School of Public Health

Tea, coffee and prostate cancer: A case-control study in Vietnam

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Declaration

To the best of my knowledge and belief, this thesis presents my own work, and does not contain material previously published by any other person, except where due acknowledge has been made.

This thesis also does not contain any material which has been accepted for the award of any other degree of diploma in any university.

Signature:

Date: 17/3/2016

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Abstract

Background

Prostate cancer is the second most common cancer for men. Its incidence continues to increase worldwide. Two-third of the incidence cases are diagnosed in developed countries, but the upward trend in incidence rate is more apparent in developing countries. Prostate cancer is also the sixth leading cause of cancer death among men, with only 60% of diagnosed cases survive beyond 5 years. Unlike incidence rate, which is increasing, mortality rate of prostate cancer remains stable globally.

So far, only age, some races and previous family history are the established risk factors for prostate cancer. Sedentary lifestyle, alcohol abuse, cigarette smoking and a diet regime with excessive intake of red meat, fat but low intake of fruits and vegetables, are believed to increase the prostate cancer risk. In contrast, physical activity, and a diet rich in isoflavones and lycopene, have been suggested to reduce the risk of the cancer. There is also evidence showing that habitual drinking of tea and coffee, the two most popular beverages after water, are associated with reduced risk of prostate cancer. However, such evidence remains inconclusive, and further epidemiological studies are required to confirm the preliminary findings.

In Vietnam, prostate cancer has been a low incident cancer, with an age-standardised incidence rate of less than 5 (4.7) per 100,000 men, which is much lower than the global average incidence rate. Traditional diet and popularity of tea and coffee consumption in Vietnam could be related to the observed low incidence of prostate cancer in the country. However, to date, there has been no epidemiological information on plausible risk and protective factors for prostate cancer in Vietnam. Therefore, the present study aimed to assess the strength of the association between tea and coffee consumption and the risk of prostate cancer in Vietnamese men. The specific objectives were: 1) To review epidemiology and prevention of prostate cancer in Vietnam; 2) To describe the consumption patterns of tea and coffee among Vietnamese older men; 3) To evaluate the association between tea consumption and risk of prostate cancer in Vietnam; 4) To evaluate the association between coffee consumption and risk of prostate cancer in Vietnam.

Methods

A case-control study of older Vietnamese men, aged 50 to 81 years, was conducted between March 2013 and September 2015, in Ho Chi Minh City located in southern Vietnam. The City has a population of approximately 8 million people, covering an area of 2,095.6 square kilometres where the prostate cancer incidence was the highest in Vietnam (5.2 per 100,000 men).

Prostate cancer cases (aged 51 to 80 years) were recruited from two urology departments, with histological confirmation. All eligible patients were consecutively approached and recruited until reaching the desired number of cases. Controls (aged 50 to 81 years), frequently matched with the cases by age, consisted of mainly community-based participants and a smaller proportion (19.8%) of hospital-based patients (both inpatients and outpatients). All eligible controls were tested for prostate specific antigen (PSA), and were only included in the study if their serum PSA was less than 4 ng/ml or their histological test result was negative. Data were collected through personal interview using a structured questionnaire, which enabled the collection of detailed information on tea and coffee consumption and frequency of intake of other foods and beverages.

Data were managed and analysed using the Stata package version 14.0. Chi-square test and Student's t-test (or nonparametric Wilcoxon rank-sum test) were used for group comparisons. Descriptive statistics were applied to describe sample characteristics, whereas multivariable logistic regression was performed to assess the potential associations between tea and coffee consumption and prostate cancer risk. Odds ratios (OR) were adjusted for plausible confounders, such as age, smoking habit and alcohol consumption. Subgroup and sensitivity analyses were also undertaken. The research project protocol was approved by the Human research Ethics Committee of Curtin University, Australia. Data collection was permitted by the participating hospital/medical facility. All the participants were informed about the purpose of the research project, and their participation was fully voluntary, without any coercion.

Results

A total of 216 prostate cancer patients (response rate: 85.4%) and 399 controls were interviewed and included in statistical analyses. According to the Gleason scoring classification, most of the cases were diagnosed at medium (30.6%) or higher grade (56.0%). Of the controls, 320 were community-dwelling men (response rate: 49.5%) while 79 were hospital-based (response rate: 69.1%). There was no significant difference in mean age between the case and control groups.

Both tea and coffee drinking were highly prevalent among older Vietnamese men. Overall, 87% of Vietnamese older men were tea drinkers. On average, they drank 4.2 ± 5.1 cups per day, and had been drinking tea for 22.8 ± 18.1 years. Similarly, coffee drinkers accounted for 81.7% of the controls. They drank 6.9 ± 7.8 cups per week, and had maintained their coffee drinking habit for 20 ± 17.5 years, on average.

Habitual tea drinking was found to be associated with a reduced risk of prostate cancer. Specifically, the adjusted odds ratio (OR) for prostate cancer when comparing drinking 100 to 500 ml versus less than 100 ml of liquid tea per day was 0.57 (95% CI 0.38, 0.85). This odds ratio was even lower when comparing consumption of > 500 ml versus less than 100 ml of tea per day (adjusted OR: 0.33, 95% CI 0.18, 0.59), p for linear trend < 0.01. Duration of habitual tea consumption was also associated with a lower risk of prostate cancer by daily drinking at least 35 years when compared to less than 15 years (adjusted OR 0.59, 95% CI 0.37, 0.94). Such inverse association was confirmed when taking both duration and frequency of daily tea drinking into account, defined as the cumulative exposure to tea consumption (cup-years). The odds of having prostate cancer was reduced by 39% (adjusted OR 0.59, 95% CI 0.34, 1.00) for men who were exposed to 60 to 150 cup-years, relative to those with less than 20 cup-years, p for linear trend = 0.01. Sensitivity analysis by control groups also confirmed the inverse association. Such inverse association was more apparent for high-grade (Gleason score of 8 - 10) than medium- and low-grade prostate cancer (Gleason score 7 or lower). In medium- or low-grade prostate cancer, the reduced risk of prostate cancer was observed among men with cumulative exposure of at least 150 cup-years, whereas in high-grade prostate cancer, this reduced risk was observed among men with at least 60 cup-years.

Unlike tea consumption, habitual coffee consumption was not associated with the risk of prostate cancer. Both total duration of coffee consumption and cumulative exposure (cup-years) did not show any significant association with the prostate cancer risk.

Conclusions

Despite an upward trend in the past decade, prostate cancer remains a low incident disease in Vietnam, which ranked 9th among the most common cancers. Overall, the age-standardised rate was 4.7 cases per 100,000. In the present study, the mean age at diagnosis of prostate cancer patients was 68.4 (SD 6.9) years, and more than half of these cases were diagnosed with high-grade (Gleason score of 8 - 10).

Tea and coffee consumption is a life-time habit of most Vietnamese older men. While tea drinking is almost daily, coffee drinking is a weekly habit. Habitual tea drinking was associated with a reduced prostate cancer risk among Vietnamese men. The inverse association was dose-responsive, and was more apparent for high grade than low grade of prostate cancer. The strength of this inverse association appeared to increase with greater number of years of tea consumption. Unlike tea consumption, habitual coffee drinking was not associated with the prostate cancer risk. The results of the present study suggest that habitual tea drinking may be a protective factor against prostate cancer, and have important implications in prevention of this chronic disease. However, previous epidemiological studies provided inconsistent findings, so that further research is required to ascertain the protective effects of tea consumption for the broader population.

Abbreviations

ASR:	Age-standardised rate
AJCC:	American Joint Committee on Cancer
CI:	Confident interval
EGCG:	Epigallocatechin-3-gallate
FFQ:	Food frequency questionnaire
IGF:	Insulin-like growth
OR:	Odds ratio
PSA:	Prostate specific antigen
RR:	Relative risk
SD:	Standard deviation
ABCD:	The Jewett-Whitmore-Prout system for cancer staging
UICC:	The Union Internationale Contre le Cancer
USA:	The United States of America
WHO:	The World Health Organisation
TNM:	Tumour-node-metastasis system for cancer classification
VACURG:	Veterans Administration Cooperative Urological Research Group, a system for cancer classification

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Chapter 1: Introduction

1.1 Background

1.1.1 Morbidity and mortality of prostate cancer

Prostate cancer is the second most common cancer in men and the fourth most common cancer in general, worldwide (Ferlay et al., 2015). Diagnosis of prostate cancer is more common in developed countries, such as Australia, New Zealand, and the United States, compared with developing countries. For instance, prostate cancer is the second most prevalent cancer in men after skin cancer in Australia (Cancer Council of Australia, 2011). Globally, the incidence of prostate cancer continues to increase. This increasing trend occurred not only in developed countries but also in low-risk countries, such as China and India, where prostate cancer has been historically low incident (Bray, 2008). There are many factors that may have contributed to this increase, including changes in lifestyle, increase in life span, and advancement in medical technology for the detection and accurate diagnosis of prostate cancer (Center et al., 2012).

Prostate cancer is also a major cause of cancer deaths in men. Unlike prostate cancer morbidity, which varies greatly worldwide, prostate cancer mortality does not significantly differ from one country to another (Center et al., 2012). The mortality rate was generally high in Caribbean, Sub- Saharan Africa, but was very low in Asia (Ferlay et al., 2010). Globally, about 60% of prostate cancer patients were estimated to survive 5 years after the diagnosis was made. This survival proportion among men in developed countries was higher than that in developing countries (Baade et al., 2009). However, the survival time of prostate cancer can be influenced by various factors, such as earlier diagnosis and effective treatment. With or without treatment, prostate cancer is a significant burden to medical care and the society (Crawford et al., 2011).

1.1.2 Risk and protective factors

A number of factors such as ethnic origin, age, family history, Insulin-Like Growth factor, sedentary lifestyle, smoking and high intake of fat and red meat have been reported to increase the risk of prostate cancer. However, only age and family history are established risk factors (Gronberg, 2003). Evidence for other potential risk factors remain inconclusive. Some ethnic origins are associated with higher risk of prostate cancer. For instance, the incidence rate of prostate cancer was the lowest in some Asian countries, but the highest in North America and Scandinavia (Gronberg, 2003).

Several modifiable factors including physical activity and some dietary factors are believed to reduce the risk of prostate cancer. For example, lycopene, soy, and isoflavone have been demonstrated to be associated with reduced risk of prostate cancer (Jian, 2009, Jian et al., 2007). Tea is the most globally popular beverage, and regularly drinking tea, especially green tea, has been reported to protect against prostate cancer (Lee et al., 2009). But, the evidence for protective effect of green tea remains inconsistent (Yu et al., 2014). Coffee is also one of the most common beverages all over the world. However, the link between drinking coffee and prostate cancer risk remains inconclusive (Hoang et al., 2014).

1.1.3 Prostate cancer in Vietnam

Although prostate cancer is one of the highest prevalent diseases in developed countries, it has been paid much less attention in Vietnam due to its historically low rate (Bray, 2008, Huynh, 2004). It was not until 1990s, prostate cancer was a rarely diagnosed disease in Vietnam. Since then, limited epidemiological information on the cancer has been reported. Despite a significant upward trend in incidence rate over the last decade (Hoang, Tran, and Lee 2014), prostate cancer remains low incident in Vietnam. In 2010, the age standardised rate of prostate cancer was less than 5 per 100,000 men (Nguyen et al., 2010) which was lower than the rates in otherSouth-East Asian countries, and much lower than the global rate (Center et al., 2012). To date, no epidemiological study on prostate cancer has been done in Vietnam.

Therefore, the reasons that could explain the low incidence of prostate cancer in this country remain unknown.

1.2 Aim and objectives of this study

Aim

The aim was to assess the associations between tea and coffee consumption and the risk of prostate cancer among Vietnamese men.

Objectives

1. To review epidemiology and prevention of prostate cancer in Vietnam.
2. To describe the consumption pattern of tea and coffee among Vietnamese older men.
3. To evaluate the association between tea consumption and risk of prostate cancer in Vietnam.
4. To evaluate the association between coffee consumption and risk of prostate cancer in Vietnam.

1.3 Study design

A case-control study comparing prostate cancer men with healthy men was undertaken in Ho Chi Minh City, Southern Vietnam. Cases were recruited from urology departments of two medical facilities. Suspected cases were confirmed with positive result of histologic examination of prostate gland's tissue. Controls were mainly community-dwelling men who were recruited from the same catchment area as the cases. A structured questionnaire was used for data collection. Participants of the studies were facet-to-face interviewed about their habitual tea and coffee drinking. Additional information on lifestyle and dietary habit was also obtained. The questionnaire used in the study was first piloted among older Vietnamese men before its implementation in the present study.

1.4 Significance of the study

As the information about epidemiology of prostate cancer was limited in Vietnam, this represents the first attempt to investigate the association between habitual tea and coffee drinking and the risk of prostate cancer in Vietnam. Although inconclusive, epidemiological evidence has suggested that tea and coffee, the two most popular beverages worldwide, could be protective against prostate cancer. Despite an upward trend in incidence rate of prostate cancer over that last two decades, prostate cancer incidence has remained relatively low compared to developed countries. This study will consolidate, and address the gap in the literature, in terms of tea and coffee consumption as potential protective factors of prostate cancer in Vietnamese men. From the perspective of public health, findings of this study will have important implications for the development of potential intervention and health promotion strategy for the prevention of this emerging chronic disease in Vietnam.

1.5 Outline of the thesis

The main body of the thesis consists of six chapters: introduction, literature review, methodology, results, discussion and conclusion. The introduction chapter presents general background on prostate cancer including brief of epidemiology and risk and protective factors, the situation of prostate cancer in Vietnam and the aim and objectives of the study. The introduction ends with an outline of the main body of the thesis. Chapter two presents detailed reviews of literature relevant to risk and protective factors of prostate cancer. This chapter describes previous findings on both established and plausible risk and protective factors of prostate cancer, such as physical activity, dietary and lifestyle factors, tea and coffee consumption. However, the main focus is on the effects of tea and coffee drinking on the risk of prostate cancer. Chapter two also presents a review of up-to-date situation of epidemiology and prevention of prostate cancer in Vietnam. Chapter three describes the methodology of the present case-control study. The results of study are presented in Chapter four. Chapter five discusses the main findings of the present study, including

limitations and strengths. Chapter six briefly summarises the main content of the thesis and presents some main conclusions drawn from the study.

Chapter 2: Literature review

2.1 Overview

This chapter will present an up-to-date review of literature on major issues of prostate cancer from the perspective of public health. The review chapter will begin with the definition, clinical features and diagnosis of prostate cancer. The main discussion of section one will focus on prostate cancer's biomarkers, and their use in clinical practice and screening. Section two will briefly present the disease's epidemiology. Specifically, it will discuss the global morbidity, mortality and trend as well as racial and geographic variation of prostate cancer. Section three will summarise the current understanding about the risk and protective factors of prostate cancer, with an extensive focus on the role of habitual tea and coffee drinking in the development and progression of prostate cancer. Section four will, then, present the current situation of prostate cancer in Vietnam and the gap in literature regarding prevention of the disease in Vietnam.

Most of the reviewed publications were identified by searching electronic databases. For general knowledge on prostate cancer such as clinical features, global situation or risk factors, the search aimed at the most updated relevant publications. An extensive and systematic search strategy was used for the review of the relationship between tea and coffee consumption and prostate cancer risk, and epidemiological research on prostate cancer and its current situation in Vietnam. The main literature search was conducted in March 2014, and updated in June 2015. The PRISMA guidelines for systematic review and meta-analysis (Liberati et al., 2009) and guideline from the National Health and Medical Research Council of Australia (1999) were used throughout the search and assessment of evidence. The search was undertaken in both English and Vietnamese publications. Databases used in the search included PubMed, Web of Science, ProQuest, Medline, CINAHL, Central Health Information and Technology Institute of Vietnam, and National Agency for Science and Technology Information of Vietnam. The initial search for articles' title used key words "prostate cancer", "tea", "coffee", "Vietnam", "epidemiolog*",

"cancer", "tiền liệt tuyến (prostate gland)", "tuyến tiền liệt (prostate gland)", and "ung thư (cancer)", and did not restrict to any specific time frame or type and language. Relevant published reports from the Vietnam National Cancer Institute and the World Health Organisation (WHO) were also searched. In the next step, titles and abstracts found were screened to identify more relevant publications. Once a list of relevant articles was generated, their full texts were retrieved from the internet, and were assessed for their suitability for subsequent inclusion in the detailed review.

