survival. Relative survival has a key advantage over the cause specific survival as it does not rely on the accurate classification of cause of death; instead it provides a measure of total PC associated excess mortality.

One and five years relative survival estimates were made by using age, gender and deprivation specific life tables provided by General Registrar Office (Scotland). These were available through 2007; so for the purposes of this study, the 2007 mortality rates were used for comparison as they are unlikely to be significantly different from those occurring in 2008. Relative survival estimates were made by age, deprivation, Gleason grade and mGPS, using the complete and hybrid approach (by STREL and STRS command in STATA) (Dickman PW *et al.*, 2008). STRS command in STATA implements the Ederer II method by default for the estimation of relative survival; however, I repeated the analyses using both the Ederer I and Hakulinen approaches. All three methods provided identical results, so the results presented in this study are based on the Ederer II Method. Using the full likelihood approach adjusted for age, deprivation and Gleason grade, the relative excess risk (RER) of death from PC was estimated (Esteve *et al.*, 1990). This approach provides the estimate of excess risk of death due to cancer after adjusting for the background population mortality.

Patients who had missing NLR (n=188, 21%) were excluded from the excess risk estimation analyses. The lowest category was used as referent for the mGPS and all other categorical covariates. All analyses were conducted using STATA version 11 (StataCorp, College Station, TX, USA). Adherence to the proportional hazards assumption was investigated by plotting smoothed Schoenfeld residuals against time; no violations of the assumption were identified. I investigated the interactions between different variables in every multivariate model, but no significant interaction was found. All statistical tests were two tailed and statistical significance was taken as $p < 0.05$.

6.4 Results

From the Glasgow Inflammation Outcome Study of 223,303 patients originally described, 27,301 patients were identified as having a diagnosis of cancer by Scottish Cancer Registry and a blood sample for C-reactive protein, albumin, white cells, neutrophil, lymphocyte and platelet counts taken between January 2000 and December 2007 (Proctor *et al.*, 2011). From this cohort, 897 patients who had a diagnosis of PC and had been sampled within two years before or after diagnosis were included in this analysis. The majority, 575 (64%), were aged 75 or over. Nineteen percent of patients lived in affluent areas (least deprived quintile of the Scottish population) and 34% in deprived areas (most deprived quintile of the Scottish population). The median follow-up from the cancer diagnosis was 2.5 years, and maximum 6.2 years.

Patients with an elevated mGPS (mGPS = 2) were more likely to be 75 years or older ($p=0.005$) and have high grade disease (Gleason 8-10) ($p<0.001$), but there was no association with socio-economic circumstances based on SIMD ($p=0.430$). Similarly, patients with an elevated NLR (NLR score 1) were more likely to be older ($p=0.022$) and have a raised mGPS ($p<0.001$) but there was no significant association with socio-economic circumstances ($p=0.338$) or Gleason grade ($p=0.074$).

The individuals who had missing NLR were significantly older (2.3 years, p value <0.002 , $t = 2.95$) than those whose NLR data were available, while no significant differences were observed in distribution of Gleason grade (χ^2 , $p = 0.08$) and socio-economic circumstances (χ^2 , $p = 0.617$). Furthermore, mean survival time was approximately 6 months higher for those whose NLR was missing compared to those whose NLR was available.

Baseline characteristics of PC patients, before and after sampling, are shown in table 6-2. Patients who were sampled in the post-diagnosis group, compared with the pre-diagnosis group, were more likely to be older ($p<0.001$), had higher Gleason grade ($p<0.001$), came from less deprived areas ($p<0.03$) and had higher mGPS ($p<0.01$) and NLR ($p<0.001$) values.

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Patients who died in the post-diagnosis group, compared with the pre-diagnosis group, were more likely to be younger ($p < 0.001$), had higher Gleason grade ($p < 0.001$), and higher mGPS ($p = 0.03$) and NLR ($p < 0.001$) values. Because of differences in pre- and post-diagnosis sample characteristics, I conducted survival analyses for each separately.

Table 6-2: Baseline characteristic of prostate cancer patients in Glasgow Inflammation Outcome Study

	All patients		P-value	All deaths		P-value
	Sampled before diagnosis n (%)	Sampled after diagnosis n (%)		Sampled before diagnosis n (%)	Sampled after diagnosis n (%)	
Age at incidence						
Age < 65	72 (19.5)	162 (30.7)		23 (11.9)	48 (21.1)	
Age 65-74	118 (32.0)	223 (42.2)	<0.001	52 (26.8)	88 (38.6)	<0.001
Age ≥ 75	179 (48.5)	143 (27.1)		119 (61.3)	92 (40.4)	
Gleason Grade						
Gleason < 7	70 (19.0)	136 (25.8)		17 (8.8)	25 (11.0)	
Gleason = 7	65 (17.6)	118 (22.4)	<0.001	10 (5.2)	34 (14.9)	<0.001
Gleason 8-10	131 (35.5)	214 (40.5)		73 (37.6)	122 (53.5)	
Unknown Gleason	103 (27.9)	60 (11.4)		94 (48.5)	47 (20.6)	
SIMD 2004, Quintiles						
1 (least deprived)	54 (14.6)	121 (23.0)		24 (12.4)	46 (20.2)	
2	46 (12.5)	64 (12.2)		23 (11.9)	27 (11.8)	
3	52 (14.1)	75 (14.3)	0.034	23 (11.9)	30 (13.2)	0.187
4	82 (22.2)	97 (18.4)		48 (24.7)	42 (18.4)	
5 (most deprived)	135 (36.6)	171 (32.4)		76 (39.2)	83 (36.4)	
Inflammation based prognostic scores						
mGPS						
0	182 (49.3)	273 (51.7)		80 (41.2)	78 (34.2)	
1	137 (37.1)	149 (28.2)	0.004	80 (41.2)	85 (37.3)	0.027
2	50 (13.6)	106 (22.1)		34 (17.5)	65 (28.5)	
NLR						
0	166 (45.0)	239 (45.3)		72 (37.1)	71 (31.1)	
1	99 (26.8)	205 (38.8)	<0.001	58 (29.9)	110 (48.3)	<0.001
missing	104 (28.2)	84 (15.9)		64 (33.0)	47 (20.6)	

P-value calculated using chi-square test.

Increasing age and high or unknown Gleason grade were associated with poorer one and 5-year relative survival in those who were sampled before diagnosis and those following diagnosis (table 6-3). The 5-year relative survival of PC patients sampled before diagnosis was modelled using the full likelihood approach and is shown in table 6-4. On univariate analysis, patients older than 75 years of age ($p < 0.05$), high or unknown Gleason grade ($p < 0.01$), raised mGPS ($p < 0.001$) and a raised NLR ($p < 0.01$) were significantly more likely to die. On multivariate analysis, high (RER 5.15, 95% CI 1.74-15.20) and unknown (RER 27.54, 95% CI 9.07-83.64) Gleason grade and mGPS of 2 (RER 2.08, 95% CI 1.13-3.81) were the major predictors of relative excess risk of death after adjusting for age, Gleason grade, socio-economic circumstances and NLR (table 6-4).

Five year relative survival of PC patients sampled after diagnosis and modelled using the full likelihood approach is shown in table 6-5. On univariate analysis, patients older than 75 years of age ($p < 0.05$), high or unknown Gleason grade ($p < 0.001$), raised mGPS ($p < 0.001$) and raised NLR ($p < 0.001$) were significantly more likely to die. On multivariate analysis, increasing or unknown Gleason grade, mGPS of 2 (RER = 2.93, 95% CI 1.81-4.78) and NLR $\geq 5:1$ (RER 2.38, 95% CI 2.38) were significant predictors of death after adjusting for other factors (table 6-5). There was no significant interaction between the NLR and mGPS while employing these excess risk models (table 6-5).

When this analysis was repeated based on Gleason grade, I observed a significant association between raised mGPS and risk of death in the low grade group (RER 7.58, 95% CI 1.44-39.76), higher Gleason grade category (RER 2.08, 95% CI 1.26-3.45) and those with unknown Gleason grades (RER 1.97, 95% CI 1.03-3.73) after adjustment for age, socio-economic circumstances and NLR (table 6-6). In grade specific analysis, NLR only showed a significant association with risk of death for unknown Gleason grade after adjustments for age, socio-economic circumstances and mGPS (table 6-5). Similarly, age-specific analyses were also carried out and raised mGPS showed significantly higher risk of death among those with age < 65 and

65-74 years at diagnosis. However, a non-significant increased risk of death was also observed among those age >75 years.

Figure 6-1 shows the relative survival of high grade (Gleason 8-10) PC patients based on the mGPS. Analysis of this subgroup showed that the mGPS was associated with reduced survival with a mGPS of 2 having 29% lower 3-year relative survival, when compared to those with a mGPS of 0.

Table 6-3: 1 year and 5 year relative survival of prostate cancer patients based on blood sampling categories; before and following a diagnosis.

	Before cancer diagnosis		After cancer diagnosis	
	Relative Survival		Relative Survival	
	1-year, % (95% CI)	5-years, % (95% CI)	1-year, % (95% CI)	5-years, % (95% CI)
Age at incidence				
Age < 65	91.7 (81.9-96.7)	69.2 (54.0-81.2)	90.7 (84.8-94.6)	75.1 (65.4-83.0)
Age 65-74	89.9 (81.9-95.1)	56.1 (41.6-69.8)	93.0 (88.0-96.5)	72.1 (62.8-80.4)
Age ≥ 75	68.2 (59.8-75.8)	49.4 (36.4-63.1)	87.1 (78.7-93.5)	55.9 (42.2-69.9)
Gleason Grade				
Gleason < 7	99.1 (89.9-100)	95.2 (74.8-100.1)	100 (97.7-100)	100 (91.5-100)
Gleason = 7	100 (100-100)	100 (82.8-100.2)	98.5 (92.4-100)	88.9 (75.4-99.3)
Gleason 8-10	81.7 (72.8-88.5)	47.2 (33.3-61.3)	83.8 (77.5-88.8)	46.3 (36.7-55.9)
Unknown Gleason	48.3 (37.6-58.6)	9.3 (3.0-20.6)	73.8 (59.3-84.7)	27.8 (14.5-44.3)
SIMD 2004, Quintiles				
1 (least deprived)	86.2 (72.3-94.8)	59.0 (35.2-81.0)	86.1 (77.9-91.9)	72.6 (61.3-82.3)
2	79.7 (63.3-90.9)	52.3 (27.8-76.9)	90.9 (79.5-97.2)	60.1 (40.5-77.6)
3	80.5 (65.9-90.2)	67.2 (47.1-84.4)	90.1 (79.6-96.2)	76.5 (60.5-89.7)
4	81.1 (69.5-89.6)	45.3 (27.9-63.5)	91.7 (82.9-97.1)	68.5 (54.1-81.2)
5 (most deprived)	77.2 (68.0-84.7)	55.7 (42.5-68.8)	93.9 (87.8-98.1)	64.9 (52.9-76.2)
Inflammation based prognostic scores				
mGPS				
0	87.8 (81.1-92.9)	65.8 (53.5-77.3)	97.2 (93.4-99.7)	85.5 (76.7-93.0)
1	77.6 (68.7-84.8)	49.5 (37.2-62.0)	88.9 (81.7-94.1)	55.0 (44.0-65.7)
2	59.1 (43.0-72.9)	30.7 (8.1-65.2)	75.5 (66.5-84.4)	45.5 (33.1-58.0)
NLR				
0	87.6 (80.5-92.9)	64.6 (51.5-76.8)	96.1 (91.8-99.0)	80.7 (70.9-89.0)
1	70.2 (59.0-79.4)	51.7 (34.9-68.7)	83.0 (76.5-88.3)	54.7 (45.1-64.1)
Missing	77.6 (67.2-85.8)	46.8 (33.3-60.6)	94.3 (84.9-99.5)	68.2 (53.1-87.6)

Relative survival estimates are age, gender, calendar year and deprivation specific.

Table 6-4: Relative excess risk of death of prostate cancer patients sampled before diagnosis modelled using the full likelihood approach

	Univariate analysis			Multivariate analysis		
	Relative Excess Risk (95% CI)	p value		Relative Excess Risk (95% CI)	p value	
<i>Age at incidence</i>						
Age < 65	1			1		
Age 65-74	1.38 (0.74, 2.58)	0.32		1.55 (0.83, 2.92)	0.173	
Age ≥ 75	2.05 (1.14, 3.69)	0.02		1.63 (0.89, 2.98)	0.122	
<i>Gleason Grade</i>						
Gleason < 7	1			1		
Gleason = 7	0.81 (0.10, 6.52)	0.84		0.46 (0.05, 4.13)	0.491	
Gleason 8-10	7.39 (1.84, 29.73)	0.005		5.15 (1.74, 15.20)	0.003	
Unknown Gleason	31.13 (7.78, 124.58)	<0.001		27.54 (9.07, 83.64)	<0.001	
<i>SIMD 2004, Quintiles</i>						
1 (least deprived)	1			1		
2	1.73 (0.69, 4.37)	0.25		1.74 (0.71, 4.27)	0.230	
3	1.49 (0.59, 3.79)	0.39		2.41 (0.97, 5.96)	0.061	
4	1.82 (0.78, 4.29)	0.17		1.06 (0.45, 2.52)	0.893	
5 (most deprived)	1.75 (0.77, 3.97)	0.18		1.39 (0.61, 3.18)	0.442	
<i>modified Glasgow Prognostic Score</i>						
0	1			1		
1	1.58 (0.97, 2.58)	0.07		0.92 (0.56, 1.49)	0.721	
2	3.05 (1.74, 5.36)	<0.001		2.08 (1.13, 3.81)	0.021	
<i>Neutrophil Lymphocyte Ratio</i>						
0	1			1		
1	1.82 (1.19, 2.78)	0.005		1.55 (0.98, 2.48)	0.064	

All estimates were adjusted for age at incidence, socio-economic circumstances, mGPS and NLR.
Patients with missing NLR were excluded from these analyses

Table 6-5: Relative excess risk of death of prostate cancer patients sampled after diagnosis modelled using the full likelihood approach

	Univariate analysis			Multivariate analysis		
	Relative Excess Risk (95% CI)		p value	Relative Excess Risk (95% CI)		p value
<i>Age at incidence</i>						
Age < 65		1			1	
Age 65-74	1.11	(0.71, 1.72)	0.65	1.28	(0.82, 0.91)	0.271
Age ≥ 75	2.07	(1.32, 3.25)	0.002	1.43	(0.91, 2.26)	0.122
<i>Gleason Grade</i>						
Gleason < 7		1			1	
Gleason = 7	3.12	(0.81, 12.06)	0.09	3.12	(1.05, 9.21)	0.043
Gleason 8-10	13.71	(3.94, 47.69)	<0.001	11.09	(4.17, 29.45)	<0.001
Unknown Gleason	19.48	(5.42, 70.04)	<0.001	20.80	(7.28, 59.44)	<0.001
<i>SIMD 2004, Quintiles</i>						
1 (least deprived)		1			1	
2	1.27	(0.68, 2.73)	0.46	1.23	(0.68, 2.63)	0.501
3	0.93	(0.48, 1.78)	0.83	0.70	(0.36, 1.34)	0.282
4	1.13	(0.64, 1.98)	0.68	1.04	(0.59, 1.83)	0.902
5 (most deprived)	1.19	(0.71, 1.98)	0.51	0.75	(0.46, 1.24)	0.261
<i>modified Glasgow Prognostic Score</i>						
0		1			1	
1	3.12	(1.89, 5.18)	<0.001	1.78	(1.10, 2.89)	0.721
2	5.36	(3.27, 8.78)	<0.001	2.93	(1.81, 4.78)	<0.001
<i>Neutrophil Lymphocyte Ratio</i>						
0		1			1	
1	2.89	(1.95, 4.29)	<0.001	2.38	(1.58, 3.59)	<0.001

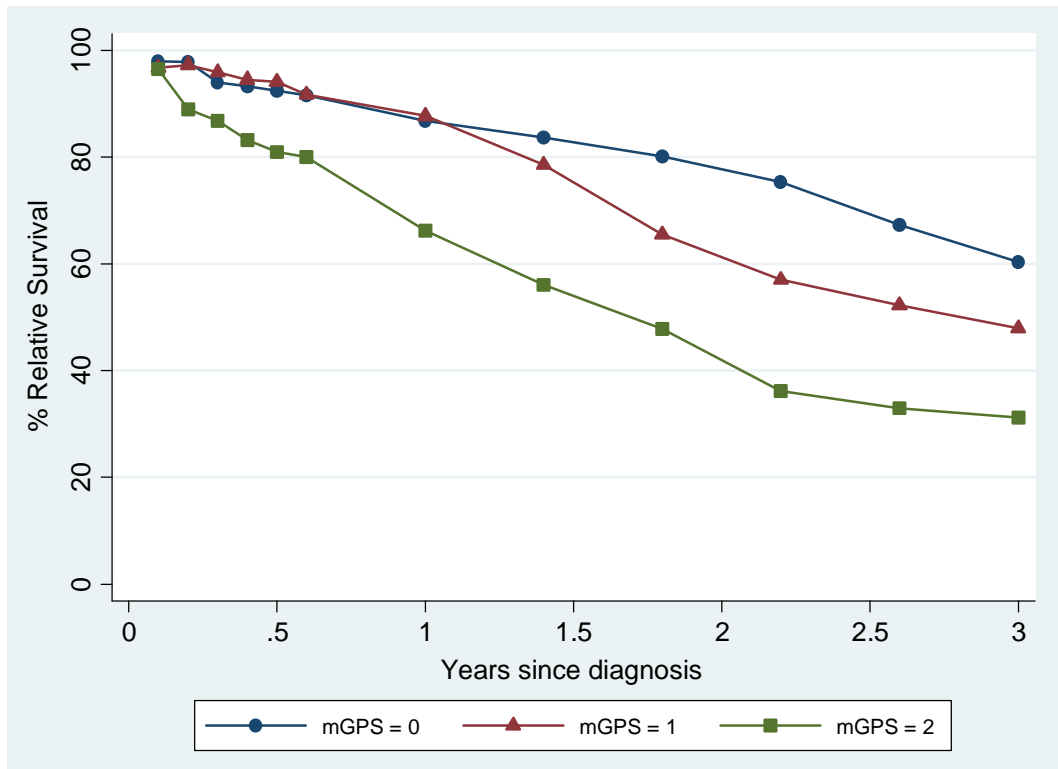
All estimates were adjusted for age at incidence, socio-economic circumstances, mGPS and NLR.
Patients with missing NLR were excluded from these analyses

Table 6-6: Five year relative survival of prostate cancer patients based on grade specific categories modelled using full likelihood approach

<i>Prognostic Scores</i>	Gleason < 7			Gleason = 7			Gleason 8-10			Unknown Gleason	
	Total patients	Number of deaths	Relative Excess Risk (95%CI)	Number of deaths	Relative Excess Risk (95%CI)	Number of deaths	Relative Excess Risk (95%CI)	Number of deaths	Relative Excess Risk (95%CI)		
<i>mGPS</i>											
0	349	(11)	1	(14)	1	(55)	1	(28)	1		
1	219	(10)	0.86 (0.08, 9.11)	(14)	3.25 (0.85, 12.34)	(43)	1.13 (0.69, 1.84)	(50)	1.36 (0.76, 2.44)		
2	141	(9)	7.58 (1.44, 39.76)	(7)	3.40 (0.86, 13.49)	(47)	2.08 (1.26, 3.45)	(23)	1.97 (1.03, 3.73)		
<i>NLR</i>											
0	405	(11)	1	(18)	1	(65)	1	(49)	1		
1	304	(19)	1.43 (0.27, 7.63)	(17)	1.84 (0.58, 5.81)	(80)	1.52 (1.00, 2.30)	(52)	2.38 (1.41, 4.00)		

All estimates were adjusted for age at incidence, socio-economic circumstances, mGPS and NLR. Patients with missing NLR were excluded from these analyses.