Most of the materials presented in this chapter have been published in one book chapter and one journal article listed below

1 Hoang, D.V., Van, D.T., & Lee, A.H. 2014. Coffee consumption and prostate cancer. *In:* Preedy, V. (ed.) *Coffee in Health and Disease Prevention.* King's College London.

2 Hoang, D.V., Lee, A.H., Nguyen, H.N., Nguyen, Q., Vu, L.C., & Binns, C. 2014. Epidemiology and Prevention of prostate cancer in Vietnam. *Asian Pacific Journal of Cancer Prevention*, 15, 9749-51.

2.2 Prostate cancer

2.2.1 Clinical features

Prostate cancer can develop latently in a long period of time without any clinical symptoms. Histologically, prostate cancer arises in the outer part of the prostate gland, and is mostly adenocarcinoma (Adami et al., 2008). When the cancer tumour grows and compresses urethra or invades the sphincter, it causes symptoms related to the obstruction of urinary tract, such as frequent daytime urination, nocturia, intermittent stream of urine or feeling of incomplete emptying. Table 1 summarises obstructive symptoms of urinary tract. However, these symptoms can be resulted from any other mass or tumour that compresses the urethra, such as benign prostate hyperplasia. Therefore, clinical symptoms cannot differentiate prostate cancer from other tumour or mass, especially benign prostate hyperplasia (Adolfsson et al., 1998, Young et al., 2000).

Table 1 Lower urinary tract obstructive symptoms

Storage of urine	Voiding	Post-micturition
Daytime frequency	Slow or intermittent stream of	Feeling of incomplete
Nocturia	Hesitancy	Post-micturition dribble
Urgency	Straining	
	Dribble	

(Michael and Pandha, 2013)

Some less frequent symptoms can occur due to damage of urethra such as painful ejaculation or blood in the urine. In case of metastasis of cancer tissue to other body organs, some general symptoms can occur. For example, tiredness, weight loss and bone pain are usually related to metastasis of the cancer to bones. These metastatic symptoms can sometimes present before any lower urinary tract obstructive symptoms. Again, these symptoms are also not specific for prostate cancer and can be resulted from many other medical conditions such as arthritis or other cancers (Michael and Pandha, 2013). For these reasons, most prostate cancer patients are often diagnosed at an advanced stage when clinical symptoms present, and the diagnosis of the disease becomes challenging without further examinations rather than clinical manifestation (De et al., 2014, Panebianco et al., 2014, Ulmert, 2014, Wirth et al., 2014). An elevated serum prostate specific antigen (PSA) and/or abnormal digital rectal examination can suggest a possibility of prostate cancer. To confirm, biopsy is required (Benedict et al., 2008).

2.2.2 Classification of prostate cancer

Classification of prostate cancers can be undertaken in several ways, but more often by the histologic nature of the cancer, or by clinical manifestation. Clinically, prostatic cancer can be classified into four main types:

- Latent carcinoma, which is asymptomatic, and can normally be diagnosed at autopsy.

- Incidental carcinoma, which is initially diagnosed as benign prostatic hyperplasia. The diagnosis of prostatic cancer is usually made after histologic examination of specimen collected during transurethral resection of prostate gland.
- Clinical carcinoma.
- Occult carcinoma, which is often diagnosed through metastases of prostate cancer, while primary tumour remains latent.

Prostate cancer has a long latent period before becoming clinically noticeable. In many cases, the diagnosis of prostate cancer can only be made by incidence or autopsy. Indeed, prostate cancer is thought to develop from prostatic intraepithelial neoplasia, a high risk form of lesion of the prostate gland. Histological types, therefore, have more practical implications than clinical types.

Based on the histologic nature, prostate cancers can be classified into three major types including prostatic adenocarcinoma, prostatic sarcoma and neuroendocrine prostate cancer (Tewari, 2013). Of the three types, prostatic adenocarcinoma is the most common, which comprises 95% of all malignant neoplasm of the prostate gland. Histologically, adenocarcinoma originates from epithelial cells in the peripheral zone of the prostate gland. Therefore, the most common variants of these tumours are acinar, which are characterised by glandular structures. The differentiation of acinar adenocarcinomas is usually moderate to poor, with predominating Gleason score of 4 (Shevchuk and Robinson, 2013b). Several uncommon variants of prostatic adenocarcinoma are:

- Foamy gland carcinoma, characterised by abundant foamy cytoplasm. These tumours are often graded 6 Gleason score.
- Pseudohyperplastic adenocarcinoma, characterised by large, dilated gland. These tumours are usually Gleason score 6.
- Atrophic adenocarcinoma, characterised by small malignant glands mimicking benign atrophy. Most of these tumours have Gleason score of 6.
- Ductal adenocarcinoma, which is located around and within the prostatic urethra. This type of prostatic cancer often presents at late stage, with Gleason score 8.

- Basal cell carcinoma, which is extremely rare and often locally aggressive.
- Sarcomatoid carcinoma, which is usually associated with high-grade acinar adenocarcinoma, and is aggressive and poor prognosis.

Non-epithelial prostatic cancers comprise less than 5% of all malignant neoplasms of the prostate gland. These tumours include sarcoma and neuroendocrine prostate cancers. Some of these types are stromal sarcoma (rare, aggressive), leiomyoma (most common sarcoma of the prostate, high-grade and poor prognosis), rhabdomyosarcoma (present with advanced stage), solitary fibrous tumour (Shevchuk and Robinson, 2013a). Neuroendocrine prostatatic cancer is characterised by small cells, and therefore is also known as prostatic small cell carcinoma. This type of cancer is rare (< 1%), and tends to be diagnosed in younger patients. Prognosis of prostatic small cell carcinoma is usually poor (Beltran et al., 2013).

2.2.3 Staging of prostate cancer

Staging is crucial in prognosis and treatment of prostate cancer. A correct stage diagnosis is prerequisite for an appropriate treatment therapy. Prostate cancer can be staged based on either clinical or histological criteria. Clinical staging uses clinical information such as digital rectal examination, ultrasonography and imaging examination. Meanwhile, pathological staging is based on histological examination to decide the stage of prostate cancer (Cheng et al., 2012). There are three main clinical staging systems including Jewett-Whitmore-Prout classification, tumour-node-metastasis (TNM) classification and the Veterans Administration Cooperative Urological Research Group (VACURG) anatomic system (Clemens et al., 1986).

The Jewett-Whitmore-Prout staging system is also known as the ABCD system, which was initially suggested by Whitmore in 1956, then modified by Jewett and Prout (Bostwick et al., 1994, Graham, 1992a). The ABCD system classified prostate cancer into four stages as follow:

- Stage A: Tumour is not clinically detectable, and is often found incidentally during prostatectomy or surgical intervention for urinary obstruction.

- Stage B: Tumour can be identified through clinical examination, but still be confined within the prostatic capsule.
- Stage C: Tumour has extend beyond the prostatic capsule.
- Stage D: Tumour has metastasised to other organs.

The most advantageous feature of the ABCD staging system is its simplicity. However, this system is less accurate in reporting the spread of cancer (Graham, 1992b).

Similarly, VACURG classifies prostate cancer into four stages based on digital rectal examination, serum level of prostatic acid phosphatase and imaging examinations (Clemens et al., 1986). Four VACURG stages are defined as follows:

- Stage I: Tumour is clinically unapparent and confined within the prostatic capsule. Serum level of prostatic acid phosphatase is in normal range.
- Stage II: Tumour is clinically apparent and confined within the prostatic capsule. Serum level of prostatic acid phosphatase is in normal range.
- Stage III: Tumour has spread through the prostatic capsule, but does not affect pelvic lymph nodes or further distant sites. Serum level of prostatic acid phosphatase is in normal range.
- Stage IV: Tumour has metastasised to pelvic lymph nodes or further distant sites. Serum level of prostatic acid phosphatase can be normal or elevated.

The TNM system, on the other hand, is more complicated than ABCD and VACURG systems because it classifies cancer into more detail stages. The TNM staging system was first introduced in 1978 by the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer (UICC). However, the definition of cancer stages was inconsistent between these two agencies. The inconsistency was only resolved ten years later when both agencies agreed on a unified version of TNM staging system (Bostwick et al., 1994). Despite the long time development and recommendation, it was not until 1992, a TNM staging system for prostate cancer was first introduced. Since then, several revisions have been undertaken upon guidelines for TNM classification of prostate cancer (Chung et al., 2013). According

to 7th manual of American Joint Committee on Cancer Staging (Edge et al., 2010), prostate cancer can be classified as:

- Primary tumor (T)
    - TX: tumour cancer cannot be assessed.
    - T0: tumour is not evident.
    - T1: tumour is not clinically apparent or palpable, nor visible by imaging.
    - T2: Tumour can be identified by needle biopsy, but is still confined within prostate gland, and is not palpable or reliably visible by imaging.
    - T3: Tumour spreads through the prostatic capsule.
    - T4: Tumour can either be fixed, or invades adjacent structures.
- Regional lymph (N)
    - NX: no assessment of regional lymph nodes is required.
    - N0: no metastasis in regional lymph nodes.
    - N1: metastasis in regional lymph node(s).
- Distant metastasis (M)
    - M0: No distant metastasis.
    - M1: Distant metastasis.

Each T, M stage can be further sub-staged, depending on the level of progression of the tumour. Namely, T stages can be further classified as T1 (T1a, T1b and T1c), T2 (T2a, T2b, T2c) and T3 (T3a, T3b); M stages can be detailed as M1a, M1b and M1c. TNM system is the most commonly used for cancer staging because it allows clinicians to select more appropriate therapeutic treatments (Chung et al., 2013).

Although TNM staging system has a number of advantages in prognosis and treatment, it also has some limitations in grading pathologic progression of prostate cancer due to its biologic heterogeneity. Therefore, pathologic grading approaches are important supplement to clinical staging system. In particular, assessment of histologic differentiation of cancer tissue can provide crucial information for

prognosis and treatment of prostate cancer. More than 40 histologic grading systems have been proposed for classification of prostatic adenocarcinoma. Among them, the Gleason grading system is the most commonly recommended (Montironi et al., 2005). This system was developed by Donald Gleason in 1966, and refined in 1974, and based entirely on histologic pattern of prostatic cancer tissue. Originally, Gleason system defined nine grades of prostate cancer based on the histologic differentiation of prostate cancer tissue. Later on, several revisions and modifications have been made upon the Gleason grading system (Delahunt et al., 2012). Principally, the Gleason scoring approach assesses the degree of histologic differentiation at two levels: tissue and cells. Based on differentiated pattern, prostatic tissue and cells are given a score of 1 to 5, in which score 1 is well differentiated, and score 5 is poorly differentiated. Prostate cancer is graded based on the total Gleason score for tissue pattern and cell pattern, which ranges from 2 to 10. It is important to note that with the same total Gleason score of 7, the prognosis of individual scores of 4 + 3 is worse than scores of 3 + 4. Therefore, a Gleason grade should be reported with both total and individual scores, for instance, Gleason score 9 (5 + 4) or 9 (4 + 5). A high Gleason score refers to more advanced stage of the cancer (Shevchuk and Robinson, 2013b).

2.2.4 Biomarkers

A number of biomarkers have been investigated in relation to diagnosis, prognosis or monitoring of prostate cancer (Table 2). However, only few markers have been made into clinical practice. The most commonly used biomarker is prostate specific antigen (PSA), a major protein in seminal fluid (Denmeade and Isaacs, 2004). This protein acts like chymotrypsin, and participates in the mediation of gel formation in semen. PSA is produced by secretory epithelial cells of prostate gland, and stored in duct system within the gland before excreted into urethra. In normal condition, basement membrane and basal cells prevent PSA from circulating in serum. Therefore, the concentration of PSA in seminal fluid ranges from 0.5 to 2.0 mg/ml, while this concentration in peripheral circulation is much lower, often less than 4 ng/ml (Balk et al., 2003, Do, 2003). Apart from prostate gland, this protein can be found in some

other organs such as paraurethral and perianal glands, apocrine sweat glands, breast, thyroid, and placenta, but at much lower concentration that is not directly detectable (Lovgren et al., 1999). PSA, therefore, is considered specific for prostate gland. In case of disruption of basement membrane and basal cell structure due to a malignant condition, inflammation or trauma of the gland, serum level of PSA can be elevated (Balk et al., 2003). In the serum, PSA can be found in two main forms including free PSA and PSA bound with protease inhibitors (i.e. α1-antichymotrypsin, α2-macroglobulin and α1-protease inhibitor). Normally, free PSA accounts for 3-35% of total serum PSA, and is inactive form, whereas bound PSA is predominant and active form (Denmeade and Isaacs, 2004).

The early clinical use of PSA was to assess the treatment progression of prostate cancer. An elevated serum PSA after radical prostatectomy could suggest a residue of prostate cancer (Papsidero et al., 1980). Later on, measurement of PSA has been used for various purposes including early detection, diagnosis, prognosis and monitor of prostate cancer. A highly elevated serum level of PSA usually suggests a possibility of prostate cancer, but needs histological examination of biopsy specimen to make a diagnosis (National Cancer Institute, 2012).

However, without further clinical examinations (e.g. digital rectal examination or ultrasonography), the interpretation of an elevated serum PSA is often confusing. This is because, serum PSA can increase not only in prostate cancer but also in some other conditions, such as inflammation or trauma of the gland (Balk et al., 2003). Furthermore, there is no clear consensus upon normal range of serum PSA. Conventionally, this threshold is set at 4 ng/ml, and a PSA level of 4 to 10 ng/ml is considered for a biopsy indication (Balk et al., 2003, Do, 2003). But, there is evidence that shows prostate cancer can be found among men with PSA less than 4 ng/ml, even at a PSA level less than 0.25 ng/ml (Yossepowitch, 2008). Baseline investigation of 4,350 Swiss men, who had PSA less than 3 ng/ml, revealed that the prevalence of aggressive prostate cancer among that cohort was about 3.2 %. When stratified these men, based on serum PSA, into 3 groups: less than 1 ng/ml, 1 - 1.9 ng/ml and 2 - 2.9 ng/ml, the prevalence of prostate cancer was 1 %, 5.8 % and 6 %, respectively (Randazzo et al., 2015). In contrast, men with PSA greater than 4 ng/ml

may not have prostate cancer. A biopsy investigation of 345 Chinese men who had PSA of 4 - 10 ng/ml revealed that only about 40 % of the participants had prostate cancer (Fang et al., 2015).

To assist the capacity of total PSA testing in detection of prostate cancer, several other PSA tests have been introduced into clinical practice, including assessment of proportion of free over total PSA, PSA density of the transition zone, aged-specific PSA, velocity of PSA or pro-PSA. For instance, continuous rise in PSA blood level indicates a greater risk of prostate cancer. Men with increased rate of more than 0.4 ng/ml/year were 8 times at higher risk of prostate cancer than those with a normal PSA blood level (Stein et al., 1992).

Since PSA testing may give a high chance of both false-positive and false-negative results (National Cancer Institute, 2012), the use of this test for population-based prostate cancer screening has remained controversial. It cannot be denied that PSA-based screening can lead to lower death rate from prostate cancer (Schroder et al., 2012). Analyses from the United States Preventive Services Task Force showed that less than 0.01 % men would avoid death from prostate cancer, while 10 - 12 % would have to undergo a biopsy due to a false-positive result. In addition, side effects from biopsy and treatment are also problematic. About 30 % of men who underwent biopsy reported at least bothersome symptoms, and about 50 % of prostate cancer patients complained about complications from treatment, such as urinary incontinence, erectile dysfunction and cardiovascular complications (Moyer, 2012).