Figure 6-1: Three year relative survival of high grade (Gleason 8-10) prostate cancer patients based on modified Glasgow Prognostic Score



Relative survival estimates are age, gender, calendar year and deprivation specific.

6.5 Discussion

6.5.1 Findings of present analysis and potential explanations

The results of the present study show that systemic inflammation based prognostic scores - whether they are the mGPS or NLR - predict PC specific survival. In particular, the mGPS had prognostic value independent of time of sample, age at diagnosis, Gleason grade, socio-economic status and NLR. I observed 35-40% lower 5-year relative survival among those with raised modified Glasgow Prognostic Score (mGPS = 2) compared to the normal (mGPS = 0) for those who were sampled either before or following diagnosis of PC.

In the present study, patients with high Gleason grade disease had a significantly raised mGPS compared with low grade disease. In Gleason grade specific analysis, a raised mGPS had significant associations with excess risk of death among patients with low, high and unknown Gleason grades, while NLR only showed significant association with poorer survival of unknown Gleason grade patients. In high grade disease, patients with higher systemic inflammation (mGPS = 2) had approximately 200% excess risk of death in the first five years after diagnosis compared to those with low level of systemic inflammation (mGPS= 0). Although there was no significant association between mGPS and survival in the intermediate Gleason grade, this could have been due to the small number of deaths in the intermediate grade disease category (n=35). The largest effect of mGPS was seen in patients with low grade PC (Gleason <7), a group for whom there is currently the greatest clinical uncertainty about their prognosis and management. Irrespective, taken together these results highlight the importance of systemic inflammation in relation to survival in patients with PC.

In the present study patients with unknown Gleason grade had poorer relative survival even when compared to those with high grade disease. These unknown Gleason grade patients may have had pre-terminal disease that was deemed metastatic and therefore histological staging was not considered appropriate. Interestingly, both mGPS and NLR were shown to have prognostic value in this group of patients. Indeed, in those patients with unknown Gleason grade, those who had raised mGPS were twice as likely to die in the first five years following

diagnosis as compared to those with lowest level of mGPS. This association remained significant even after adjusting for age, socio-economic circumstances and NLR.

6.5.2 Strengths and limitations

Systemic inflammation measured by C-reactive protein has been associated with many chronic conditions including incidental and prevalent cardiovascular diseases (Kaptoge *et al.*, 2010;Wensley *et al.*, 2011). Given that PC is a disease of old age, patients in the present study may have co-morbid conditions leading the activation of the systemic inflammatory response. If this is the case, then differences in survival (estimated by conventional techniques using overall and cancer specific survival) between mGPS categories, may be explained by the distribution of co-morbidity between groups. However, in the present study, relative survival was adjusted for the background population mortality and so is based on cancer associated deaths. Moreover, when adjusted for NLR, age, socio-economic status and Gleason grade, patients with an elevated mGPS were significantly more likely to die at five years.

To my knowledge this is the first study to compare the prognostic value of mGPS and NLR in PC patients, taking into account the background population mortality, age, Gleason grade and socio-economic status. The present study has, however, a number of limitations. Firstly, patients were selected on the basis of availability of C-reactive protein, albumin and calcium levels. This is an important point need to be considered before interpreting the results of the present analysis. The main question is that why these men were sampled to obtain the C-reactive protein? Was there any significant clinical condition associated with the raised C-reactive protein other than the cancer? Due to these issues directly related to the C-reactive protein make this cohort a group of patients with uncertain characteristics, C-reactive protein and other measurements were taken incidentally. There is a possibility that these patients might have had concurrent morbidity for which they were clinically investigated. Therefore this cohort of patients might not be representative of all the PC patients diagnosed and treated in the north of Glasgow. However, co-morbidity is unlikely to have had a major effect on results of this analysis, as I adjusted for

background mortality using age, sex and deprivation specific population mortality rates. Third, there was no information on the exact timing of treatment following diagnosis and it is possible that early treatment may have been responsible for increases in acute phase proteins. However, the relationship between inflammation and prognosis was similar in samples taken before and after diagnosis, suggesting that early treatment was not a significant confounding factor. Finally, the existing data did not have the information on PSA or disease stage and patients may have had higher inflammatory status due to metastatic disease. However, previous studies have shown systemic inflammation to be associated with survival, independent of disease stage, for gastroesophageal, colorectal (including those with liver metastases), renal, breast and PCs (Pierce *et al.*, 2009;Roxburgh and McMillan, 2010). Similarly, earlier small studies on PC patients also showed that systemic inflammation measured by C-reactive protein was associated with poorer survival both in localised and metastatic PC (McArdle *et al.*, 2006;McArdle *et al.*, 2010).

6.5.3 Implications for practice and research

The prognosis of PC patients is not well understood and clinicians treating cancer patients make decisions on the basis of individual's age, fitness, comorbidity, PSA, Gleason grade and disease stage. Novel genetic and immunological biomarkers have been identified but these, to date, have not been incorporated into routine clinical practice (Castelli *et al.*, 2010;Huang *et al.*, 2010). The results of the present study indicate that systemic inflammation is of clinical importance and may suggest the routine use of the mGPS as a readily available tool for risk stratification in patients with PC.

Given the limitation of the data presented in this chapter, there is an uncertainty about the patients for whom CRP was measured. Current data do not have any information about the conditions which led to sampling for inflammatory markers and some unknown confounders may have influenced the findings of present analysis. Therefore, further work is required to investigate this relationship in a larger, representative sample of PC patients including information on other measures of prognosis (e.g. disease stage and PSA) and treatment offered to patients.

7 Discussion

This chapter will briefly review the principal results of the thesis and then discuss epistemological aspects of PC epidemiology, before suggesting how public health practice and future scientific enquiry might be directed.

7.1 Review of principal results

7.1.1 Incidence and risk factors

The analysis of Scottish cancer registry data found that the incidence of PC increased steeply in the West of Scotland since 1991. Both low and high grade disease increased. Incidence rates, particularly of low grade disease, increased more in men from more affluent areas, leading to the emergence of a deprivation gap. PC incidence increased to a greater extent among men aged less than 65 years.

Two analyses of the MIDSPAN prospective cohort study were performed. The first suggested that plasma cholesterol level had a significant positive relationship with the development of aggressive PCs. Furthermore, height appeared as a significant risk factor for PC. The second analysis suggested that tea had a positive (harmful) relationship with overall risk of PC. This finding was not consistent with previously published analyses of the relationship between tea and PC. This may be because other published research reflects the preventive effects of green tea while Scottish data reflect consumption of black tea. In contrast, coffee consumption appeared to have a weak inverse relationship with overall PC risk but a stronger inverse relationship with aggressive PC.

It seems most likely that incidence patterns reflect PSA testing - whose use may have increased over time and to a greater extent in more affluent men - rather than a true increase in risk. The effect sizes of cholesterol, tea and coffee are relatively small and unlikely to explain the temporal, socio-economic or age patterns in PC incidence.

7.1.2 Survival and prognosis

Survival of PC patients has improved since 1991 in the West of Scotland, consistent with other constituent countries of the UK and Europe. However, the

improvement has been greater among least deprived men, leading to increasing socio-economic inequalities in survival. These inequalities developed in earlier study period and increased over time. Adjustment for age and grade at diagnosis attenuated but did not remove the socio-economic differential in survival.

Analysis of the Glasgow Inflammation Outcome Study data found that systemic inflammation (either measured by the modified Glasgow Prognostic Score or Neutrophil Lymphocyte Ratio) was an independent determinant of both short term and long term survival of PC patients. However, the mGPS appeared to be a better prognostic indicator and may help in the clinical management of patients.

7.2 Epistemology of prostate cancer epidemiology

The epidemiology of PC is particularly affected by temporal, geographical and individual influences on detection of the disease. These affect the interpretation of both its incidence and survival. In this section, I consider to what extent patterns of incidence and survival may be genuine or the result of artefact. This leads to conclusions for two areas; ways in which methodological improvements might be made to reduce artefact in future research and public health implications of the most reliable findings.

7.2.1 Incidence, aetiology and prevention

PC incidence is measured so that future healthcare needs can be predicted and to evaluate potential risk factors for the disease. These in turn should lead to action to plan appropriate health services and to implement preventive strategies, respectively. However, factors that are associated with greater likelihood of detection may appear themselves to be risk factors for PC. For example, PSA testing has been increasingly used over time to test men for possible PC and this may partially or wholly explain the temporal rise in PC incidence. Other behavioural or anthropometric factors that have also increased over time - for example, obesity - may therefore be artefactually associated with PC risk. The differential use of PSA testing in men from more affluent circumstances, or at younger ages, may also largely explain increases in incidence in both groups.

If the associations between tea, coffee and cholesterol and PC are not artefactual, what is the strength of evidence that they are causal? The findings of the MIDSPAN studies presented in this thesis suggest that coffee consumption and plasma cholesterol level have a significant relationship with aggressive PCs while tea consumption has a strong relationship with overall risk of PC. Considering in turn Bradford Hill's criterion, the sine qua non is a temporal association, that exposure always precedes the outcome. In the analysis of coffee consumption and cholesterol, data on all exposures were recorded at least two decades before incidence of aggressive PC. For tea and overall PC, data were recorded at baseline and cancers that occurred within the first ten years of follow-up were removed to minimise any effect of reverse causality. Thus, there was a clear temporal relationship between exposures (tea, coffee and cholesterol) and outcomes (PC and aggressive PC) in the analysis of MIDSPAN data. The criterion for strength of association is more equivocal, as many truly causal factors have small relative risks or hazards in population-based analyses and arbitrary values of a "strong relationship," such as relative risks or odds of 3 or more, may not be found. However, hazard ratios of 2 or more were found for several associations from the MIDSPAN data. A dose-response relationship was found for tea, coffee and cholesterol. For coffee consumption, the risk of disease was reduced with increasing consumption of coffee while an inverse relationship was found for cholesterol and tea consumption. The findings of this thesis are consistent with results published elsewhere for both coffee and cholesterol and aggressive PC. In contrast, the evidence for tea consumption reported elsewhere has been that its effects, if any, are protective, while I found an increased risk with greater consumption. This may be because the majority of research reports the effects of green tea, whereas our findings reflect black tea consumption. Thus, there is a biologically plausible explanation for the inconsistency. The criterion of coherence is similar to that of consistency. There is emerging evidence from biological studies that supports the plausibility of coffee and cholesterol in the development of aggressive PC. With respect to alternative explanations for the findings, I have considered above the role that differential PSA testing might explain temporal, socio-economic and age specific patterns of PC incidence. It is difficult to hypothesise that consumption of tea or coffee may affect the likelihood of PSA testing but it is possible that they act as markers for other healthcare-seeking behaviours. It is

easier to speculate that patients with higher cholesterol levels would be more likely to obtain ongoing medical attention and thereby increase their likelihood of incidental PSA testing. I am not aware of experimental evidence to support the hypothesis that lowering cholesterol or increasing consumption of coffee will prevent aggressive PC. The criterion for specificity is considered to be the weakest of Hill's criteria and most of the chronic diseases, including cancers, have multifactorial aetiologies. The role of cholesterol as a risk factor in other disease, particularly cardiovascular diseases, is well established (Lewington *et al.*, 2007).

On balance, then, the associations between cholesterol and coffee consumption and aggressive PC do fulfil some of the main components of Hill's criteria of causation. There is a temporal but not consistent relationship between tea and PC. These findings are relatively recent, and it would be too early to recommend that coffee and cholesterol can prevent or cause PC. Further epidemiological and biological evidence may explain these associations and provide better insight into their role in disease aetiology.

Several established risk factors of PC are non-modifiable (for example, age, family history and race) and thus there is little that can be done with such knowledge, except, perhaps, to target information on awareness and prompt diagnosis. The substantial body of evidence on dietary and lifestyle factors remains equivocal and results are so conflicting that no definitive recommendations can be made. Although I found some associations between tea, coffee and cholesterol level in relation to overall and aggressive PC, the effects were either inconsistent with previous studies or the effect sizes too small to recommend public health action compared with, for example, the need for more effective health promotion on smoking, obesity and alcohol consumption. The question remains that if a cohort of tens of thousands of men followed-up for decades does not provide any compelling evidence on PC risk, should further primary research be carried out and if so, what would be the most efficient methodology? A meta-analysis of existing studies may be appropriate. The addition of PSA testing has also significantly influenced efforts to understand the natural history of PC by adding indolent and asymptomatic tumours into the pool of clinically relevant PCs. Most population-based studies

which have attempted to understand the aetiology of PC have not had information on PSA levels and could not differentiate between clinically manifested cases and screen detected cases.

Case control studies often estimate exposure status by interviewing participants following their diagnosis, when exposure may have been affected by asymptomatic disease. For instance, most of the evidence from case control studies that circulating hormone levels are related to PC is inconsistent, and these studies suffered from a major problem that disease status may well alter serum concentrations of androgens even before its manifestation (Hsing, 2001). Thus an apparent “reverse causal” relationship may be observed. Case control studies suffer from a number of other biases, including survivor bias (where information on exposure is gathered from living patients only) and recall bias (where patients with PC are more likely to report putative exposures than patients without cancer). Prospective cohort studies provide better evidence of the temporal relationship between hormonal levels and PC risk. Prospective studies reduce the likelihood that changes in hormone levels are due to disease presence if blood samples are taken some years prior to diagnosis. However, prospective studies may also suffer from reverse causality as most recruit participants in middle age when early PC may already be present. For instance, the prevalence of asymptomatic invasive carcinoma among middle age men has been reported from 40% to 60% (Sakr *et al.*, 1993). Thus, observed risk factors may have some association with the progression of the disease from asymptomatic to clinically significant disease rather than a true primary causal role (Giovannucci, 2011). Studies with a follow-up of 5-10 years may also be prone to a similar problem of describing factors related to progression rather than true incidence of disease. Prospective studies with longer follow-up may add something in understanding the aetiology of this complex cancer.

One limitation of using prospective cohort studies to study risk factors for PC, however, is that PC has a long, although uncertain, natural history and it may be several decades after exposure to a risk factor before PC is diagnosed. Thus, exposure to baseline risk factors may not have continued during the at-risk period. In the present data, with a long follow-up period, I found limited evidence that any modifiable risk factor can reduce the risk of PC. While a

prospective trial with long follow-up can provide some insights into disease aetiology, additional PC-specific information is needed. This might include further diagnostic testing to confirm the presence or absence of a prostatic tumour or lesions at baseline screening along with information on demographics, anthropometric measurements, food intake, lifestyle habits and haematological measures. The outcome of such a trial can also be subdivided by “testing for a cause” or “not for a cause” as reported elsewhere (Giovannucci, 2011).

7.2.2 Survival of prostate cancer patients

The patterns of survival reported in chapter 5 (page 165) over a 17 year period suggest a real improvement in survival and reflect a rapid and substantial shift in the biological and clinical spectrum of PC. Improvements in the effectiveness of therapeutic interventions and increasing likelihood of active treatment may well have made contributions to the observed survival benefits over time. However, data from cancer registries on treatment modalities is limited, particularly in earlier years. The observed survival benefits in recent years may be driven by other factors such as lead time bias and a change in case-mix towards less aggressive disease, rather than advances in treatment modalities (Clarke, 2008).

The relationship between socio-economic circumstances and survival is complex. When considering the “deprivation gap” in survival between socio-economic groups, it is important to adjust for higher incidence rates of less aggressive disease among more affluent men, as these would be expected to have better survival. However, the deprivation gap persisted even when after adjustment for age and disease grade. This suggests two things. The first is that the overall deprivation gap would not be removed by efforts to ensure that men from more deprived areas were diagnosed at an earlier grade. The second is that further work is needed to understand what other prognostic factors explain socio-economic differences in survival of men with the same grade of PC. It may be that higher prevalence of co-morbidities in more deprived individuals explains some of their excess mortality, but cancer registry data do not contain such information. Furthermore, cancer stage is also a significant determinant of survival of patients with PC. The socio-economic differential in survival may be due to differential distribution of advanced disease between different socio-

economic groups, however, this analysis couldn't control for the effect of disease stage on survival due to lack of information on stage in cancer registry data for the studied period (1991-2007).

Socio-economic differences in incidence and survival of PC are of concern for two main reasons. First, they suggest unacceptable inequities, either in the broad determinants of health or in the quality of healthcare (Marmot and Feeney, 1997). Second, governments set the targets for health improvements and if the health improvements occur at a slower rate in some socio-economic groups, then the remainder of population must show much faster and greater improvements to keep up the average for the society as a whole (Marmot and Feeney, 1997).

Geoffrey Rose noted that, "the determinants of individual risks of disease - why one individual gets sick and other remains healthy - may be different from the determinants of population rates of disease" (Rose, 1992). The fundamental questions arising from this are, whether there are individual behavioural factors (for example, diet, smoking, alcohol, BMI, or physical activity) or health care related factors which influence the survival of different socio-economic groups. Deprived men, generally, may have poorer general health due to lifestyle and dietary factors compared with affluent men (Mensah and Hobcraft, 2008). Poor general health can have negative effects on the survival of patients who are diagnosed with PC in a number of ways. Men with poorer overall health are less likely to receive aggressive surgical, radiological or hormonal therapy due to their increased risks of side-effects. The independent effects of co-morbidities may be another explanation for observed differences in survival. Although, some effects of socio-economically patterned co-morbidities are minimised through relative survival analysis, they cannot be removed completely. Cancer registry data do not hold information on patients' lifestyle-related factors or information about access and quality of health services.

Currently, all diagnosed patients are treated by a multidisciplinary team (MDT) of specialists. There are no available data either on individual factors or on aspects of access, availability or effectiveness of health care, in the West of Scotland MDT database. There is a need to collect information about patients'

lifestyle habits which could be obtained conveniently while other routinely collected information is obtained during clinical assessment. In addition, service related information such as waiting times and availability of supportive care services during treatment could also be obtained to better understand the role of differential survival patterns between socio-economic groups.