Table 2 Biomarkers for early detection of prostate cancer

Marker	Type	Sensitivity/specificity	Usage
PSA	Serum/ plasma	Sensitivity: 90% Specificity: 10-31% **Free to total PSA ratio:** Sensitivity: 90% Specificity: 10-45%	Screening/ diagnosis/ prognosis To differentiate benign prostate hyperplasia from prostate cancer
PSA isoform	Serum/ plasma	**Human kallikrein 2/pro-PSA:** Sensitivity: 90% Specificity: 31% **Combination of total, free and pro- PSA:** Sensitivity: 90% Specificity: 44%	Limited use
PSA kinetics	Serum/ plasma	**PSA velocity:** Sensitivity: 72% Specificity: 95% **PSA doubling time:** Sensitivity: 36.6% Specificity: 60.7%	Monitoring treated prostate cancer patients Diagnosis
Early prostatic cancer antigen (EPCA)	Serum/ plasma	Sensitivity: 94% Specificity: 92%	Diagnosis, but need further characterisation
Circulating nucleic acids (microRNA)	Serum/ plasma	Sensitivity: 60% Specificity: 87-100%	Monitoring prostate cancer
DNA markers: hypermethylation, glutathione S-transferase P-1 (GSTP1)	Urine	Sensitivity: 73% Specificity: 98%	Mainly for research purpose
RNA markers (prostate cancer antigen 3 (PCA3), E-twentysix (ETS) gene fusions	Urine	Sensitivity: 67% Specificity: 83%	Limited use as standalone marker, but increasing use in combination with PSA
Protein markers (sarcosine, telomerase, metalloproteinases (MMPs), urinary PSA)	Urine	**Sarcosine:** Sensitivity: < 7% Specificity: 100%	limited use, and need further research
		Telomerase: Sensitivity: 58% Specificity: 100%	limited use, and need further research
Alpha-methylacyl-coenzyme A racemase (AMACR)	Urine	Sensitivity: 82–100 % Speci fi city 79–100 %	Mainly for research purpose
Basal cell markers	Tissue		To differentiate malignant glands from benign lesions,

(Nair et al., 2013)

2.2.5 Diagnosis and treatment

Since there are no specific signs and symptoms for prostate cancer, diagnosis of this cancer mainly relies on imaging examinations, and is confirmed by histological examination of a biopsy specimen. In many cases, prostate cancer is incidentally detected by an elevated PSA level that leads to a biopsy indication. In other cases, patients often visit a doctor for their lower urinary tract symptoms, such as slow or intermittent stream of urine (Table 1). Abnormalities on digital rectal examination, ultrasonography of prostate gland, plus elevated serum PSA usually suggest a possibility of prostate cancer, and often lead to an indication of biopsy. A diagnosis of prostate cancer is confirmed when histological examination of a biopsy specimen found malignant lesions (American cancer society, 2014).

In clinical practice, diagnosis of prostate cancer often includes staging the cancer. Staging prostate cancer can be undertaken using TNM and Gleason scoring systems, the two most commonly recommended systems for staging prostate cancer. Correctly staging prostate cancer is crucial in selection of appropriate treatment therapy (Chung et al., 2013, Shevchuk and Robinson, 2013b). Evaluation of prostate cancer stage usually requires different imaging examinations, such as bone scan, computed tomography scan, magnetic resonance imaging or ProstaScintTM scan (American cancer society, 2014).

Dependent on grades, prostate cancer can be treated in different ways. Conventionally, there are five main methods of treatment of prostate cancer including surgery, radiation therapy, hormone therapy, chemotherapy and biologic therapy. Some other methods may also be effective, including cryosurgery, high-intensity focused ultrasound, and proton beam radiation therapy. However, these methods need to be further tested in clinical trials (National Cancer Institute, 2012).

2.3 Morbidity and mortality of prostate cancer

2.3.1 Morbidity of prostate cancer

Prostate cancer has posed a significant burden on public health worldwide. In 2012, there were approximately 1.1 million diagnoses of prostate cancer, globally. This number represented about 8 % of all cancer cases for both men and women, and made prostate cancer the fourth leading common cancers, after cancers of lung, breast and bowel (Ferlay et al., 2015). In men, prostate cancer accounted for 15% of all incident cancers, and ranked the second among the leading men's cancers. On a global scale, the age-standardised rate (ASR) of prostate cancer incidence was about 31.1 cases per 100,000 in 2012. However, there was a significant variation in the distribution of prostate cancer incidence across countries. It was estimated that about 70 % of incident cases were diagnosed in developed countries, and that it was 25 times difference between the lowest and the highest ASR for prostate cancer (Ferlay et al., 2015). The rates were particularly high in some countries such as France (ASR 127.34 per 100,000), Norway (ASR 129.74 per 100,000) and Martinique (ASR 227.25 per 100,000). Overall, the ASR in more developed world was 69.5 per 100,000 men while, in less developed world, the ASR was 14.5 per 100,000. The lowest ASR was recorded in South-Central Asia, 4.5 per 100,000 (Ferlay et al., 2015).

At a regional level, Oceania has the highest ASR for prostate cancer with 101.86 new cases per 100,000 men in 2012, followed by America (ASR 75.01), Europe (ASR 64). Asia has the lowest ASR of 9.34 incident prostate cancer cases per 100,000 men in 2012. At country level, there were eight countries (Ireland, Sweden, France, Norway, Trinidad and Tobago, Martinique, New Caledonia and Australia) with the ASR greater than 110 incident cases per 100,000 men, of which Martinique has the highest ASR of 227.25 incident cases per 100,000 men. Some Asian countries (Bhutan and Nepal) have particularly low ASRs that were less than 2 incident cases per 100,000 men in 2012 (Cancer Research UK, 2014).

Regarding the rank of prostate cancer's disease burden in comparison with other cancers, there is also a variation across countries and regions. In more developed

countries, prostate cancer was the most common cancer for men, followed by lung cancer. Whereas, in less developed regions, prostate cancer ranked fourth among leading common cancers in men (Figure 1).

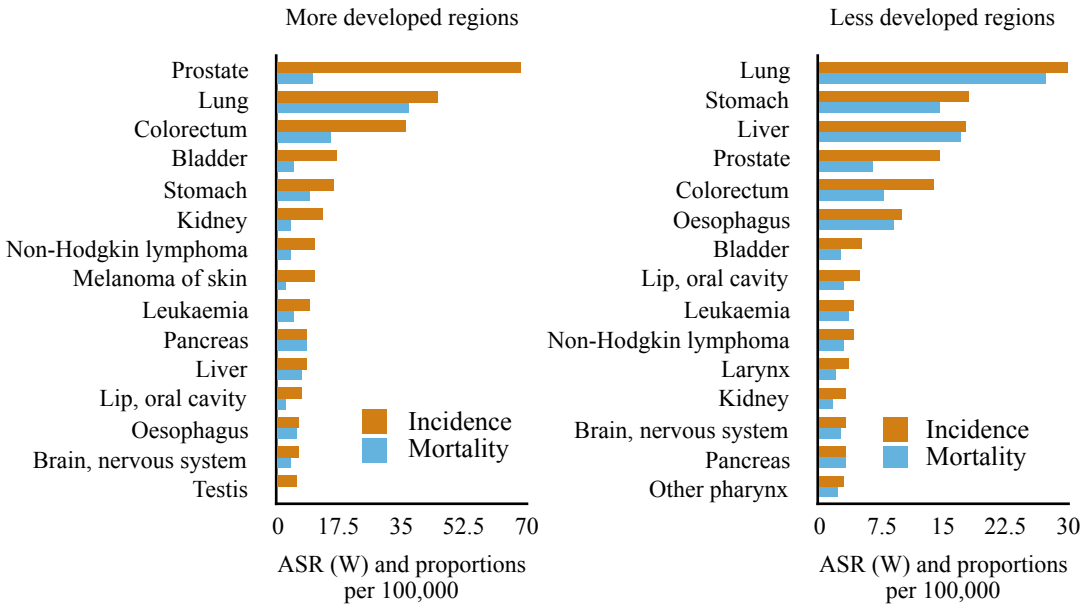

Figure 1 Estimated age-standardised incidence and mortality rates worldwide (International Agency for Research on Cancer, 2015)

The geographic and racial variation in the incidence of prostate cancer was obvious. However, such large variation is difficult to interpret in terms of its geographic and racial distribution. This variation could be attributable to a number of factors. The most favourable explanation could be the introduction of PSA test in developed countries. Although PSA test is not specific for prostate cancer, it usually leads to more chance for the cancer to be diagnosed. For example, a recent report from Australia showed that about 4,629 PSA tests per 100,000 men, being made per year between 2001 - 2008 (Ranasinghe et al., 2014). In Sweden, where the ASR for prostate cancer was 118.97 per 100,000, 25% of men aged 50 - 59 and 49% of men aged 70 - 79 had PSA test in 2011 (Nordström et al., 2013). Meanwhile, PSA testing is much less prevalent in developing countries (Center et al., 2012). The low PSA threshold used in screening also increases the chance for the diagnosis to be made. Current Australian guideline recommends the PSA level of 3 ng/ml to be the threshold. In higher risk cases, this threshold can be set at 2.5 ng/ml (Armstrong and

Lowe, 2014), whereas this threshold in some developing countries is higher. For instance, in Vietnam this threshold is set at 4 ng/ml to 10 ng/ml depending on individual hospitals (Vu Le et al., 2010).

Although PSA test could be attributable for a higher chance of prostate cancer diagnosis, the prevalence of PSA test alone cannot explain the variation in prostate cancer incidence rates across countries. This is because the variation was even larger before the introduction of PSA testing. Furthermore, there was a similarity in the geographic distribution of incident prostate cases before and after introduction of PSA testing (Baade et al., 2009). Race is another important contributor to this variation. According to Baade et al. (2009) men originating from Sub-Saharan African were more likely to develop prostate cancer than those originally from Europe. Obinata et al. (2012) also reported a similar difference between Asian men and African descent men living in the French Caribbean archipelago of Guadeloupe. In a more recent study conducted in the United States, incidence of prostate cancer varied significantly across race groups: African American men (ASR 228.7 per 100,000), White men (ASR 141.0 per 100,000), Hispanic/Latino men (ASR 124.9 per 100,000), American Indian and Alaska native (ASR 98.8 per 100,000) and Asian American and Pacific Islander (ASR 77.2 per 100,000) (Siegel et al., 2013).

Finally, different dietary habits and lifestyle could also explain the variation. Western diet that is typically rich in fat and red meat have been found to be associated with increased risk of prostate cancer (Crawford, 2003), while traditional diet in most Asian countries and Mediterranean region was found to have protective effects on prostate cancer (Itsiopoulos et al., 2009, Li et al., 2008, Mori et al., 2009, Sonoda et al., 2004). A comparison between Vietnamese men living in Hanoi and Vietnamese men migrated to the United States of America (USA) showed that the rate of incident prostate cancer among those living the USA was much higher than that among those living in Hanoi (Le et al., 2002). A similar difference was also observed between Japanese American and Japanese living in Japan (Marks et al., 2004, Shimizu et al., 1991).

Trend in incident rate

Since 2000, the incidence rate of prostate cancer continues to rise globally. On average, the ASR increased from 25.3 incident cases per 100,000 men in 2000 to 31.1 new cases per 100,000 men in 2012. In terms of ranking, prostate cancer has gone up from number 6th in 2000 to number 4th in 2012 among the leading cancers worldwide (Ferlay et al., 2015, Parkin, 2001, Parkin et al., 2005). In men, prostate cancer has always ranked second among leading men's cancers over the last 15 years. When exploring trend in incidence rates of prostate cancer of 53 countries, Center et al. (2012) found that the upward trend was seen in almost 40 countries. However, this upward trend differed from one country to another. China experienced the largest change (increased by 12 - 16 %) whereas Sweden, Thailand, and the United Kingdom experienced minor changes (increased by 2 - 3 %). Interestingly, countries where the incidence rate of prostate cancer was the highest, such as Australia, USA or New Zealand, they experienced a stabilised trend (Center et al., 2012). In Europe, an upward trend in the prostate cancer incidence was observed in 24 of the 37 countries, over the past 20 years. The annual rate of increase was from 3% to 7%. This increase was consistent throughout Europe (Bray et al., 2010). In some Asian countries where incidence of prostate cancer was low, there was also an increasing trend reported. In India, the incidence rate of prostate cancer continuously increased over the last two decades (Yeole, 2008). A similar trend was also observed in China, Taiwan, Japan, and Singapore (Chia et al., 2010b, Hsing et al., 1998, Suzuki, 2008, Tseng, 2011, Zhang et al., 2009). The increasing use of PSA test, and the westernisation of diet in Asian countries, could be the most convincing explanation for this upward trend (Center et al., 2012).

2.3.2 Mortality of prostate cancer

Despite advances in medical care and treatment, prostate cancer remains the fifth leading cause of death from cancer in men in 2012. It accounted for 6.6% of total male death from cancers (Ferlay et al., 2015). An estimation in 2008 showed that

prostate cancer ranked the sixth, and accounted for 6.1% of the total cancer mortality in men (Center et al., 2012).

Unlike incidence, the geographic variation in prostate cancer mortality was smaller, worldwide. It ranged from 3 per 100,000 to 30 per 100,000 across countries (Zhu et al., 2015). In 2012, this variation was slightly smaller, from 3 to 26 deaths per 100,000 (International Agency for Research on Cancer, 2010). The highest mortality rates were observed in African descent populations, while the lowest mortality rates were seen in Asia (Zhu et al., 2015). In developed countries this rate was 10.6 per 100,000 while in developing countries, it was 5.6 per 100,000. However, the number of deaths from prostate cancer in developing countries was almost the same as that in developed countries, probably due to advances in treatment of prostate cancer in developed countries, and the differences in population size.

Similar to racial variation in prostate cancer incidence, the mortality of prostate cancer appears to vary from one race to another. Baade et al. (2009) reported that the death rate of prostate cancer among African-American men was two times higher than that of European-American men. Also, higher mortality rate was observed in men from Sub-Saharan Africa, Brazil and Scandinavian even though they were residing in Europe. This variation could be related to genetic susceptibility (Bock et al., 2009).

Trend in mortality

Since 1994, mortality of prostate cancer has shown a downward trend, worldwide. Based on an analysis of prostate cancer incidence and mortality of 53 countries representative of five continents, Center et al. (2012) noted that more than 50% of countries analysed (27 per 53 selected countries) showed a declining trend over the last two decades. The increasing trend was seen in less than one third of countries, while the mortality rate stayed the same in the rest of the selected countries. The decreasing trend was seen mostly in more developed world (Figure 2), such as Oceania, Western Europe or North America (Center et al., 2012). A consistent decline in the mortality of prostate cancer was reported in thirteen of the 37 European

countries, over the last two decades. This decline could be attributable to improvement in treatment. Also, the introduction of massive screening by PSA testing could be another reason (Bray et al., 2010). In contrast, an upward trend in mortality was seen in some Asian countries, such as Taiwan, Japan, Hong Kong and the Republic of Korea (Matsuda and Saika, 2010, Tseng, 2011). Despite improvement in diagnosis and treatment of prostate cancer, increase in mortality of prostate cancer suggested the involvement of other risk factors (Bray et al., 2010).