It might be asked whether, on balance, the incidence and survival differences of PC truly disadvantage deprived men. More deprived men may have been spared the physical and psychological effects of over-diagnosis and over-treatment which is currently the main concern with early detection of PC by PSA-testing (Yao and Lu-Yao, 2002). They may also have been spared from the subsequent health risks associated with treatment discussed earlier. In this sense, the deprived men may, for once, appear better off than their affluent counterparts. However, other men in the deprived group, whose cancer is a high risk, aggressive disease and a significant threat to their life would have been disadvantaged (Clarke, 2008).

Another aspect is the growing evidence on systemic inflammation and its relationship with survival of cancer patients. Compelling evidence has suggested that systemic inflammation has a significant prognostic value in many cancers (Gomez *et al.*, 2008; Proctor *et al.*, 2011; Walsh *et al.*, 2005). In this thesis, systemic inflammation also appeared to have a significant prognostic value in PC patients. This could help in multiple ways. The first is in its role in decision making for cancer patients. Systemic inflammation-based prognostic scores can help in stratifying high-risk groups who need urgent and aggressive treatment. Secondly, some preliminary evidence suggests that anti-inflammatory drugs may have some role in regulation or reversal of inflammation in cancer tissue, which may ultimately reduce the risk of progression of disease and improved survival (Vaish and Sanyal, 2011). Further research is required in this area to understand the role of inflammation and survival of PC patients.

The substantial improvements in survival from PC are encouraging but it remains uncertain whether these have been driven by greater diagnoses of low risk PCs and or are the effects of lead time bias and not true increases in life expectancy. Better survival among more affluent patients is not wholly

explained by lower grade disease or younger age at diagnosis and further insights are needed into socio-economic differentials in survival.

7.3 Living with prostate cancer

The results presented in thesis suggest an increasing incidence and improving survival of men with PC, leading to substantial increases in the prevalence of the disease. In Scotland, 12,887 men were diagnosed with PC during 2003-2007 and this is expected to increase to 15,547 in 2008-2012. Five and ten year relative survival of these men was 80% and 70% respectively (Information Services Division, 2011).

In recent years, evidence has emerged that after a diagnosis of PC men experience increased risks of developing other serious health conditions including anxiety, depression, cardiovascular disease, pathological fractures and self-harm. Following PSA-testing, a significant proportion of men who are diagnosed with either localised or advanced PC develop anxiety and depression. The prevalence of these conditions has been reported to be from 20% to 50% in different populations (Bennett and Badger, 2005; Couper *et al.*, 2010; Dirksen *et al.*, 2009).

A population-based study from Sweden found that self-reported psychological distress among men with PC was significantly higher compared to the general population (Bill-Axelsson *et al.*, 2011a). The risk of psychiatric hospitalisation due to depression, anxiety and post-traumatic stress disorder were significantly increased (RR 1.29, (95% CI 1.14-1.45), RR 1.42 (95% CI 1.12-1.80) and RR 1.61 (95% CI 1.16-2.24), respectively) (Bill-Axelsson *et al.*, 2011a). However, hospitalisations due to anxiety were only increased in men with more advanced tumours (RR 2.28, 95% CI 1.45-3.57). The use of antidepressants was increased in all men with PC (RR 1.65, 95% CI 1.54-1.77). The risk of depression increases up to five times independent of cancer risk group and treatment strategy (Bill-Axelsson *et al.*, 2011a).

These psychological conditions not only affect the general health related quality of PC survivors (Sharpley *et al.*, 2010; Zenger *et al.*, 2010; Lev *et al.*, 2009) but also increase the risk of suicide among these men (Bill-Axelsson *et al.*,

2010;Llorente *et al.*, 2005). Compared to the general population, the risk of suicide was significantly increased during the first and second years following diagnosis and even after two years there was a two-fold increase in risk in patients with locally advanced tumour stages T3 and T4 (Bill-Axelson *et al.*, 2010). For patients with distant metastases (M1), there was a two-fold increase in the risk of committing suicide (SMR: 2.1; 95% CI, 1.2-3.6). These findings point towards the risk of subsequent psychological conditions among PC survivors.

Most of the studies investigating these psychological conditions are based on small numbers of cases using cross sectional approaches, with limited information on treatment related factors, and in some cases with short follow-up periods. Determinants associated with these conditions are largely unknown and how the incidence of these psychological conditions changes over time after the diagnosis remains unclear. The stress of having disease, chronicity of pain, treatment related adverse effects, comorbidity and socio-economic status have been suggested to have significant roles in the development of these conditions. However, most studies did not reach a consensus on the major determinants of psychological conditions because of different times since diagnosis when subjects were interviewed, different stages of disease, treatments offered and differences in populations from which the samples were drawn.

Recent data suggest that half of men diagnosed with PC receive hormonal therapy at some point after the diagnosis and most men take it for at least two to three years (Alibhai *et al.*, 2009). Besides the poorer quality of life among PC survivors who receive hormonal therapy, a growing body of evidence suggests that PC survivors who receive hormonal therapy experience increased risk of diabetes (Alibhai *et al.*, 2009;Keating *et al.*, 2010;Kintzel *et al.*, 2008;Leahy, 2008;Smith, 2008), metabolic syndrome (Faris and Smith, 2010;Kintzel *et al.*, 2008;Leahy, 2008;Nobes *et al.*, 2009), cardiovascular diseases (Keating *et al.*, 2010;Kintzel *et al.*, 2008;Ribeiro *et al.*, 2010;Saylor *et al.*, 2011) and pathological fractures (Abrahamsen *et al.*, 2007;Alibhai *et al.*, 2010;Lau *et al.*, 2009;Melton, III *et al.*, 2011).

The relationship between hormonal therapy and metabolic and cardiovascular disease is thought to be due to the adverse effects of suppression of

testosterone and development of androgen deprivation syndrome (Abrahamsen *et al.*, 2007) - the condition characterized by many metabolic changes, including increasing fat mass, dyslipidemia and insulin resistance (Faris and Smith, 2010). All these metabolic changes increase the risk of cardiovascular and cerebrovascular events in later life. Although the evidence is limited, there is some suggestion of significant variations in metabolic syndrome following hormonal therapy between men of different racial origins (Beebe-Dimmer *et al.*, 2009). There may also be variations in the development of these conditions between socio-economic groups but research is not available.

PC survivors who receive hormonal therapy are at an increased risk of bone loss and osteoporosis. These delayed effects of hormonal therapy increase the risk of fractures (Egerdie and Saad, 2010). Hormonal therapy may also increase the risk of some fractures (including skull, rib and foot) which are not typical of osteoporotic fractures (Alibhai *et al.*, 2010). In 75% of men who had a fracture following hormonal therapy, it occurred in the first five years of treatment (Abrahamsen *et al.*, 2007). The excess risk of fractures increased from two to nine times depending on the site and age of patients with the highest risk among men aged 50-65 years (Abrahamsen *et al.*, 2007).

I am unaware of any published evidence on any of these prevalent health conditions among PC survivors in the UK or Scotland in particular. As the prevalence of PC continues to increase steeply, there is an urgent need to examine these health risks. A thorough investigation into these psychological, cardiovascular and musculoskeletal disorders may be able to identify high risk groups of PC survivors, which will ultimately help health professionals to make better choices when offering treatment and support to patients.

7.4 Strengths and limitations of this thesis

The particular strengths and weaknesses of each component study in this thesis have been discussed with each relevant chapter. This section considers some of the general strengths and limitations of the thesis.

7.4.1 Strengths

The present thesis has made many contributions to the understanding of PC epidemiology, particularly in Scotland. Population-based data were used to analyse incidence and survival trends in the West of Scotland. The quality of cancer registration data is good with high levels of accuracy and completeness (Brewster *et al.*, 1994). These data provide a valid picture of the cancer burden in the region and consistent methodology has been used over time. Additionally, the potential to link cancer registry data with death records and other available databases (biochemistry records) provided valuable information on survival and determinants of survival.

The epidemiological studies carried out to understand the aetiology of PC, used data from large population-based cohort studies. Perhaps the most cited justification for conducting a population-based study is its external validity - that is, the applicability of its results to a defined population. The Midspan cohorts comprise large samples, very long follow-up periods and low losses to follow-up, making them a valuable source of information in understanding the aetiology of PC. In addition, the availability of a large number of variables including demographic and physical measures further strengthens their value.

7.4.2 Limitations

Study-specific design and analytical limitations have been described in each chapter. Some methodological limitations related to observational epidemiology that are relevant to this research will be discussed in this section. The discussion on these limitations will bring forward some new ideas and suggestions that may help improve future research studies and understanding of PC epidemiology. Some general limitations of epidemiological approaches - that is the descriptive and analytical epidemiology - will also be covered in this section. Limitations of confounding, bias and ecological fallacy will also be discussed in the context of this thesis.

7.4.2.1 Descriptive epidemiology

In this thesis, both the incidence and survival trends of PC have been reported in relation to time, place and person, the basic principles of descriptive

epidemiology (Esteve *et al.*, 1994). A difficulty of descriptive epidemiological studies is that both the exposure and outcome measurements are collected at one point - which in case of PC incidence was the date of PC diagnosis. Socio-economic circumstances had a significant relationship with both the outcomes (incidence and survival) reported in chapters 2 and 5.

As discussed above, exposure assessment should be made prior to the occurrence of the outcome, while in cancer registry data socio-economic circumstances are derived from area of residence using the post code information at the time of diagnosis. Thus, it may be that risk factors or symptoms of PC have negative effects on socio-economic circumstances (for example, by restricting employment) rather than socio-economic effects increasing risks of PC.