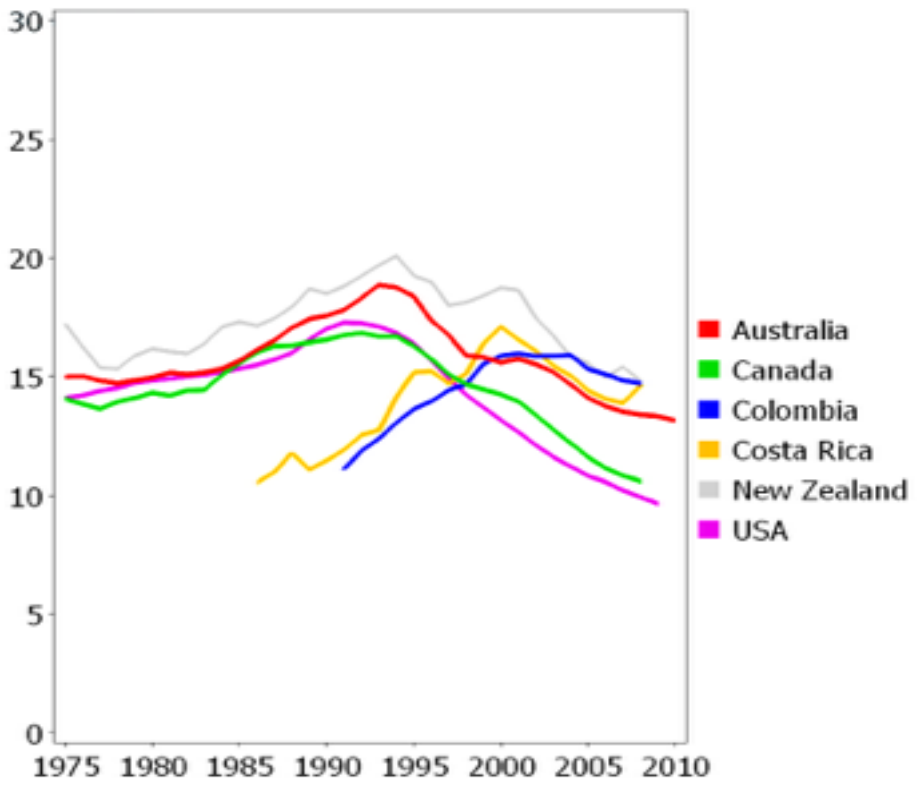

Figure 2 Trends in mortality from prostate cancer in some selected countries
(International Agency for Research on Cancer, 2015)

2.4 Risk and protective factors of prostate cancer

There are a number of factors that could have influence on the development and progression of prostate cancer. Some factors, such as age and race, are associated with increased risk of prostate cancer, whereas some other factors, such as habitual tea drinking and physical activity, are associated with decreased risk of this cancer.

Regarding classification, these factors can be categorised into various groups depending on the nature of exposure, such as dietary factors, hormonal factors or genetic factors, or depending on their effect on prostate cancer development, such as risk and protective factors. However, from the perspective of public health practice, these factors are classified as modifiable and non-modifiable factors in this chapter.

2.4.1 Non-modifiable factors

Age

Age is the most notable risk factor of prostate cancer. Prostate cancer is very rare in men under 40 years old. However, when men become older, the incidence rate increases faster. The Figure 3 shows an exponential rise in the incidence rate in some selected countries when age increases from 50 to 70 years old. While the estimated age specific rate among men aged 45-54 years was 10.6 per 100,000, it was 72.9 per 100,000 among men aged 55-64 years (Baade et al., 2009). In Australia, 85% of cases of prostate cancer are over 65 years old. By the age of 85, about 25% of Australian men are at risk of being diagnosed with prostate cancer (Cancer Council of Australia, 2011). Advanced age is also associated with higher PSA level and more advanced stage of prostate cancer. Internationally, the age-specific mortality rate for age groups of 15-44 years, 45-54 years, 55-64 years and 65 years or over were estimated to be 0.1, 1.9, 11.8, and 100.4 per 100,000, respectively.

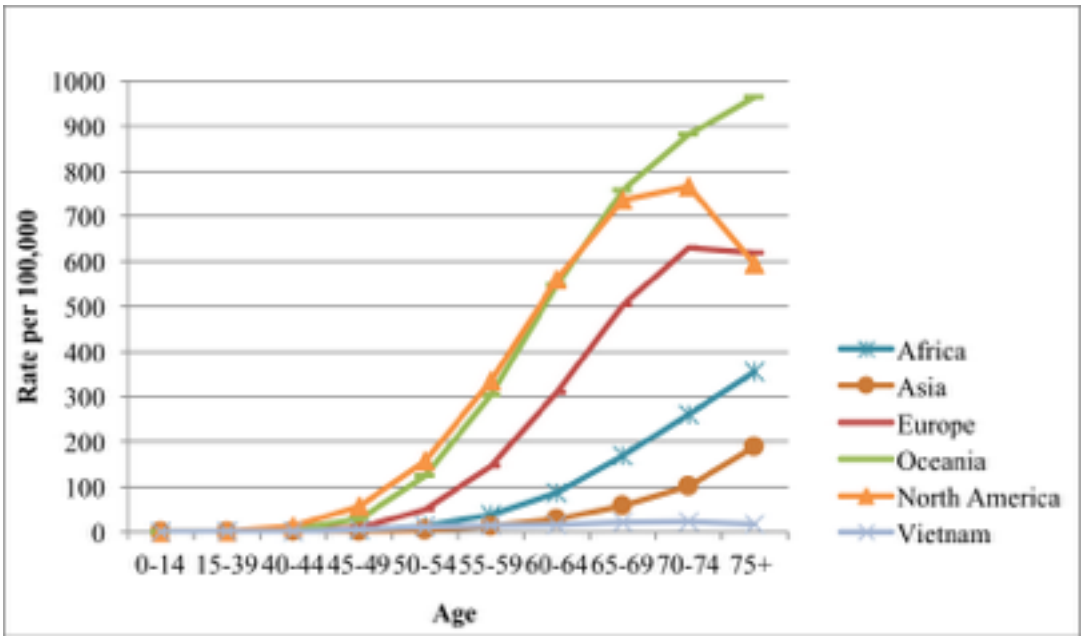

Figure 3 Age-specific incidence rates of prostate cancer in five continents and Vietnam

(International Agency for Research on Cancer, 2015)

Family history and genetic factors

Men with family history of prostate cancer are at higher risk of having the cancer than those without affected family members. About 5% to 10% of all prostate cancer cases had at least one relative who had the cancer (Whittemore et al., 1995). On average, family history of prostate cancer is associated with an increase by two- to four-fold in prostate cancer risk (Grönberg, 2003, Klingler, 2011). Furthermore, positive family history is also associated with early-onset prostate cancer (Carter et al., 1993). Closer familial relationship is associated with higher risk of having prostate cancer. Specifically, a recent retrospective study showed that the relative risks (RR) of prostate cancer for men with first-degree cancer relatives ranged from 2.46 to 7.65 when compared to controls. Meanwhile, these risks for men with second- and third-degree cancer relatives ranged from 1.51 to 3.09 and from 1.15 to 1.50, respectively (Albright et al., 2015). Remarkably that, having brother with prostate cancer is associated with a higher risk of prostate cancer than having father with the disease (Monroe et al., 1995), and that both maternal and paternal family history of prostate cancer plays an equal role in the increased risk of prostate cancer for men with affected family (Albright et al., 2015).

To further bolster the evidence for a familial predisposition to prostate cancer, a twin study showed that monozygous twin pairs expressed higher concordance rates compared to dizygous twin pairs did (27.1% versus 7.1%). This finding also underscored the role of genetic influences versus environmental influences (Page et al., 1997). Sharing of genetic susceptibility could be a convincing explanation for the clustering of prostate cancer in families (Grönberg, 2003). In fact, there are similarities in susceptible genes to prostate cancer between prostate cancer patients and their first degree relatives who have prostate cancer, and these susceptible genes in sons are inherited from their father (MacInnis et al., 2010). A novel speckle-type POZ protein gene mutation was discovered that tracks prostate cancer within a family. This mutation could be a candidate gene for hereditary prostate cancer (Zuhlke et al., 2014).

There could be susceptible or mutated genes that confer the susceptibility to the development of prostate cancer. Men with these genes are more likely at higher risk of prostate cancer than men without these genes (Rubin and De Marzo, 2004). The case of BRCA mutations is a typical example of influence of hereditary susceptibility on the risk of prostate cancer and its clinical feature. Men with BRCA2 were at five to seven times higher risk of prostate cancer compared to men in the general population. Relatives of these men also had 4.65 times higher risk of prostate cancer in comparison with men from general family. The presence of BRCA2 mutation is also associated with aggressive prostate cancer (Narod et al., 2008, Tryggvadottir et al., 2007). Another good example of the relationship between genetic factors and prostate cancer risk is the HPC1 locus on the long arm of chromosome 1. Carriers of this locus tend to have higher-grade prostate cancer, at younger age (MacInnis et al., 2010). Some genes and genetic variants can be found in different populations and races. Wang et al. (2012a) reported three variants (rs12653946, rs339331 and rs9600079) associated with increased risk of prostate cancer that were observed in both Japanese and Chinese men. Similarly Wang et al. (2011) reported variants of chromosome 8q24 associated with increased risk of prostate cancer in both European-original men and African Americans in the United States.

Race

It is evident that the incidence rate of prostate cancer for some races is particularly higher than that for others. The prostate cancer tends to develop more frequently in men who are African descents than those from other races. Meanwhile, Asian descents appear to be safer in terms of suffering from prostate cancer (Baade et al., 2009). In 2012, the cancer statistics within the USA showed that the African American men had the highest incident rate of prostate cancer (ASR 228.7 per 100,000), followed by White men (ASR 141.0 per 100,000), Hispanic/Latino men (ASR 124.9 per 100,000) and American Indian and Alaska native (ASR 98.8 per 100,000). The Asian American men and Pacific Islander men had the lowest incident rate (ASR of 77.2 per 100,000) (Siegel et al., 2013). In addition, African men also have prostate cancer at younger age. Gaines et al. (2014)reported that the average age at diagnosis of Black men was 61 years old, that was 4 years younger compared to white men. In another study, while 8.3% African American prostate cancer patients were diagnosed before 50 years old, this proportion in Caucasian prostate cancer patients was 3.3% (Parker et al., 2011). Black men are also at higher risk of aggressive form of prostate cancer than are white men (Freeman et al., 1997).

Although environmental factors play an important role in the development of prostate cancer, they cannot fully explain the variation in prostate cancer ASR across races within the same country, such as the United States (Kittles et al., 2001, Siegel et al., 2013). Genetic predisposition appears to be a more favourable explanation (Brawley et al., 2007). Indeed, BRCA1,2 mutations, major risk factors for prostate cancer, are more frequent in African American than other ancestries (Kurian, 2010). There is also difference in the androgen receptor gene CAG between Sub-Saharan Africa Americans and European Americans. Sub-Saharan descents appear to have shorter CAG repeats in comparison with European descents (Kittles et al., 2001). Finally, differences in multiple genes encoding androgen and IGF are also involved in the development of prostate cancer between black and white men (Freedland and Isaacs, 2005).

Hormonal factors

Prostate cell proliferation and function of prostate gland are regulated by sex hormones (androgens, testosterone and dihydrotestosterone) and androgen receptor. Testosterone is the most important circulating androgen in serum. When circulating in serum, this hormone is bound to sex hormone-binding globulin, and, therefore, is inactive. Inside the prostate gland, it is released from the bounded protein, and is converted to dihydrotestosterone by 5α-reductase isoenzymes. This product acts as regulator of prostate cell proliferation and secretory function through intracellular androgen receptor (Slater and Oliver, 2000). Disorders in any of these components could lead to abnormality in the function and cell proliferation of the gland.

There has been evidence that showed association of abnormal concentration of sex hormones with a higher risk of prostate cancer (Klap et al., 2014). Results from a prospective, nested case-control study in the United States (Gann et al., 1996) showed a positive association of high concentration of serum testosterone and low concentration of sex hormone-binding globulin with the prostate cancer risk. However, the evidence for the harmful effect of testosterone remains inclusive. A cohort study of 1,008 men in the United States (Barrett-Connor et al., 1990) showed that baseline plasma testosterone was not related to prostate cancer risk. Based on a cross-sectional study of 600 patients hospitalised for onset of lower urinary tract symptoms, Mearini et al. (2013) even reported that low serum levels of testosterone was frequently associated with prostate cancer. However, pooled data from eight cohort studies provided no conclusive evidence for the association between testosterone level and prostate cancer risk (Wigle et al., 2008).

Insulin-like growth (IGF) factor is also related to the development of prostate cancer. This polypeptide hormone is produced by the liver, and is involved in regulation of the growth, proliferation, differentiation and apoptosis of cells in many tissues including the prostate gland (Pollak, 2001). Both in vitro and epidemiological studies showed a link between IGF and prostate cancer (Lima et al., 2009). In laboratory, IGF was found to be involved in different stages of differentiation and growth of prostate cancer cells (Ma et al., 2012). Epidemiological findings showed that elevated blood levels of IGF1 are linked to an increased risk of prostate cancer

(Grönberg, 2003). Men with higher level of IGF1 have 1.7 - 4.3 fold higher prostate cancer risk (Hsing et al., 1990). However, the role of IGF is stronger in the progression of prostate cancer than in its initiation (Rowlands et al., 2012a). Indeed, more recent studies showed that IGF1 was positively associated with mortality of prostate cancer (Rowlands et al., 2012b). In another study, both serum IGF1 and IGF2 were not associated with the prostate cancer risk, but the serum IGF-binding protein 2 could increase the risk for total and low-grade cancers.

Some other hormonal factors, such as growth hormone and thyroid-stimulating hormone, may also believed to be involved in the development of prostate cancer. Results from a population-based case-controls study revealed that lower serum level of the growth hormone was associated with increased risk of prostate cancer (Fuhrman et al., 2005). However, the mechanism for role of this hormone in the development of prostate cancer remains unclear. A randomised controlled trial in the United States (Mondul et al., 2012)showed that elevated level of thyroid-stimulating hormone could decrease the risk of prostate cancer. Finally, androgen receptors have also been postulated to play a mediating role in the carcinogenesis of prostate cancer. Mutations in genes that encode androgen receptors could be predisposition of prostate cancer. Some gene mutations result in elevated activity of these receptors, and therefore lead to imbalance in ratio of the cell proliferation rate to the cell death rate, by which proliferation rate is greater than death rate (Tan et al., 2015).

2.4.2 Modifiable factors

Cigarette smoking

Despite some conflicting reports, cigarette smoking has been demonstrated to be a risk factor for prostate cancer (Huncharek et al., 2010). Results of a 20-year follow up study of more than 17,000 men in the United States (Hsing et al., 1990) showed a significant association between smoking cigarettes and increased prostate cancer risk. In contrast, another cohort study of nearly 300,000 men did not support findings of this study (Watters et al., 2009). The authors of the second study even found an inverse association between former smokers and prostate cancer risk. These

inconsistent findings could be due to a limitation that smoking status was only assessed at baseline, meanwhile accumulative exposure was not taken into account (Zu and Giovannucci, 2009).

Recent studies provided more consistent findings to support the link between cigarette smoking and increased risk of prostate cancer. Results from a population-based case-control study showed that cigarette smoking was associated with 50% higher risk of prostate cancer (Weinmann et al., 2010). In a review of 19 cohort studies, Zu and Giovannucci (2009) noted the link between cigarette smoking and prostate cancer risk. These authors also reported that tobacco use could increase not only the risk of aggressive form but also mortality of prostate cancer. Their findings was supported by a meta-analysis of 24 cohort studies (Penson, 2010).

Alcohol use

There has been increasing evidence for the harmful effects of alcohol use on prostate cancer. Results of a five year-cohort study of 7,612 Harvard alumni showed that moderate amount of liquor was associated with an increased risk of prostate cancer (Sesso et al., 2001). Sharpe and Siemiatycki (2001) reported that habitual beer consumption was associated with increased risk of prostate cancer, and that the strength of association increased with cumulative consumption. These authors also noted that the risk was particularly high among men who started drinking beer at the age of 15 years. Velicer et al. (2006) observed a modest increased risk of prostate cancer among men who had more than one drink per month (HR = 1.20) when comparing to men who had less than one drink per month. These findings were supported by a later meta-analysis, which concluded that the risk of having prostate cancer was significant among heavy drinkers (Fillmore et al., 2009).

Physical activity

Physical activity is important not only for maintenance of general health but also for prevention of prostate cancer (Courneya and Friedenreich, 2007). Despite conflicting

findings, a majority of studies showed that physical activity could be protective against prostate cancer (Young-McCaughan, 2012). A cohort study conducted by Giovannucci et al. (2007) showed that vigorous physical activity could lead to lower risk of both advanced and fatal prostate cancer. However, this study did not show protective effect of physical activity against non-advanced prostate cancer. In a recent 13 year-cohort study of 13,109 Swedish men, Grotta et al. (2015)reported a dose-response relationship between occupational physical activity and decreased risk of prostate cancer. However, these authors did not confirm an association between total physical activity and prostate cancer risk. The inconsistent findings from the two mentioned studies could be due to the information on physical activity that was obtained only at baseline. While individual publications showed conflicted findings about the relationship between physical activity and prostate cancer risk, pooled data from 19 cohort and 24 case-control studies confirmed that physical activity was associated with reduced risk of prostate cancer. This inverse association was stronger in men aged between 45-65 years old, compared to other age groups (Liu et al., 2011).

Physical activity is associated with not only lower risk but also increased survival of prostate cancer. Based on a cohort study of 2,705 prostate cancer patients, Kenfied et al. (2011)reported that moderate physical activity such as tennis, jogging, biking or swimming for at least 3 hours per week could increase prostate cancer survival. About three hours of vigorous activity per week could reduce the death risk of prostate cancer by 61%. These findings were strengthened by a more recent cohort study of 4,623 prostate cancer patients, in which Bonn et al. (2015) demonstrated that either walking or bicycling for at least 20 minutes a day can reduce cancer-specific mortality of prostate cancer. Even about one hour of physical exercise each week could show a protective effect on prostate cancer mortality.

Dietary factors

The influence of diet regimes on the risk of prostate cancer was observed when comparing the incident rate of prostate cancer among men from the same race but

residing in different countries. Le et al. (2002) found that the rate of prostate cancer among Vietnamese men who had immigrated to the United States was higher than that among Vietnamese who were residing in Hanoi, Vietnam. Similarly, Japanese immigrants in the United States had a higher rate of prostate cancer in comparison to those staying in Japan (Marks et al., 2004, Shimizu et al., 1991). Western diet, characterised by a higher intake of fat, dairy products, and meat, particularly red meat, is associated with an increased risk of prostate cancer (Crawford, 2003). Meanwhile, traditional diet in most Asian countries and Mediterranean region was found to have protective effects on prostate cancer (Itsiopoulos et al., 2009, Li et al., 2008, Sonoda et al., 2004).

However, the relationship between dietary factors and prostate cancer risk is far more complicated, and remains inconclusive. Some factors can be positively associated with the prostate cancer risk, while some other factors can be negatively associated with the risk, depending on diet regimes (Crawford, 2003). A population-based case-control study in the United States (John et al., 2011)showed an association of increased risk of advanced prostate cancer with red meat (OR: 1.63, 95% CI: 99, 2.68), and processed meat (OR: 1.57, 95% CI: 1.04, 2.36) consumption. These findings were supported by results from another case-control study in the same country (Joshi et al., 2012). While the harmful effect of processed meat on prostate cancer risk was further supported by later systematic review and meta-analyses, the harmful effect of red meat was not. For instance, a systematic review and meta-analysis of 15 prospective cohort studies did not observe any association between red meat and prostate cancer risk (Alexander et al., 2010). The authors only found a weak association between processed meat and the risk of prostate cancer (summary RR: 1.05, 95% confident interval [CI]: 0.99, 1.12). Another pooled analysis of 15 cohort studies also partly supported the association between processed meat, but not red meat, and increased risk of prostate cancer (Wu et al., 2015). Similarly, there is inconsistency in the evidence for dairy products. Reports from a cohort study of 17,049 Australian men in 2006 (Severi et al., 2006)and a meta-analysis of 45 observational studies (Huncharek et al., 2008)did not support any association between dairy product consumption and prostate cancer risk. In contrast, the most

recent analysis of pooled data from 37 prospective studies showed a positive association between prostate cancer risk and dairy products including total dairy, milk and cheese, with the RR of 1.07, 1.03 and 1.09, respectively (Aune et al., 2015).

Several nutrients are known to be positively associated with the prostate cancer risk, including calcium, polyunsaturated lipids, and n-6 fatty acids (Crawford, 2003, Kristal et al., 2010). However, evidence for the role of these nutrients remains inconsistent. A recent six year-follow up of nearly 300,000 participants showed that the association between calcium and dairy products and prostate cancer was inconclusive (Park et al., 2007). Meanwhile, Kristal et al. (2010) found that consumption of calcium was positively associated with low-grade prostate cancer, but negatively associated with high-grade prostate cancer. In addition, the effects of nutrients on the development of prostate cancer were significantly influenced by age. For instance, while polyunsaturated lipids tend to increase the risk of prostate cancer in young men, tomatoes tend to increase the risk of prostate cancer in older men. Similarly, inverse association between vitamin E and prostate cancer was stronger in young men than in older men (Key et al., 1997).

In a twenty-four year cohort study of 47,885 men, Wilson et al. (2015) reported that calcium was an independent risk factor for prostate cancer after a long exposure period, albeit not strong. Specifically, a higher intake of calcium (> 2000 mg/d) was found to be associated with higher risk for both total and advanced prostate cancer. However, after adjusting for phosphorous intake, this relationship reduced to be associated with prostate cancer with long latency period (about 12 to 16 years after exposure). In contrast, high intake of phosphorus was an independent prostate cancer risk factor, with shorter latency period (0 to 8 years). These findings suggest a more complicated relationship between calcium intake and prostate cancer. Also, not all sources of calcium are associated with increased risk of prostate cancer. For instance, total calcium has positive relation with the prostate cancer risk, but not for non-dairy or calcium supplement (Aune et al., 2015).

Traditional diet pattern in most Asian countries, typically rich in fruits and vegetables, is believed to reduce the risk of prostate cancer (Marshall, 2012, Sonoda et al., 2004). Shahar et al. (2011) reported that low fat diet, high intake of fruits,

vegetables and lycopene rich foods have protective effects against prostate cancer. The finding was supported by a meta-analysis (Ma and Chapman, 2009). Isoflavones, prevalent in soybeans, was particularly found to have prophylactic effects on prostate cancer (Lee et al., 2003). This finding was supported by a later study in Japanese men (Kurahashi et al., 2007), that showed consumption of both soy and isoflavone was associated with decreased risk of prostate cancer. A case-control study in China reported a similar finding (Jian, 2009). Habitual consumption of tea and coffee is also potentially protective against prostate cancer (Lee et al., 2009, Liu et al., 2015). Detail discussion on the relationship between tea and coffee consumption and prostate cancer risk is presented in section 2.4.3 and 2.4.4.

Overweight and obesity

Although there have been a large number of attempts to investigate the role of obesity in the development and progression of prostate cancer, the link remains unclear. In a 13 year-cohort study conducted in Sweden, Grotta et al. (2015) reported that high BMI was not associated with prostate cancer risk. This finding was partly consistent with a previous cohort study in which BMI was found to be associated with fatal, but not incident prostate cancer (Giovannucci et al., 2007). It seems that higher BMI was associated with increased risk of fatal than total prostate cancer (Andersson et al., 1997, Calle et al., 2003, Rodriguez et al., 2001). This evidence suggests that adipose tissue has stronger influence on progression of the cancer rather than on the development of the cancer. However, there are several factors that need to be taken into account when interpreting this relationship. For example, prostate cancer in obese men could be diagnosed at later stage than in non-obese men, due to several reasons. Firstly, digital rectal examination may not be sensitive enough to detect an abnormal mass in obese men. Secondly, obesity is usually linked to cardiovascular diseases or other health conditions. Therefore, it could lead to less effectiveness in treatment of prostate cancer (Van den Broeck et al., 2014). Thirdly, obese men tend to have lower serum PSA level than non-obese men (Oh et al., 2013). If not being adjusted, the general PSA threshold could reduce the chance for obese

men to have prostate biopsy, thus reducing the chance for prostate cancer to be detected.

Agent Orange

Although Agent Orange has been recognised as a human carcinogenesis (Chang et al., 2014), its role in the development and progression of prostate cancer remains inconclusive. Some initial studies found an association between this agent and prostate cancer (Giri et al., 2004, Zafar and Terris, 2001). However, their findings showed conflicting results which could be due to weaknesses in the measurement of exposure, and small sample sizes. A large cohort study of 13,144 American veterans who participated in Vietnam War showed a positive link between Agent Orange exposure and both incidence and high-grade prostate cancer. The incident rate of prostate cancer among exposed group was two times higher than that among unexposed group, and the cancer was also diagnosed at younger age and at more advanced stage (Chamie et al., 2008). However, the measurement of exposure to this agent was not convincing as it relied on self-report from participants without any blood test confirmation. This could lead to misclassification bias (Schecter et al., 2009). A more recent study, on the other hand, suggested that Agent Orange could have stronger influence on the progression of prostate cancer rather than its development. Ansbaugh et al. (2013) found that 75% increase in the high-grade prostate cancer risk could be attributable to Agent Orange. Nevertheless, a systematic and critical review by Chang et al. (2014) showed that evidence for this relationship remains neither consistent nor convincing. The main reason for the inconsistency was inaccuracy in the measurement of exposure.

Other risk factors

Several other factors, such as Vitamin D deficiency, sunlight, selenium also appear to be related to the development and progression of prostate cancer. However, their findings remain inconsistent.

Although a number of studies have been carried out to investigate the relation between vitamin D deficiency and prostate cancer risk, their results remained inconclusive (Braun et al., 1995, Polek and Weigel, 2002, Schwartz and Hulka, 1990). A meta-analysis of 9 cohort, 10 nested case-control and 6 case-control studies (Gilbert et al., 2011) showed only a weak reduction in risk of aggressive prostate cancer (OR 0.86; 95% CI 0.72, 1.02). However, this association was based on only two publications. In a later review, Schwartz (2013) found a growing evidence for the association between low level of vitamin D and increased risk of prostate cancer. This author also found evidence implicating that the role of vitamin D in prostate cancer development can be altered by other factors such as serum calcium intake and sunlight exposure. In line with these findings, results from a large prevention trial showed a linear relationship between high circulating vitamin D concentration and decreased prostate cancer risk (Schwartz, 2014).

Selenium is an important constituent of antioxidant enzymes found in the mammalian body. However, the role of this element in the development of prostate cancer is unclear. A review in 2009 (Platz and Lippman) showed an inverse association between selenium and nonaggressive, but not aggressive prostate cancer. However, a case-cohort study of 1,739 prostate cancer cases and 3,117 men in the United States (Kristal et al., 2014) found an association between excess use of selenium supplements and increased risk of prostate cancer. Kenfield et al. (2015) also reported that supplementation of more than 140 μg selenium per day can also increase prostate cancer mortality.

There remains conflicting findings about the relationship between hypertension and prostate cancer risk. In a cohort study of 82,098 Norwegian men, Martin et al. (2010) observed that about 4% increased risk of prostate cancer could be attributed to increase in one standard deviation (SD) of both systolic and diastolic blood pressure. This association appeared to be stronger in advanced prostate cancer than localised prostate cancer. In the general population, elevated blood pressure is responsible for an estimated 3% of prostate cancer. In contrast, another cohort study of more than 300,000 Swedish construction workers did not support these results. Stocks (2010) reported that hypertension was a protective factor for overall incident and

nonaggressive prostate cancer, but had no effect on the risk of advanced prostate cancer. However, there could be a competing risk bias in this observation because hypertension has been known to increase risk of death from cardiovascular diseases. Meanwhile, prostate cancer is usually diagnosed at old age. Hence, if it is possible, some men died from cardiovascular conditions before being diagnosed with prostate cancer. In addition, the use of antihypertensive medications among men with hypertension could lead to misclassification bias regarding assessment of exposure (Rodriguez et al., 2009).

There is some evidence showing that dietary α-linolenic acid from both vegetable and animal sources being associated with increased risk of prostate cancer (De Stefani et al., 2000). This association was supported by a meta-analysis of 10 studies including both prospective and case-control designs, showing a positive association (Brouwer et al., 2004). However, a later study failed to support this relationship. In a follow-up study of almost 30,000 men, Koralek et al. (2006) did not find any association of either total intake of this acid or a specific food source with prostate cancer risk. Even after stratifying by grade and stage, no association was found. The findings of this study appeared to be contradictory to several previous studies. A systematic review and meta-analysis by Simon et al. (2009) showed a small increased risk of prostate cancer being associated with high intake or high serum level of α-linolenic acid. Meanwhile, the review pointed out an inconsistency in previous studies. According to Azrad et al. (2012), this inconsistency could be due to influence of genetic variation on the relationship between α-linolenic acid and prostate cancer. These authors found interaction between this acid and some genetic variation such as rs498793, rs99780 and rs174545. Therefore, interpretation of the relationship between α-linolenic acid and prostate cancer without consideration of genetic variation could lead to contradictory results across studies.

Sunlight has also been examined in relation to prostate cancer risk. A cohort study in the United States showed that sunlight exposure can reduce the risk of prostate cancer. Specifically, the high solar radiation attributed to a reduction of 51% in the RR of prostate cancer (John et al., 2004). In a more detailed analysis, lifetime cumulative exposure to ultraviolet light, adult sunbathing and childhood sunburning

all have positive associations with reduced prostate cancer risk (Bodiwala et al., 2003). However, not every study supported these findings. A review conducted by Donkena and Young (2011) showed that while a large number of studies were consistent in regard to the protective effects of sunlight exposure on prostate cancer risk, various other studies failed to demonstrate this link. One study even showed that sunlight exposure could be a risk factor for prostate cancer (Grant, 2004). To date, there have been an overwhelming body of evidence for the protective effects of sunlight against prostate cancer development despite several contradictory findings (Schwartz, 2013).

2.4.3 Tea and prostate cancer

2.4.3.1 Tea antioxidants

Tea has been one of the most popular beverages historically. This type of beverage is produced from leaves of *camellia senesis*. Depending on the method of production, there are different types of tea. For example, green tea is produced from fresh tea leaves based on a process of heat treatment, while black tea is produced from crushed tea leaves. On the other hand, Oolong tea is made from oxidised tea leaves (Graham, 1992a). In some cultures, diluted extract from boiling fresh green tea leaves can be used directly as a daily beverage (Jian et al., 2004). Studies show that tea, especially green tea, contains important bioactive compounds such as catechins and flavonols. These polyphenols possess a strong antioxidant property, especially epigallocatechin-3-gallate (EGCG) that is the major antioxidant among green tea polyphenols. There are differences in the concentration of polyphenols among different tea types due to their method of production. For instance, to produce green tea, fresh tea leaves are steamed or heated immediately after harvest. Therefore, this method results in minimal bioactive compounds lost during production. Whereas, to produce black tea, fresh tea leaves are crushed, then dried up. Considerable bioactive compounds can be lost during this process. In fact, a comparison (Lee et al., 2002) showed that total phenolic content in green tea was much higher than that in black tea (equivalent of 165 versus 124 mg gallic acid), and that antioxidant capacity of

green tea was higher than that of black tea. Both laboratory and animal experiments showed that EGCG could be a strong candidate for chemoprevention against prostate cancer (Adhami and Mukhtar, 2007). Indeed, laboratory experiments showed that EGCG has a range of protective effects against the development and progression of prostate cancer, such as inducing cell cycle arrest and apotosis, acting as sensitising agent in prostate cancer cells, targeting androgen receptor and reducing PSA, or targeting insulin-like growth factor axis (Johnson et al., 2010). A recent in vitro experiment showed that polyphenols from green tea can inhibit the proliferation of prostate cancer cells (Liang et al., 2013). This effect is even increased when quercetin, a flavonol in tea, is present (Wang et al., 2012b). These findings are supported by a more recent animal experiment (Khan et al., 2014). In this study, EGCG was orally given to cancer mice using nano-techonolgy. The nano-EGCG was found to significantly inhibit tumour growth and PSA secretion.

2.4.3.2 Epidemiological evidence

Despite convincing evidence from laboratory studies, epidemiological evidence for the protective effect of habitual tea consumption remains inconsistent. To date, an overwhelming number of research studies have been conducted to demonstrate the protective effect of tea against the development and progression of prostate cancer. These include observational studies (case-control and cohort designs), randomised clinical trials and meta-analysis. However, inconsistencies exist in the conclusion of different studies, even among various review articles on the same topic. This section will review the extent of evidence based on different types of study design, and several aspects of the relationship between habitual tea consumption and prostate cancer risk, such as type of tea and prostate cancer risk, or tea consumption and progression of prostate cancer (see Section 2.1 Overview for the detailed criteria and date of literature search). Following the PRISMA guideline for systematic review and meta-analysis (Liberati et al., 2009), a total of 40 studies published over the last 25 years have been identified and reviewed. These include 16 case-control studies, 13 cohort studies, 6 clinical trials and 5 meta-analyses. Summary of the process of searching, identifying and assessing eligible publications for the review is presented

in Figure 4. The statement about level synthesis evidence was made based on the guideline developed by Tulder (2003). Accordingly, strong evidence should come from consistent findings of high quality studies. At a lower level, moderate evidence can be drawn from medium quality studies with consistent findings. Limited evidence refers to consistent findings from multiple low quality studies or one medium quality study. Conflicting evidence results from inconsistent findings. The lowest level is "no evidence".