However, socio-economic circumstances of men may still have some role in the detection of PC as affluent men may be more likely to access health services or be tested by PSA due to greater awareness and health consciousness. In relation to socio-economic circumstances and survival, there is a long time lag between the diagnosis and death of the individuals. The temporal relationship is fairly clear in survival analysis as socio-economic status is measured years before the outcome. A further consideration is that both individual and area-based inferences of socio-economic status are less valid in older individuals, where current income and employment, for example, do not reflect those throughout an individual's lifecourse.

Descriptive epidemiological studies generate rather than testing hypotheses. In both the incidence and survival chapters (chapter 2 & 5) of this thesis, many questions have been raised that might be answered in future studies using analytical techniques. Therefore, in relation to this particular thesis, this limitation does not invalidate any of the results. Indeed, both incidence and survival analyses have provided useful insights on the burden of disease and its outcome and differential patterns of incidence and survival between sub-groups of the population.

7.4.2.2 Analytical epidemiology

An analytical epidemiological approach was used in this research to investigate risk factors of PC using the prospective cohorts. Study specific limitations have

been discussed in relevant chapters but some broader limitations of analytical epidemiology which may have some influence on findings are discussed here.

There are several separate dimensions to critique current epidemiological practices as outlined by George Davey Smith and colleagues (Davey Smith, 2001; Davey Smith and Ebrahim, 2002). First he highlighted the over-emphasis on the use of risk factor epidemiology, which he described as “risk factorology” - that is the practice of conducting epidemiological studies that relate potential exposures with the risk of disease and identifying those which are positively related as “risk factors” and those negatively associated as “preventive factors” (Davey Smith, 2001). One of the major limitations of such epidemiological studies is that different investigators often report contradictory findings using data from different settings (Davey Smith, 2001). The findings of analytical studies reported in this thesis, perhaps also fall in the category of “risk factorology” however, this thesis does not claim that cholesterol level, tea or coffee consumption are causally related with the incidence of PC. The other side of the argument is, as Petr Skrabanek pointed out, that this apparent weakness of contradictory findings in risk factor epidemiology can be turned to an advantage. Since one positive association has been identified, it needs further investigation and replication, and if re-confirmed, perhaps a real cause of the disease is identified while negative findings may be controversial but are still of interest (Skrabanek, 1993). Coffee and cholesterol findings reported in this thesis confirm recently reported findings from large cohort studies but still require further confirmation before recommendations for public health practice or policy can be made.

Another strand of George Davey Smith's critique was the ability of epidemiological studies to examine the relationship of a large number of exposure variables with multiple outcomes by stratifying analysis on sub-categories, suggested as “data dredging” (Davey Smith and Ebrahim, 2002). They debated that large numbers of exposure and outcome variables can lead to at least one in 20 associations examined being “statistically significant” at a conventional p-value of <0.05 (Davey Smith and Ebrahim, 2002), when in reality it may be a false positive association due to chance alone. Although this is a major problem of epidemiological studies it is acknowledged in this thesis that

presented findings may have been influenced by small numbers of cases and may have been affected by unknown confounders as well. Further details of biases and confounding are discussed in the subsequent section.

7.4.2.3 Bias

A major limitation of epidemiological studies is the potential for bias, defects in the design, implementation or both of the study that affect the internal validity of that research (Grimes and Schulz, 2002). The main systematic errors in epidemiological studies are selection and information biases.

Selection bias originates from an absence of comparability between groups being studied (Grimes and Schulz, 2002). All epidemiological studies, particularly observational studies, have built-in bias. A major question to address in cohort studies is whether participants who had an exposure were similar to the non-exposed group except for their exposure. In relation to the prospective studies presented in this thesis, selection bias could be a major problem. However, the study population was drawn from a defined population using a population-based approach, which minimised some of the risk associated with selecting participants based on their exposure status. Nonetheless, there were some major differences between exposed and non-exposed groups and these may have influenced the results in ways that have been discussed and acknowledged in relevant chapters.

In relation to the chapter on systemic inflammation and survival of PC patients, selection bias may be an important consideration. The study population was identified based on the availability of C-reactive protein and albumin and then linked to the cancer registry to ascertain the outcome, that of a diagnosis of cancer and death. The external validity of this study can be challenged as participants included in the study may not truly represent the population from which they were drawn and may not even truly represent all cases of PC in that population. Given that selection biases may have had an important impact on the findings of this study, its generalisability may be limited. In future, an investigation will be carried out in which biochemistry records will be extracted for all those patients who had a diagnosis of PC and relationships between

systemic inflammation and survival will be examined using a true cohort approach.

Information bias comprises the incorrect determination of exposure and outcome, or both (Grimes and Schulz, 2002). It is also called classification or measurement bias. In cohort studies, the main concern is not the measurement of exposure but any differential ascertainment of outcome between exposed and non-exposed groups. In this thesis, prospective studies were carried out using data from a population-based cohort study which was set up three to four decades earlier and all men were followed-up by flagging in the NHS. Few participants were lost to follow-up (0.1%) in these prospective cohort studies, so information biases in outcome measurements are unlikely. A further potential information bias, which has been described above, is whether baseline exposures are valid over the at-risk period of follow-up. No information was available on whether cholesterol, tea or coffee consumption remained valid measures after their assessment at baseline.

7.4.2.4 Confounding

Confounding is an extraneous factor mixing or blurring the effects of other factors and is inherent in epidemiological studies (Davey Smith and Ebrahim, 2002; Grimes and Schulz, 2002). A confounding variable is associated with the exposure and it affects the outcome under study, but it is not in an intermediate link in the chain of causation. Confounding factors can be minimised at different stages of a study; by restricting and matching at the recruitment stage or by stratifying or making multivariate statistical adjustments at the analysis stage. This latter approach was the main one used in this thesis.

In relation to the empirical research in this thesis, particular attention was given to the confounding effects of co-variates. In the descriptive epidemiological studies (incidence and survival chapters of the thesis), lack of ability to control for the effect of potential confounders associated with socio-economic circumstances, limited the hypothesis testing around socio-economic circumstances and incidence or survival. However, the effects of age and Gleason grade on survival of patients were removed both by stratifying the analysis as well as by multivariate adjustments. Despite multivariate

adjustments, socio-economic circumstances had an independent association with survival of patients. These findings may still have some confounding effects of unknown factors associated with socio-economic circumstances. However the presented analysis generated hypotheses which warrant further investigation.

In addition to these, in chapter 5 and 6, lack of data on co-morbidity and disease stage which are well known determinants of survival of cancer patients, may have some confounding effects on apparent associations. The potential confounding effects of co-morbidity have been controlled by adjusting for the background population mortality in those analyses. However there may still be some effects of disease stage which could not be studied due to unavailability of cancer stage information and this is recognized as a potential limitation of this thesis.

Finally, in prospective studies, there was an opportunity to tease out the effects of demographic, lifestyle and physical factors on associations between cholesterol levels, coffee and tea consumption on risk of PC. The associations remained and were largely unchanged after multivariate adjustments. For some well established confounders, stratified analyses were also carried out, such as for alcohol consumption, BMI and cigarette smoking but overall relationships remained unchanged. Age has a strong independent relationship with incidence of PC and so an alternative analysis was conducted which took into account the age at which an individual was enrolled in the study and at what age they developed the disease. The overall relationship between cholesterol, coffee and tea consumption and PC incidence did not change with this alternative analysis.

Although confounding is inherent in the research presented in this thesis, its potential effects were considered seriously in all analyses and findings were presented after applying a variety of methods to minimise its effects.

7.4.2.5 Ecological fallacy

The ecological fallacy is a type of confounding effect which occurs when it is assumed that the characteristics of the population of an area (the ecology) in which a study participant lives are true for a given individual within that population (Levin, 2006). Although the ecological fallacy is more common in

ecological studies, it may be relevant to this thesis for both incidence and survival chapters, where an area-based measure of socio-economic circumstances has been used. The inference is not fallacious provided that the interpretation of socio-economic circumstances is limited to describing the environment in which an individual lives. This may reflect access to health and social services, environmental factors, or education and employment opportunities, amongst others. However, the inference is usually extended to suggest that socio-economic circumstances reflect aspects of an individual's socio-economic status - their income, employment and associated health-related behaviours. Because very affluent and deprived populations must be relatively homogeneous to rank at the extremes, it is more likely that any individual in a very deprived or very affluent population is themselves deprived or affluent. Area-based measures become less valid in the heterogeneous middle categories. Thus, most information is gained by comparisons of most affluent and most deprived populations, such as in the "deprivation gap" analysis presented in this thesis.

Population-based cohort studies presented in this thesis used individuals' socio-economic status measured by social class based on occupation did not show any significant difference in risk of PC between these groups. This particular finding suggests that there may not be any difference in risk among individuals from different socio-economic groups or this particular finding may have been affected by the small number of cases (n=650). In addition, these cases may not have been truly representative of their respective socio-economic groups in the population.

Apparently, these two differential findings look contradictory, where individuals' socio-economic status show no significant role in disease development and area-based measures show differential incidence and survival. Given that most of the lifestyle related evidence on risk of PC remains "limited suggestive" and the role of PSA-testing has substantial effects on observed incidence and survival patterns, these apparent conflicting findings may be reconciled. Assuming that PSA-testing was a major determinant and driver of the increasing incidence and improving survival in the West of Scotland, the area-based measure provides some clues that uptake of PSA may be higher among the least deprived men

compared with the most deprived men. There is substantial evidence to suggest that men in higher socio-economic groups are more health conscious and access health services at earlier stages of disease compared with lower socio-economic groups (Clegg *et al.*, 2009). So the area-based measure may represent the access-to-services factors more than the individual's lifestyle and health risk behaviours. On the other hand, an individual's socio-economic status measured by occupation may better represent lifestyle-related factors, and as their causal effects appear to be small no significant risk differences were observed between socio-economic groups.

7.4.3 Concluding remarks on strengths and limitations

This thesis comprises research work that originated from observational epidemiological studies. The best available population-based datasets were used to understand the epidemiology of PC. These data had relatively large numbers of cases, long follow-up periods and the population-based nature of the samples may have minimised some of the potential biases and confounding inherent in observational epidemiology. However, some associations may have been influenced by ecological fallacy or the effect of unknown confounders, so caution should be taken before making any definitive conclusions.

7.5 Outstanding hypothesis and future research

It may be true of observational epidemiology that it generates more questions than it answers. This is what George Davey Smith highlighted as the bottom line always being that "more research is needed" - a conclusion which is very comforting to epidemiologists working in the field (Davey Smith, 2001). A more positive perspective is taken by Petr Skrabanek, who considers that "replication is the hallmark of science" and we always need more evidence, both positive and negative, to understand the risk factors for diseases (Skrabanek, 1993). Both the outstanding hypotheses and directions for further research are outlined here.

7.5.1 Outstanding hypotheses

Several hypotheses have emerged from the work of this thesis and merit further research. These are briefly outlined in this section.

The true reason for the differential increase in incidence of PC between socio-economic groups in the West of Scotland remains uncertain. One suggestion is that it is due to differential uptake of PSA-testing. A study of population-based data of PSA testing may help to determine whether rates of testing are greater among more affluent men and if any differential is of a similar magnitude to that seen for incidence rates.

Prospective studies presented in this thesis highlighted that the factors which are associated with longevity - desirable BMI, no smoking habit, low alcohol intake - may be linked with greater risk of PC. It seems less likely that these risk factors have a direct causal relationship with the development of PC and more likely that they reduce competing causes of death and therefore increase the at-risk period in which PC may be diagnosed. However, further work is needed both at a basic sciences level to determine whether causality is biologically plausible, as well as in competing-risk models using epidemiological data.

Similarly, further basic science research is needed to determine what biological mechanisms may explain a preventive effect of coffee consumption on high grade disease, or that explains whether coffee may slow the progression of PC so that it is less likely to be diagnosed.

The extent to which disease stage and co-morbidity contribute to the socio-economic gradient in survival of PC patients remains unclear. If disease stage and co-morbidity do not completely explain the differences in survival between socio-economic groups, as described in this thesis, what are the other explanatory factors for the effects of socio-economic status and circumstances on survival?

Systemic inflammation is emerging as an important prognostic factor for many cancers. Although, the evidence on systemic inflammation and survival of patients with PC is very preliminary its effect size is relatively large. Further

research in this area with a well defined cohort of patients for whom complete information on disease stage, PSA and comorbidity is available may provide useful prognostic evidence for clinicians and patients.

Given that both the incidence and survival is increasing, a large proportion of men diagnosed with PC are living with the disease. It is critical to understand the survivorship experience of these men, their quality of life and their risk of subsequent health outcomes. This area of research is still developing and in the UK, very little is known about the survivorship of PC patients.

7.5.2 Future research

7.5.2.1 Local context

In relation to the future research to address these outstanding hypotheses, a list of ideas and potential projects could be outlined. However, some projects which may have potential benefits and implications are briefly described here.

To understand the differences in incidence of PC between socio-economic groups, the author as lead investigator has obtained approval to obtain PSA uptake data in North and South Glasgow from year 2000 to 2008. This project will help understand recent incidence trends. It may also explain whether the deprivation gap in incidence of PC in the West of Scotland is likely to be due to differential PSA testing as complete testing information - in both cancer and non-cancer patients - has been obtained. Full biochemistry data has also been obtained and this will allow the role of systemic inflammation in survival of PC patients to be described in a well-defined, large cohort with long follow-up.

There may be merit in conducting a cohort study of PC patients and following them up to understand the risk of developing subsequent chronic diseases. The aim of this research is to estimate the prevalence of anxiety, depression and risk of suicide among PC survivors. The risk of developing diabetes mellitus, cardiovascular diseases, cerebrovascular disease and pathological fractures among PC survivors who received hormonal therapy will also be investigated. A grant proposal for this project has been submitted to the Chief Scientist Office to obtain funding to carry out this research project.

The urological cancer managed clinical network (MCN) also collects detailed clinical audit data on PC patients. PSA and disease stage data are available in the MCN audit dataset although it is not complete for all patients, even in more recent years. However, attempts are being made to improve the quality and completeness of MCN data. In the near future, MCN data could be linked with cancer registry records to provide useful insights into the diagnosis, presentation and survival of patients from different socio-economic groups.

7.5.2.2 Broader context

A major problem associated with PC testing or screening is the low sensitivity and specificity of PSA for PC. Although there is some evidence that it helps to identify and diagnose patients at an earlier stage, it has been widely criticized as it leads to over-diagnosis and over-treatment of many slow growing tumours. Keeping in view the principles of primary prevention, we might therefore need to have a definite screening marker, which could identify high risk disease at an earlier stage. Further research is needed to identify a biomarker with high sensitivity, specificity and low cost. Early detection with a more accurate new biomarker may help clinicians and patients.

On the other hand, identification of prognostic factors may also be important as many more men are now diagnosed with PC. Identification of high risk cases who are likely to progress or relapse after treatment, may improve the treatment related decision making process and the survival of patients. The emerging interest in “personalised medicine” requires information from, for example, tumour specific genes or epigenetic markers and their association with response to different treatments, so that optimal treatment can be tailored for each patient.

Prevention of PC is only possible once risk factors are more clearly identified. Although much work has been done without identifying useful modifiable risk factors, a large clinical trial with more accurate information at baseline about the presence or absence of disease along with conventional risk factor information might provide some useful insight of this disease. As noted already, it is unlikely that a single classic risk factor could be identified such that modifying that risk would eliminate the disease. Nonetheless, identification and

modification of some risk factors may reduce the burden of disease. Given that it is one of the most frequent cancers among men and due to aging population incidence will continue to increase in the coming decades, a modest decline due to modification of some factors might have a sizeable impact at a population level.

7.6 Recommendations

This section of the thesis will attempt to provide some recommendations based on research findings presented in this thesis.

The main aim of epidemiology is to understand the determinants of disease and ultimately reduce the burden or occurrence of disease by modifying those determinants. Although completely preventing a cancer is an attractive goal, and may be feasible where a single causal agent, such as Human papillomavirus, has been identified, it is unlikely to be a realistic ambition in PC. PCs are likely to arise from a combination of many risk factors and its very high prevalence in men in middle and later life suggests that the main public health priorities are to better understand the natural history of the disease so that the large majority of men for whom it is unlikely to cause significant morbidity can be separated from those for whom it is life-threatening. The large and widening socio-economic inequalities in incidence and survival are also of public health concern. Recommendations have been made below for public health policy and for clinical practice.

7.6.1 Public health policy

Although most developed countries with overall public health policies have an overarching goal to reduce inequalities in health, the extent and success of such efforts is variable. The US has recently published “Healthy People 2020”, which is an extension of a previous policy “Healthy People 2010” (US department of health and human services, 2011). Cancer incidence and mortality is one of the main focuses in this policy. The policy highlights groups where disparities lie; however, it does not provide any strategy on how the disparities should be tackled (US department of health and human services, 2011). The education and insurance status of the US population has been suggested to be a stronger

determinant of inequalities compared to other components of socio-economic status that are strongly related to health in the UK.

Scotland also has a national policy “Better Cancer Care” and tackling inequalities is one of the main goals of that policy. A clear commitment has been shown to strengthen cancer prevention including tackling inequalities in both access to healthcare and cancer outcomes across Scotland (The Scottish Government Edinburgh, 2008b). As the incidence and mortality for most cancers is higher among the most deprived groups so the policy focuses mainly on reducing the burden of overall cancers as well as paying particular attention to the most deprived groups (The Scottish Government Edinburgh, 2008b).

In contrast to other cancers, PC is less common among deprived groups. However, the differential appears to lie more in low grade than in high grade disease. It might therefore be argued that there remains a need to increase awareness among deprived men to have routine clinical assessments so that aggressive and clinically significant cancers might be detected at an earlier stage and cured. This may reduce the gap in survival between socio-economic groups, although evidence from this thesis indicates that survival remains poorer in more deprived populations irrespective of PC grade. Public health strategies need to be targeted and resources should be allocated to address the issues of low socio-economic groups where most problems of inequalities in PC exist. Although, the evidence on benefits of screening is very limited, further research may help in relation to decisions of screening for certain groups. However, currently high risk individuals, that is, those with a family history of PC or any other cancer and men from deprived group, may be suitable for PSA testing to reduce late presentation of the disease.

From a broader policy perspective there is a need to understand and redress the wider determinants of socio-economic inequalities in health and cancer. The Scottish Government and Convention of Local Authorities published a joint Framework to Tackle Poverty in Scotland in 2008 (The Scottish Government Edinburgh, 2008a). The framework was intended to deliver improvements in four main areas - reducing income inequalities, introducing longer-term measures to tackle poverty and the drivers of low income, supporting those experiencing

poverty and making the tax and benefit system work for Scotland (The Scottish Government Edinburgh, 2008a). Although these recommendations are at an early stage, there is a need to strengthen and deliver in these areas to reduce the socio-economic gaps and ultimately reduce the health, and specifically cancer, inequalities.