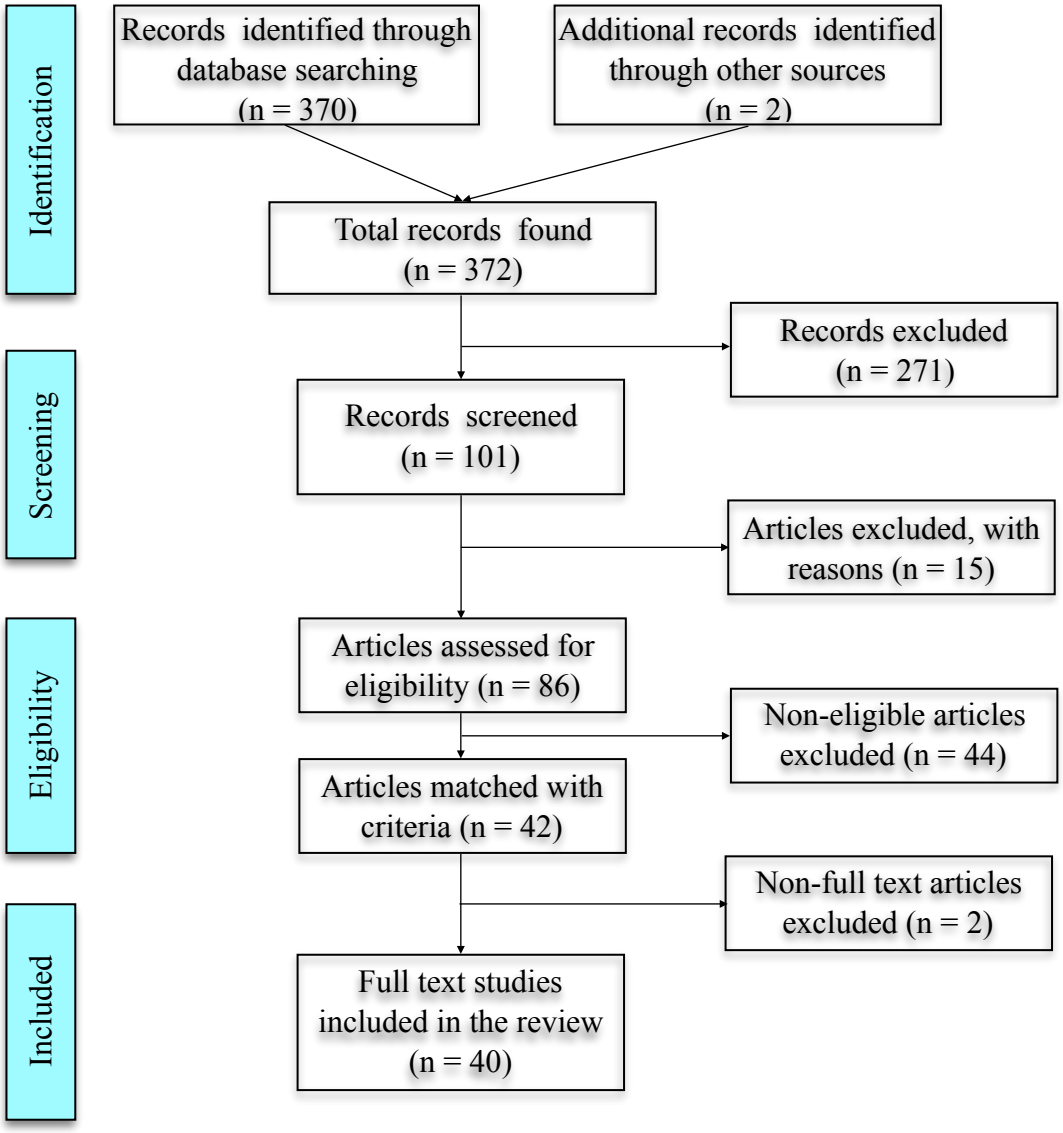

Figure 4 PRISMA flow diagram for systematic review of tea consumption and prostate cancer

Evidence of tea consumption from case-control studies

Table 3 presents summary findings from 16 case-control studies. Nine of these studies came from Asia (China: 4, India: 2, Japan: 1, and Singapore: 1), where tea is popular. The rest of studies came from Canada (3), the USA (2), Algeria (1) and Uruguay (1). Findings from half of these studies support the hypothesis that habitual consumption of tea is protective against prostate cancer. All of the studies from China showed a reduced risk of prostate cancer among men who drank tea more frequently compared to men who drank tea less frequently. Three of them were hospital-based case-control studies (Jian et al., 2007, Jian et al., 2004, Wu et al., 2009) with relatively small sample sizes (130, 130 and 142 cases, respectively). These studies investigated the relation between green tea and prostate cancer risk. The inverse association between green tea and prostate cancer risk was observed in all comparisons, from ever drinking versus none to 1.5 kg tea leaves per year. There seemed to be a dose-response relationship between the amount of consumed green tea and prostate cancer risk (Jian et al., 2007). Jian et al. (2004) also reported that drinking 1.5 kg tea leaves per year had the strongest influence on prostate cancer risk compared to other categories (i.e. ever drinking, drinking more than 40 years, and drink more than 3 cups per day versus none). In a more recent study, Hu et al. (2014) did not specify the type of tea investigated, but also found a significant inverse association with prostate cancer risk when comparing seldom versus regular tea consumption. Another study from India also showed that men who drank tea irrespective of amount of consumption could be at a lower risk of prostate cancer (Tyagi et al., 2010). Slightly different from studies conducted on Chinese and Indian men, a study in Canada (Jain et al., 1998) found that the protective effect of tea (type not specified) against prostate cancer was only significant among men who drank more than 500 g per day (approximately 2 cups per day). One study in the United States also reported the protective effect of tea (type not specified) among men who drank two or more cups per day (Geybels et al., 2013a). Of the three studies on black tea, only one conducted in Uruguay showed that drinking at least one cup of black tea per week could lower prostate cancer risk (Stefani et al., 2011). However, this study did not found any protective effect of black tea when being served with milk.

Table 3 Evidence of tea consumption from case-control studies

Reference	Study design [Sample size]	Country	Type of tea	Tea consumption assessment	Comparison of tea intake	prostate cancer risk (adjusted OR (95% CI)
a. (Hu et al., 2014)	PCC [108/242]	China	NS	Interview: never, ≥ 4 times/week)	Seldom or never vs. ≥ 4 times/ week	0.58 (0.35, 0.96)
b. (Geybels et al., 2013a)	PCC [892/863]	USA	NS	Interview: 9 categories: < 1 time/month to ≥ 6 times/day	≥ 2 cups per day vs. ≤ 1 cups/ week	0.63 (0.45, 0.90) overall 0.65 (0.45, 0.94) G 2-7 0.51 (0.25, 1.04) G 7-10 0.68 (0.47, 0.97) L PCa
c. (Berroukche et al., 2012)	HCC [160/160]	Algeria	GT	Interview: cups per day	> 6 cups per day vs. ≤ 1 cups per day	0.6 (0.3, 1.1)
d. (Stefani et al., 2011)	HCC [345/ 1296]	Uruguay	BT Tea with milk	Interview: cups/week	1 - 6 cups/week vs. none ≥ 7 cups/week vs. none 1 - 6 cups/week vs. none ≥ 7 cups/week vs. none	0.46 (0.29,0.72) 0.43 (0.22, 0.81) 0.56 (0.34, 0.91) 1.47 (0.88, 2.45)
e. (Ganesh et al., 2011)	Unmatched HCC [123/167]	India	NS	Interview: yes or no	Yes vs. no	0.7 (0.1, 3.4)
f. (Tyagi et al., 2010)	PCC [303/606]	India	NS	Interview: yes or no	Yes vs. no	0.45 (0.21, 0.97)
g. (Chia et al., 2010)	CC [240/268]	Singapore	BT GT	Interview: yes or no	Drinking vs. none	1.55 (0.93 ,2.59) 1.45 (0.93-2.27)
h. (Wu et al., 2009)	HCC (142/142)	China	GT	Interview: yes or no	Drinking vs. none	0.52 (0.28, 0.96)
i. (Jian et al., 2007)	HCC [130/274]	China	GT leaves	Interview using FFQ and structure questionnaire	0.3-2.9 g/day vs. none 3.0-4.9 g/day vs. none ≥ 5 g/day vs. none	0.45 (0.25, 0.82) 0.24 (0.10, 0.57) 0.13 (0.05, 0.32)
j. (Jian et al., 2004)	HCC [130/274]	China	GT	Interview using FFQ and structure questionnaire	Drinking vs. none ≥ 40 years drinking vs. none > 1.5kg tea leaves/year vs. none	0.28 (0.17, 0.47) 0.12 (0.06, 0.26) 0.09 (0.04, 0.21) 0.27 (0.15, 0.48)
k. (Sonoda et al., 2004)	MCC [140/140]	Japan	GT BT	Interview	> 3cups per day vs. none ≥ 10 cups per day ≥ cup/day vs. none	0.67 (0.27, 1.64) p trend = 0.30 1.51 (0.89, 2.56)

Table 3 Evidence of tea consumption from case-control studies (*continued*)

Reference	Study design [Sample	Country	Type of tea	Tea consumption assessment	Comparison of tea intake	prostate cancer risk (adjusted OR (95% CI)
l. (Sharpe and Siemiatycki, 2002)	PCC [399/476]	Canada	NS	Interview	≥ 5 times/day > 107 drinks/year vs. < 54 drink/ year > 119 drinks/year vs. < 57 drink/	1.9 (1.0, 3.4) 0.9 (0.5, 1.7) population controls 1.6 (1.0, 2.4) cancer controls 1.1 (0.6, 2.0) population controls
m. (Villeneuve et al., 1999)	PCC [1,623/ 1,623]	Canada	NS	self-administered questionnaire	≥ 4 cups per day vs. none	1.1 (0.8, 1.5) p trend = 0.11
n. (Jain et al., 1998)	CC [617/637]	Canada	NS	Interview	0 g/day > 0 - 500g/day > 500g/day	1.0 0.89 (0.69, 1.16) 0.7 (0.50, 0.99) p trend = 0.05
o. (Slattery and West, 1993)	PCC [362/685]	The USA	NS	self-administered questionnaire	> 5 cups per day vs. none	OR for those ≤ 67 years olds: 1.06 (0.72, 1.57) OR for those .67 years olds: 0.90 (0.59, 1.63)
p. (Lavecchia et al., 1992)	HCC [107/6,147]		NS	Interview	Yes vs. no	0.9 (0.5, 1.7)

PCC: population-based case-control; HCC: hospital-based case-control; MCC: matched case-control; CC: case-control; NS: not specified; GT: green tea; BT: black tea; OT: Oolong tea; NS: type of tea is not specified; vs.: versus; p trend: p-value from test of linear trend; G: Gleason score; L PCa: localised prostate cancer; M PCa: metastasised prostate cancer; OR: odds ratio;; USA: the United States of America

In contrast, 8 other studies which investigated the protective effect of green tea, black tea and tea in general (type not specified) did not support the hypothesis that tea drinking can prevent prostate cancer (Table 3). These studies came from Algeria (1), India (1), Singapore (1), Japan (1), Canada (2), Italy and the USA (1). Most of these studies reported no association between tea drinking, irrespective of the amount of consumption, and the prostate cancer risk. One study in Canada (Sharpe and Siemiatycki, 2002) even found that men who drank tea at least one time per day could be at higher risk of prostate cancer. The odds ratio for men who drank 5 times per day compared to men who drank less than 1 time per day was 1.9 (95% CI: 1.0, 3.4). However, this study did not specify the type of tea, nor the amount of consumption when comparing the risk of prostate cancer between cases and controls. Also, when estimating the odds ratio for controls, this study did not adjust for other dietary factors such as total energy or diet confounding risk factors for prostate cancer. Most of the studies that reported no association between tea consumption and

prostate cancer risk did not specify the type of tea, while antioxidative property of tea differs from one type to another. These studies also did not consider the cumulative exposure to tea consumption.

In general, 16 case-control studies reported conflicting results. The protective effect of green tea was supported by 7 studies, but not by 3 other studies. The protective effect of black tea was demonstrated by only one study, while 3 others failed to prove it. Tea in general (either green, black or Oolong tea) was found to be protective by 4 studies, but increase in risk by one study (Sharpe and Siemiatycki, 2002), meanwhile, 4 other studies (Ganesh et al., 2011, Lavecchia et al., 1992, Slattery and West, 1993, Villeneuve et al., 1999) did not found any association between tea consumption and the prostate cancer risk.

Evidence of tea consumption from cohort studies

Since 1990, 10 cohort studies have been conducted to investigate the influence of tea consumption on prostate cancer risk (Table 4). These studies were conducted in Japan (4), the USA (1), Netherlands (1), Scotland (1), Singapore (1), Canada (1) and Italy (1). Among them, 5 studies focused on green tea, 3 studies focused on black tea. 4 other studies did not specify the type of tea. However, black tea was assumed because of its popularity among study populations. Only one prospective cohort study conducted in Netherlands (Geybels et al., 2013c) showed protective effect of black tea against prostate cancer. Men who drank 5 or more cups of black tea a day could be at lower risk of prostate cancer compared to those who drank one or less than one cup a day. This inverse association was observed among prostate cancer patients at stage III and IV, meanwhile, no association was observed among other prostate cancer stages. The adjusted RRs for these stages were 0.75 (95% CI 0.59, 0.97) and 0.67 (95% CI 0.5, 0.91), respectively. Green tea was also found to be protective by one study in Japan (Kurahashi et al., 2008). This study followed up nearly 50,000 men for 14 years, and found that drinking more than 5 cups of green tea a day was associated with lower risk prostate cancer in comparison to drinking 1 cup per day. However, this association was apparent only in advanced prostate

cancer. For localised prostate cancer, no association was found. Findings from 8 other studies did not support the hypothesis that regular tea consumption can prevent prostate cancer. Most of these studies did not observe association between tea consumption and prostate cancer risk. Two studies from Singapore and Scotland (Montague et al., 2012, Shafique et al., 2012) even showed that drinking tea could increase the risk of prostate cancer. After 11.2 years of following up 27,293 Singaporean men, Montague et al. (2012) found that monthly or daily consumption one cup of black tea could increase the RR of prostate cancer. However, this positive association was not seen in those who drank two or more cups of black tea a day (RR: 1.17, 95% CI: 0.67, 2.07). In Scotland, Shafique et al. (2012) reported a positive association between drinking seven or more cups of tea per day and prostate cancer risk. In this study, about 6,000 Scottish men had been followed up for 28 years, but the type of tea was not specified.

Given the fact that findings from these cohort studies were inconsistent, several weaknesses need to be considered. Firstly, the statistical analyses of tea consumption in relation to the prostate cancer risk were based on baseline data. Meanwhile, tea drinking habit could change over time. Because habitual tea drinking not assessed during the follow up, cumulative exposure was unable to be accounted. On the other hand, prostate cancer has a long latent period before being detectable, many other factors could be involved in the course of disease development. Therefore, habitual tea consumption at baseline could not fully explain the risk of prostate cancer after a long latent period. Moreover, the measurement of tea exposure was based on self-administered questionnaires, which are subjected to measurement bias.