7.6.2 Clinical practice

Health care services have an important role in reducing inequalities. For PC, there is a need to ensure that patients are appropriately and equitably referred from primary care for diagnostic services. There is no *prima facie* evidence that treatment of PC patients in the NHS Scotland is inequitable or that if inequalities in treatment were identified they should be considered to be unfair without fully understanding the clinical basis on which decisions were made. However, future clinical audit data should allow treatment patterns by socio-economic circumstances to be described so that any inequities might be identified.

It may be appropriate to give patients from more deprived circumstances additional care because of their poorer survival from PC. As noted above, there is a lack of evidence of whether co-morbidities might explain the excess mortality among more deprived patients and this work is needed before recommendations might be more conclusively made. However, a diagnosis of PC may also be an opportunity for health services to optimise treatment for other chronic illnesses and to support patients to adopt more healthy behaviours, particularly by stopping smoking, reducing excessive alcohol consumption and losing weight. There is evidence that a significant health event may lead patients to adopt more healthy behaviours (McBride *et al.*, 2008).

Modification of systemic inflammation may have some role in routine clinical practice. Further clinical evidence is required and this may help to identify high risk groups of patients and inflammation-based prognostic scores might help in the treatment related decision making process.

7.7 Conclusion

PC is a frequently diagnosed malignancy in men and its incidence continues to increase. Despite attempts in this thesis to identify modifiable risk factors using large prospective cohort studies with long follow-up periods, few convincing answers have emerged. The continuing increase in reported incidence over time is probably a reflection of greater testing rather than a true increase in incidence but a true increase cannot be dismissed. The increasing socio-economic differentials in incidence described in this thesis are probably artefacts of greater testing of more affluent men rather than reflections of true differences in incidence rates. Instead, the priority will be to differentiate better between indolent disease that will not cause significant morbidity or mortality and more aggressive disease that requires effective and prompt treatment. This thesis has provided evidence that the addition of a simple measure of systemic inflammation may greatly increase the prognostic accuracy of conventional PC grading but further work is needed on other prognostic indices. The socio-economic differentials in survival described in this thesis are not completely explained by differences in age and disease grade, it may be possible that differential distribution of co-morbidities and metastatic disease may have some role in socio-economic differentials in survival. Further work is needed to gain a fuller understanding of socio-economic differences in co-morbidities, disease stage at presentation and responses to treatment so that effective ways of reducing inequalities in outcomes might be found.

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Appendix 1: Confidentiality of data (West of Scotland Cancer Surveillance Unit)

CONFIDENTIALITY OF PERSONAL INFORMATION		Version	Final 1.0
<p>We agree to handle the data according to the terms below:</p> <ul style="list-style-type: none"> • We will adhere to the Cancer Surveillance Unit's procedures for maintaining confidentiality of data. • The data requested is consistent with the needs of the study. • The data may be used only for the purposes specified in the project plan. If the investigator later wishes to use the data in a new project, a new project proposal must be submitted. • The data may be shared within the team conducting the project. Requests from other individuals for access to the data should be referred to the West of Scotland Cancer Surveillance Unit. • Copies of all manuscripts arising from the project must be sent to the West of Scotland Cancer Surveillance Unit. Approval of the manuscript is not a condition for use of the data. • Data will not be transferred electronically to or from personal email addresses such as hotmail etc. • Where patient identifiers* have been supplied, data will be anonymised as early as possible after completion of the work. The privacy of the individual persons included in the data file must be respected. Only authorised contacts with patients through a treating unit are allowed. • Data protection measures (described) must be adhered to. Data both electronic and paper will be stored securely. • The data must be destroyed or archived according to the project plan. A notification to the West of Scotland Cancer Surveillance Unit must be made when this is done. • Acknowledgement of the data source should be included in any publications. • Appropriate acknowledgement of the contribution of these data will be made in publications arising from this study. 			
Signature of investigator	<u>Kashif</u>	Printed Name	<u>KASHIF SHAFIQUE</u>
Role/Title	<u>PhD Student</u>	Phone	
		Email	<u>K.shafique.1@research.gla.ac.uk</u>
Signature of supervisor	<u>[Signature]</u> 13/5/10	Printed Name	<u>DAVID MORRISON</u>
Role/Title	<u>DIRECTOR OF WEST OF SCOTLAND CANCER SURVEILLANCE UNIT</u>	Phone	<u>4041</u>
		Email	<u>David.morrison@nhs.uk</u>
Other persons with access to the data	<u>with</u>		
Office Use: Ref no.			

Appendix 2: Application for permission to use MIDSPAN data

MIDSPAN STUDIES

Application for permission to use data from Midspan studies for research and statistical analysis.

Details of Applicant	
Name	KASHIF SHAFIQUE.
Position	PHD STUDENT.
Department	DEPARTMENT OF PUBLIC HEALTH & HEALTH POLICY.
Organisation	UNIVERSITY OF GLASGOW.
Address	ROOM # 113. DEPARTMENT OF PUBLIC HEALTH & HEALTH POLICY.
Tel. No.	0141-330 3687.
Email	K.Shafique.1@research.gla.ac.uk
Names of collaborators	PROF. HING LEUNG, DR. KHAVEL QURESHI, DR. CAROLE HART. DAVID MORRISON PHILIP MCLOONE

Details of Project	
Title of project	PROSTATE cancer & cholesterol in MIDSPAN.
Start & finish date of project	JUNE - DECEMBER 2010 APPROX.
Data requested	COLLABORATIVE - REFERRAL TRIPLET SELECTED FIELDS (ANONYMOUS) + LINKED SMROB, SMROT - GLO DEATH RECORDS
Intended use of data (publications, presentations)	ORAL PRESENTATION IN RESEARCH SEMINAR / CONFERENCE. AT LEAST ONE PEER REVIEWED PUBLICATION RESULTS WILL ALSO BE DESCRIBED IN PHD THESIS.
Funding sponsor	DOW UNIVERSITY OF HEALTH SCIENCES, PAKISTAN.

User's declaration: I declare that I will abide by the Terms and Conditions contained in Appendix I of this document.

Signature of investigator Kashif Shafique Philip McLoone Date 01-06-2010

Signature of supervisor (if appropriate) [Signature] Date 7/6/10

Return to: Professor Graham Watt, General Practice & Primary Care Section, Division of Community Based Sciences, University of Glasgow, 1 Horselethill Road, Glasgow G12 9LX

Appendix 3: ISD approval to use the linked MIDSPAN data.

Information Services Division

Area 114E
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Professor Graham Watt
Chair of the MIDSPAN Studies Steering Group
General Practice and Primary Care
Division of Community Based Sciences
1 Horselethill Road
GLASGOW
G12 9LX

Date 18 March 2010
Your Ref
Our Ref JM/sh/

Enquiries to Janet Murray
Direct Line 0131 275 6954
Email janet.murray1@nhs.net

Dear Graham

FURTHER USE OF SMR LINKAGE TO MIDSPAN DATA, ANALYSIS OF CHOLESTEROL AND PROSTATE RISK

Thank you for your letter of 2nd February. Please accept my apologies for not having responded before now.

I think that this work appears to be in line with that for which the linked dataset has been used previously and I am prepared to approve the request without circulating it to the Privacy Advisory Committee. I would be grateful if you would send me a copy of the protocol and information regarding the secure storage of the extracted data. Please would you confirm that only the people listed in your application will have access to the data and that no additional copies will be made?

Yours sincerely

Dr Janet Murray
Consultant in Public Health Medicine

Headquarters

Gyle Square, 1 South Gyle Crescent, EDINBURGH EH12 9EB

Chairman Bill Matthews
Chief Executive Ian Crichton
NHS National Services Scotland is the common name of the
Common Services Agency for the Scottish Health Service.

Appendix 4: Management approval for the Glasgow Inflammation Outcome Study.

Research & Development
R&D Management Office
1st Floor, Tennent Institute
Western Infirmary
GLASGOW G11 6NT
Tel: 0141 232 9447



Our Ref: EP/LR
Enquiries to: Dr Erica Packard
Direct Line: 0141 211 8544
e-mail: Erica.Packard@ggc.scot.nhs.uk

18th Dec 2009

Professor Donald McMillan
Professor of Surgical Science
Walton Building, 4th Floor
Glasgow Royal Infirmary
Glasgow
G4 0SF

R&D Management Approval

Dear Professor McMillan

Project Title: Circulating Inflammatory markers as a predictor of survival: A Glasgow wide cohort study.

Chief Investigator: Professor Donald McMillan

R&D Reference: GN09ON379

Protocol no: V1.4 dated 18/08/09

I am pleased to confirm that Greater Glasgow Health Board is now able to grant **Management Approval** for the above study.

As a condition of this approval the following information is required during the lifespan of the project:

1. SAES/SUSARS – If the study is a **Clinical Trial** as defined by the Medicines for Human Use Clinical Trial Regulations, 2004 (CTIMP only)
2. Recruitment Numbers on a quarterly basis (not required for commercial trials)
3. Any change of Staff working on the project named on the ethics form
4. Change of CI
5. Amendments – Protocol/CRF etc
6. Notification of when the Trial / study has ended
7. Final Report
8. Copies of Publications & Abstracts

Please add this approval to your study file as this letter may be subject to audit and monitoring.

Yours sincerely

Dr Erica Packard
Research Coordinator

cc: Michael Proctor, Research Fellow, GRI ✓

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