Table 4 Evidence of tea consumption from cohort studies

Reference	Study design [cohort size; cases; follow-up]	Country	Type of tea	Tea consumption assessment	Amount of consumption	Adjusted relative risk (95% CI)
a. (Geybels et al., 2013b)	Retrospective [894 prostate cancer cases; 140 recurrence cases; 6.4	USA	NS	Self-completed FFQ: nine categories: never to ≥ 6 cups per day	≤ 1 cups/week 2 - 6 cups/week ≥ 1 cups per day	1.00 1.14 (0.73, 1.79) 1.08 (0.65, 178)
b. (Geybels et al., 2013c)	Prospective [58,279; 3,362 cases; 17.3 years]	Netherlands	BT	Interview: standard cups per day	≥ 5 cups per day vs. ≤ 1cups per day	0.75 (0.59, 0.97) stage III/IV PCa 0.67 (0.5, 0.91) for stage IV prostate cancer
c. (Shafique et al., 2012)	Prospective [6,016; 318 cases; 28 years]	Scotland	NS	Self-administered questionnaire at baseline: 4 groups (0 - 3, 4 - 5, 6, ≥ 7 cups per day)	0-3 cups per day 4-5 cups per day 6 cups per day ≥ 5 cups per day Cups of tea (continuous)	1.00 1.11 (0.79, 1.48) 1.10 (0.79, 1.57) 1.50 (1.06, 2.12) 1.05 (1.01, 1.09)
d. (Montague et al., 2012)	Prospective [27,293; 298 cases; 11.2 years]	Singapore	GT	Interview using FFQ, at baseline: cups per day, week and month, during 12 months prior to interview	None Monthly Weekly Daily 1 cup/day ≥ 2 cups per day	1.00 1.07 (0.73, 1.56) 1.09 (0.80, 1.48) 1.08 (0.79, 1.48) 1.22 (0.82, 1.82) 0.96 (0.62, 1.45)
			BT		None Monthly Weekly 1 cup/day ≥ 2 cups per day	1.0 1.17 (0.75, 1.83) 1.40 (1.05, 1.86) 1.41 (1.06, 1.92) 1.50 (1.06, 2.13) 1.17 (0.67, 2.07)
e. (Kurahashi et al., 2008)	Prospective [49,920; 404 cases; 14 years]	Japan	GT	Self-administered questionnaire at baseline: cups per day, week, month or never	≥ 5 cups per day vs. < 1 cup/day ≥ 5 cups per day vs. < 1 cup/day > 5 cups per day vs. < 1 cup/day	0.89 (0.65, 1.21), overall 1.04 (0.72, 1.52), localised PCa 0.52 (0.28, 0.96), advanced PCa
f. (Kikuchi et al., 2006)	Prospective [19,561; 110 cases; 7 years]	Japan	GT	self-administered questionnaire at baseline	1 - 2 cups per day vs. < 1 cup/ day 3 - 4 cups per day vs. < 1 cup/ day	0.77 (0.42, 1.40) 1.15 (0.69,1.94) 0.85 (0.50, 1.43)
g. (Allen et al., 2004)	Prospective [18,115; 196 cases; 16.9	Japan	GT	self-administered questionnaire at baseline	≥ 5 times/day vs. < 1time/day	1.29 (0.84, 1.98)
			BT		Almost daily	0.86 (0.47, 1.59)
h. (Nagano et al., 2001)	Prospective [14,873; 92 cases; 14	Japan	GT	Self-administered questionnaire: times/day	Data not showed	No association was found
i. (Ellison, 2000)	Retrospective [3,400; 145 cases; 20 years]	Canada	NS	Interview using one-month FFQ and then converted to ml/day	> 500 ml/day vs. none	1.02 (0.62, 1.65)
j. (Lavecchia et al., 1992)	Retrospective [data not shown; 107 cases; 7 years]	Italy	NS	Interview	≥ 1 cups per day vs. none	0.90 (0.50, 1.70)

NS: not specified; GT: green tea; BT: black tea; OT: Oolong tea; NS: type of tea is not specified; PCa: prostate cancer; USA: the United States of America

Evidence from clinical trials

To date, 5 clinical trial studies have been published to investigate the protective effect of tea and tea extract on the progression of prostate cancer (Table 5). These studies were conducted in the USA (3), Italy (2) and Canada (1). In an open label, single arm trial for at least two months, Choan et al. (2005) treated 19 hormone refractory prostate cancer patients with green tea extract in the form of capsule containing 250 mg. These patients were given two capsules per day. After at least two months of intervention, no clinical significance was found. Green tea extract was found to only slow down PSA progression, at a modest pace. These authors concluded that green tea extract did not result in any discernible clinical activity among these patients. In an earlier study, Jatoi et al. (2003) treated their patients with green tea powder (6 g per dose). 42 patients were given 6 doses per day for 1 month. This treatment resulted in only minimal antineoplastic activity. This study was also an open label single arm. Different from these two studies, 4 later trials showed a significant clinical activity of green tea and its bioactive compounds. After one-year treatment with green tea catechins, the main component of tea polyphenols, Bettuzzi et al. (2006) found that green tea catechins were safe and effective for treatment of premalignant lesions that can gradually develop to prostate cancer. In this double blinded, two arm trials, 60 high-grade prostatic intraepithelial neoplasia (HGPIN) patients were given 3 capsules (each contains 200 mg green tea catechins) per day. As the results, only one tumour was detected in green tea catechins arm, meanwhile, nine tumours were detected in placebo arm. The green tea catechins were also found to reduce symptoms of lower urinary tract. The authors continued to follow up 21 HGPIN patients from this trial for two years, without any further treatment of green tea catechins, only one out of 13 control patients developed prostate cancer, while two out of 9 placebo patients had tumour (Brausi et al., 2008). These results again confirmed the protective effects of green tea catechins on the progression of prostate cancer. In another open label, single arm trial, a higher dose of catechins (800 mg EGCG) was applied for 6 weeks to prostate cancer patients who had been scheduled for radical prostectomy. This treatment resulted in a remarkable reduction in serum level of prostate cancer's biomarkers including PSA, hepatocyte growth factor and

vascular endothelial growth factor. The most recent trial tested the effect of both green and black tea on localised prostate cancer patients (Henning et al., 2014). The results reconfirmed the protective effects of green tea consumption against the progression of prostate cancer. There were significant reductions in the systemic antioxidant activity, nuclear staining and serum PSA in patients who were given 6 cups of brewed green tea per day, which amounted to 562 mg EGCG included in 1,010 mg total green tea polyphenols. However, this protective effect was not found in patients who were given 6 cups of black tea per day. This could be due to the lower EGCG content in black tea, as 6 cups of brewed black tea provide only 80 mg of total tea polyphenols and 20 mg of EGCG.

In summary, clinical trials showed a significant protective effect of green tea and green tea polyphenols against the progression of prostate cancer. Admittedly, two earlier trials failed to demonstrate these effects. However, these conflicting results could be explained due to the much lower dose of tea polyphenols given to the patients. Moreover, the duration of treatment and follow up was fairly short (from 1 to two months). Finally, the study subjects could also be a reason. In these studies, hormonal refractory prostate cancer patients were tested. Studies have shown that androgens and androgen receptor play an important role in the development and progression of prostate cancer, while the molecular mechanism by which tea polyphenols express their effects on prostate gland was related to androgens and their receptors (Saleem et al., 2003).

Table 5 Evidence from clinical trials

Reference	Study design [duration]	Country	Participant	Tea preparation	Amount of consumption	Result
a. (Henning et al., 2014)	Open label, three arm phase II [3-8 weeks]	USA	113 localised prostate cancer patients who are scheduled to undergo radial prostectomy	Green tea bags and black tea bags brewed in boiling water (one tea bag in 240 ml water, in 5 minutes)	Group 1: 6 cups of brewed green tea each day Group 2: 6 cups of brewed black tea each day Group 3: water used as control	Black tea: no difference found
b. (McLarty et al., 2009)	Open label, single arm phase II [6 weeks]	USA	26 prostate cancer patients, scheduled for radical prostatectomy	Capsules containing 1.3 g tea polyphenols (800 mg EGCG)	4 capsules daily with a meal	Reduction in serum level of PSA, HGF and VEGF
c. (Brausi et al., 2008)	Double blinded, placebo-control [2 years]	Italy	9 placebo and 13 controlled HGPIN volunteers	Capsules containing 200 mg green tea catechins	3 capsules per day for one year prior to this two-year follow-up No treatment applied during this follow-up	Green tea catechin arm: 1 tumour detected Placebo arm: 2 tumours detected
d. (Bettuzzi et al., 2006)	Double blinded, two arm [1 year]	Italy	60 HGPIN	Capsules containing 200 mg green tea catechins	3 capsules per day for one year	Green tea catechin arm: 1 tumour detected Placebo arm: 9 tumours detected
e. (Choan et al., 2005)	Open label, single arm [≥ 2 months]	Canada	19 HR prostate cancer patients	Capsules containing 250 mg green tea extract	2 capsules per day	No discernible clinical activity
f. (Jatoi et al., 2003)	Open label, single arm phase II [1 month]	USA	42 HR prostate cancer patients	Green tea powder, 6 g per dose	6 doses per day	Minimal antineoplastic activity: PSA remains unchanged

HGPIN: high grade prostatic intraepithelial neoplasia; HR: hormone refractory; PSA: prostate specific antigen; EGCG: epigallocatechin gallate; HGF: hepatocyte growth factor; VEGF: vascular endothelial growth factor; USA: the United States of America

Evidence of tea consumption from meta-analyses

Overall, evidence from meta-analyses remains inconclusive. Table 6 summarises findings from five meta-analyses on the relationship between tea consumption, including green tea, black tea and Oolong tea, and the risk of prostate cancer. By comparing highest level versus none or lowest level of tea consumption, the overall RRs of all analyses did not show significant association between tea consumption and prostate cancer risk, except one analysis of pooled data from 21 cohort and 13 case-control studies. In this review, Fei et al. (2014) reported an overall RR of prostate cancer of 0.84 (95% CI: 0.71, 0.98). It seems that tea consumption has protective effect against the development of prostate cancer, albeit the level of risk reduction was small (about 16%). However, when stratifying by type of tea, no association was found for black tea. Although not statistically significant (RR: 0.73; 95% CI: 0.52, 1.02), consumption of green tea appeared to be associated with reduced risk of prostate cancer. Further stratification by study designs, only pooling data from case-control studies demonstrated the inverse association, meanwhile pooled data from cohort studies failed to show this association. Moreover, this negative association was only observed among low-grade prostate cancer, but not high-grades. The protective effect of tea consumption against prostate cancer was also supported by three other meta-analyses (Kim and Lee, 2012, Lin et al., 2014, Zheng et al., 2011), but only demonstrated by pooled data from case-control studies. Overall, these studies did not support the protective effect of tea. Stratification by geographic region revealed that the strongest association between tea consumption and reduced prostate cancer risk came from studies in China (Zheng et al., 2011).

Table 6 Evidence of tea consumption from meta-analyses

References	Studies analysed [pooled data]	Type of tea	Consumption category	Relative risk (95% CI) and conclusion
a. (Yu et al., 2014)	6 cohort studies 1 case-cohort study	GT: 2 studies BT: 1 studies GT & BT: 2 studies NS: 2 studies	3 cups per day	1.02 (0.96, 1.09) Insufficient evidence supporting protective role of tea intakes
b. (Lin et al., 2014b)	7 cohort studies 14 case-control studies	GT: 9 studies BT: 11 studies OT: 1 study NS: 7 studies	highest versus non/ lowest tea consumption levels	0.86 (0.69, 1.04): overall 0.98 (0.86, 1.09): cohort 0.77 (0.55, 0.98): case-control There is not enough evidence for the protective effect of tea consumption
c. (Fei et al., 2014)	8 cohort studies 13 case-control studies	GT: 10 studies BT: 17 studies OT: 1 study NS: 7 studies	Highest vs. lowest	0.84 (0.71, 0.98): overall 0.73 (0.52, 1.02): GT 0.95 (0.82, 1.11): BT 1.04 (0.92, 1.19): cohort 0.69 (0.54, 0.88): Case-control 0.66 (0.46, 0.93): low-grade PCa
d. (Kim and Lee, 2012)	6 studies (cohort and case-control)	GT: 6 studies	Highest vs. lowest amount	0.82 (0.75, 1.07): overall 0.40 (0.17, 0.92): case-control 1.08 (0.89, 1.32): cohort
e. (Zheng et al., 2011)	6 cohorts studies (4 prospective designs, 2 retrospective designs) 7 case-controls studies	GT: 7 studies BT: 5 studies NS: 6 studies	highest vs. non/lowest	0.72 (0.45, 1.15): GT, overall 0.43 (0.25, 0.73): GT, case-control 1.00 (0.66, 1.53): GT, cohort 0.37 (0.20, 0.71): GT, China 0.99 (0.82, 1.20), BT, overall 0.83 (0.63, 1.08), BT, cohort 1.07 (0.78, 1.48), BT, case-control

NS: not specified; GT: green tea; BT: black tea; OT: Oolong tea; NS: type of tea is not specified; vs.: versus; PCa: prostate cancer

2.4.3.3 Discussion and summary

Although there are three main types of tea namely green tea, black tea and Oolong tea, most reviewed studies focused on green tea and black tea. Existing studies showed that tea consumption appears to be protective against the development and progression of prostate cancer. In fact, biochemical studies showed that tea produced from leaves of *camellia senesis* contains important antioxidants, such as catechins and flavonols (Adhami and Mukhtar, 2007). One of the most important antioxidants

is EGCG. Both in vivo and in vitro experiments showed that EGCG can inhibit the growth, and can induce apotosis of prostate cancer cells, resulting in delay or slower the development and progression of the tumour (Johnson et al., 2010). Green tea rather than black tea appears to be more protective according to the larger number of studies. This difference could be explained by its higher antioxidant content than that in black tea (Lee et al., 2002).

It appears that tea, especially green tea, has protective effects on both the development and the progression of prostate cancer. There has been evidence showing that incidence of prostate cancer is lower among men who regularly drink tea than those who never or less regularly drink tea (Table 3, 4 and 5). Regarding the progression of prostate cancer, evidence from observational studies (case-control and cohort studies) shows that tea consumption has stronger effect on advanced prostate cancer than lower-grade prostate cancer (Table 3). This effect is more apparent in clinical trials. Most trials showed that green tea and tea polyphenols can be protective against the progression of prostate cancer (Table 5).

While clinical trials showed a fairly strong association between green tea and decreased risk of prostate cancer, observational studies provided conflicting results. Indeed, most cohort studies did not support the protective effect of tea, whereas, 8 out of 16 reviewed case-control studies demonstrated the inverse association between tea consumption and prostate cancer risk (Table 3 and 4). Regarding the level of strength of evidence, all of the reviewed studies, met at least level III-2 of the sixth levels scale (National Health and Medical Research Council, 1999). Although, cohort design ranks higher than case-control design, statistical analysis of all reviewed cohort studies used baseline data when estimating the effect of tea consumption on prostate cancer risk, and did not assess the pattern of tea consumption during the follow up period. The duration of follow up ranges from 6.4 years to 28 years, therefore, change in tea drinking habit could subsequently affect the risk of prostate cancer. Moreover, cumulative exposure to tea consumption was also not considered, which could lead to conflicting findings. As recall bias is a major concern regarding the strength of case-control studies, the evidence from this type of study is not convincing for making recommendation for the general public.

In summary, most supporting evidence for the protective effect of tea consumption against prostate cancer comes from clinical trials and case-controls studies. Synthesis of meta-analyses also suggests an inverse association between green tea and the risk of prostate cancer. The effects of both green tea and black tea on prostate cancer had been extensively investigated by epidemiological studies. However, the protective effect of green tea received more support than that of black tea, as shown by both observational and clinical studies. Higher EGCG content in green tea compared to black tea could be a plausible explanation.

2.4.4 Coffee and prostate cancer

2.4.4.1 Coffee antioxidants

Coffee is one of the most consumed beverages in the world. Its popularity is probably just after water and tea. This type of beverage has been recognised as a rich source of antioxidants. In comparison to some of the most common beverages, coffee together with tea and wine contain the highest concentration of phenolic compounds that contribute substantially to antioxidant activity (Svilaas et al., 2004). The main antioxidant components of coffee include caffeic acid, chlorogenic acid and caffeine, cafestol and kahweol (Liang and Kitts, 2014). Brezová et al. (2009) reported that both instant and ground coffee expressed remarkable antioxidant activity, and also reconfirmed that coffee is a rich source of antioxidant compared to other common beverages. Other bioactive compounds, such as polyphenols and phenolic acids, also contribute significantly to coffee's antioxidant property (Chu et al., 2008). A comparison of antioxidant activity of several common beverages including coffee, tea and cocoa showed that antioxidant capacity of coffee was the highest among the tested beverages, on the basis of a cup-serving (Richelle et al., 2001). However, brewing method and time can greatly impact the antioxidant extraction and activity of coffee (Ludwig et al., 2012).

There is link between coffee consumption and health benefits. A wide range of anticarcinogenic properties of coffee has been reported, such as inhibition of tumour cells proliferation, DNA repair and involvement in cell cycle checkpoints (Porta et

al., 2003). In humans, clinical trials showed that drinking coffee can significantly increase plasma antioxidant activity, protect the body from oxidative damages, and prevent endogenous formation of oxidative damage (Liang and Kitts, 2014).

2.4.4.2 Epidemiological evidence

The effect of coffee consumption on the development and progression of prostate cancer has been investigated for more than four decades. In 1964, Takahashi (1964) reported a strong correlation between average coffee consumption and prostate cancer mortality based on pooled data from 20 countries. Although the study had a number of flaws, such as not adjusting for other plausible risk factors, it drew the attention of researchers to investigate the relationship between coffee consumption and prostate cancer risk. Indeed, later studies provide some evidence that can clarify this relation. Using a systematic approach in searching and reviewing publications, my review identified a total of 37 publications that address the relation between coffee consumption and the risk of prostate cancer over the past 25 years (see Section 2.1 Overview for the detailed criteria and date of literature search). The process of searching for literature and review was undertaken in compliance with the PRISMA guideline (Liberati et al., 2009) and Australian National Health and Medical Research guideline (1999). Initially, the search resulted in 179 articles. The screening for relevance narrowed the initial search results to 98 articles. Further exclusion of ineligible publications led to a shortlist of 38 articles. However, one study from Iran just included coffee into the definition of Western style diet, without any detail on assessment of coffee intake. Therefore, this article was excluded. The final results consisted of 37 full text articles to be included in the review. Figure 5 summarises the process of searching.

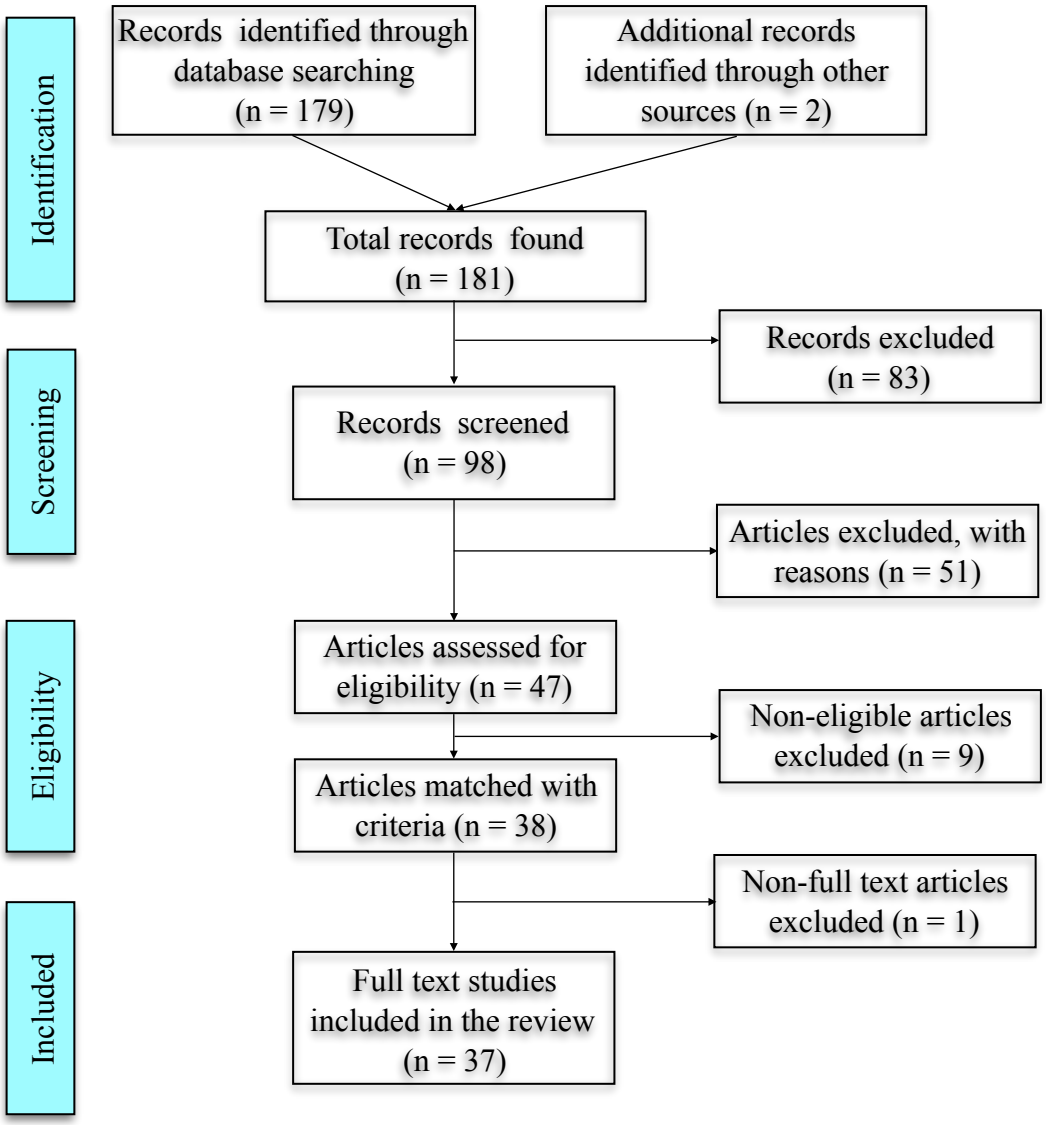

Figure 5 PRISMA flow diagram for systematic review of coffee consumption and prostate cancer

Evidence of coffee consumption from case-control studies

Since 1990, a total of 13 case-control studies, that investigate the influence of coffee drinking on the risk of prostate cancer, have been documented. Table 7 summarises main findings of these studies. The reviewed publications came from the USA (3 studies), Canada (3 studies), Japan (1 study), Sweden (2 studies), Greece (1 study), Taiwan (1 study), Italy (1 study) and India (1 study). Most of them were population-based studies.

There were 3 studies that found coffee drinking to be associated with the prostate cancer risk; see Table 7 (a), (e) and (f). However, findings of these studies were inconsistent. Only one study found protective effects of coffee consumption against prostate cancer risk. This was a population based study that consisted of 1,499 prostate cancer incident cases and 1,112 controls, in Sweden. The study reported that drinking more than 5 cups of coffee per day can reduce the risk of high-grade prostate cancer by 50% (OR: 0.5, 95% CI: 0.26, 0.98) when compared to drinking less than 1 cup per day. Consumption of 1 to 5 cups of coffee per day was also found to be inversely associated with reduced risk of high-grade prostate cancer, but not statistically significant. Further analysis showed that coffee consumption had no effect on total, localised, grade 7 or lower prostate cancer (Wilson et al., 2013). Coffee consumption also appeared to be inversely associated with the risk of fatal and advanced prostate cancer. However, this association was not statistically significant. In contrast to these findings, two earlier hospital-based studies showed completely different results that implicate coffee drinking could pose a risk for prostate cancer. Chen et al. (2005) found that coffee drinkers could be at 1.88 times higher risk of prostate cancer compared to those who never drink coffee (OR: 1.88, 95% CI: 1.07, 3.30). Similarly, Gallus et al. (2007) reported that men who drank more coffee could be at higher risk of prostate cancer compared to those who drank less coffee (third versus first tertile level of coffee consumption). This positive association was unchanged even when being stratified by Gleason score (Gleason < 7 versus Gleason ≥ 7).

Ten other studies failed to demonstrate association between coffee consumption and prostate cancer risk; see Table 7 (b) - (d) and (g) - (m). Not only overall risk of total prostate cancer was found not associated with coffee consumption but also subgroups of the cancer. Geybels et al. (2013b) stratified prostate cancer sample into four subgroups: Gleason 2 - 7, Gleason 7 - 10, local stage, and regional/distant stage, but only found non-statistically significant association. Other authors stratified by race, aggressiveness and type of coffee (Arab et al., 2012), but again, no association was found. One study even considered the total years of drinking coffee, and calculated

the number of drink-years for comparison (Sharpe and Siemiatycki, 2002), but also came up with the same conclusion.

There are several possible explanations for this inconsistency. Recall bias, as the nature of case-control study design, could result in misclassification between drinkers and non-drinkers, or in mis-stratification into different levels of coffee consumption. Some studies just classified level of consumption as ever drink and never drink coffee. In addition, cup size was not considered when assessing the habit of coffee drinking. This could lead to misclassification of level of coffee consumption since drinkers could use different cup size. While prostate cancer is characterised by a long latent period, cumulative exposure to coffee consumption was assessed by only one out of thirteen reviewed studies. It is less likely that recent coffee drinking, within months to one year, would lead to development of prostate cancer to be clinically diagnosable. There is evidence showing that antioxidant capacity of coffee could be altered by method of production and brewing (Ludwig et al., 2012). However, the type of coffee consumed was not specified in the reviewed studies. Finally, self-completed questionnaire is another reason. Although consisting of a large sample size, the Canadian survey (Villeneuve et al., 1999) was not by face-to-face interview, but conducted via email. This method might incur misunderstanding of the questions together with inaccurate estimation of coffee intake, therefore could lead to recall bias and error in the results.

Table 7 Evidence of coffee consumption from case-control studies

Reference	Study Design [Cases/controls]	Country	Coffee consumption assessment	Coffee Intake	Adjusted Odds Ratio (95% Confidence Interval)
a. (Wilson et al., 2013)	PCC [1499/1112]	Sweden	Self-admistered FFQ: cups per day or week; cups size not specified	**High-grade prostate cancer** < 1 cup/day 1 - 2 cups per day 2 - 4 cups per day 4 - 5 cups per day > 5 cups per day	 1.00 0.54 (0.29, 1.01) 0.59 (0.36, 1.95) 0.61 (0.36 ,1.03) 0.50 (0.26, 0.98)
b. (Geybels et al., 2013b)	PCC [892/863]	USA	Interview; nine categories: never, < 1cup/ month to ≥ 6 cups per day	**Total prostate cancer** ≤ 1 cup/week 2 - 6 cups/week 1cup/day 2 - 3 cups per day ≥ 4 cups per day	 1.00 1.22 (0.88, 1.69) 1.13 (0.84, 1.51) 1.16 (0.90, 1.50) 1.16 (0.82, 1.63)
c. (Arab et al., 2012)	PCC [1,049 African-American cases, 1,083 Caucasian-American cases]	USA	Interview; cups per day	> 0 - 1 cup/day vs. none > 1 - 2 cups per day vs. none > 2 - 4 cups per day vs. none > 4 cups per day vs. none	0.86 (0.59, 1.24) 1.13 (0.95, 1.36) 0.85 (0.60, 1.19) 0.92 (0.61, 1.39)
d. (Ganesh et al., 2011)	HCC [123/167]	India	Interview; yes or no	Drinkers vs. non-drinkers	1.3 (0.60, 2.70)
e. (Gallus et al., 2007)	HCC [219/431]	Italy	Interview	Third vs. first tertile of coffee consumption	1.8 (1.00, 3.40), Gleason < 7 3.4 (1.50, 7.70), Gleason ≥ 7
f. (Chen et al., 2005)	HCC [237/481]	Taiwan	Interview; yes, no or unkown	Drinkers vs. non-drinkers	1.88 (1.07, 3.30)
g. (Sonoda et al., 2004)	HCC [140/140]	Japan	Interview; cups per day	≥ 3 cups per day vs. none	0.92 (0.40, 2.11)
h. (Sharpe and Siemiatycki, 2002)	PCC [399/476 population controls, 621 cancer controls]	Canada	Interview; drinks/day; year of drinking	> 39 years of daily drinking vs. never weekly ≥ 5 times/day vs. never weekly > 119 drink-years vs. never weekly	1.2 (0.70, 2.10) 0.9 (0.50, 1.70) 1.1 (0.60, 2.00)
i. (Villeneuve et al., 1999	PCC [1,623/ 1,623]	Canada	Self-completed questionnaire	≥ 4 cups per day vs. none	1.1 (0.80, 1.50)
j. (Hsieh et al., 1999)	HCC [320/246]	Greece	Interview; cups per day	cups per day	p for trend = 0.79
k. (Jain et al., 1998)	PCC [617/637]	Canada		> 500 g/day vs. none	0.97 (0.65, 1.44)
l. (Gronberg et al., 1996)	PCC [406/1,218]	Sweden	Self-completed questionnaire; cups per day	1 - 2 cups per day vs. none 3 - 5 cups per day vs. none 6 - 9 cups per day vs. none	1.77 (0.65, 5.09) 1.99 (0.78, 5.46) 1.91 (0.73, 5.30)
m. (Slattery and West, 1993)	PCC [362/685]	USA	Interview; cups/ week	> 20 cups/week vs. none Caffeine > 250 mg/day vs. ≤ 50 mg/day	1.09 (0.75, 1.60) for subjects ≤ 67 years 0.88 (0.58, 1.34) for subjects > 67 years 1.17 (0.81, 1.69) for subjects ≤ 67 years 0.85 (0.56, 1.28) for subjects > 67 years

PCC: population-based case-control; HCC: hospital-based case-control; USA: the United States of America; FFQ: food frequency questionnaire; vs.: versus

Evidence of coffee consumption from cohort studies

Table 8 presents main findings of 14 cohort studies from the USA (6), Japan (3), Sweden (2), Norway (1), United Kingdom (1) and Canada (1). All of them were prospective cohort studies, except one retrospective study conducted in Canada (Ellison, 2000). Overall, half of the reviewed studies reported inverse association between coffee consumption and prostate cancer risk (Table 8 (a) - (e), (g) and (h)), whereas the other half did not find any association (Table 8 (f) and (i) - (n)).

The earliest study was conducted in the USA by Hsing et al. (1990). This cohort study consisted of 17,633 participants who had been followed up for 20 years. During the follow up, 149 cases were diagnosed with incident prostate cancer. At baseline, participants were asked to tell the number of cups of coffee they drank a day. There was no significant difference in prostate cancer risk between those who drank five or more cups of coffee a day and those who drank less than 3 cups of coffee day (RR 0.8; 95% CI 0.6, 1.2). Similarly, three other studies conducted in North America found little association between prostate cancer risk and coffee drinking. Lemarchand et al. (1994) and Ellison (2000) found that coffee intake seems increase prostate cancer risk, while Bosire et al. (2013) found a borderline inverse association although it was not significant. A modest reduced risk was seen in total, advanced and fatal prostate cancer. Three other studies undertaken before 2011 in Japan (Allen et al., 2004, Kikuchi et al., 2006) and Sweden (Nilsson et al., 2010) also provided no significant association between coffee intake and prostate cancer risk. It was the first time, brewing method had been considered when assessing health effect of coffee consumption on prostate cancer risk. However, Nilsson et al. (2010) did not find any association for both filtered and boiled coffee.

In contrast to cohort studies published before 2010, most cohort studies published within the last 5 years found protective effect of coffee intake against prostate cancer. After 20 years follow up of nearly 48,000 men, Wilson et al. (2011)reported that drinking 6 or more cups of coffee a day can reduce the risk of prostate cancer by 12%. However this effect seemed to be more remarkable for lethal prostate cancer than other prostate cancer; RR 0.82 (95% CI: 0.68, 0.98). The authors also reported that this effect was seen in both decaffeinated and caffeinated coffee. Although this

study had some potential biases and limitations related to methods of brewing and measurement of coffee consumption level, it suggested that coffee drinking could be a potential protective factor for prostate cancer. Their finding was substantiated by six subsequent studies. Shafique et al. (2012) reported a similar inverse association between coffee intake and prostate cancer risk. Instead of drinking 6 or more cups of coffee, these authors showed that three or more cups of coffee a day could be enough to reduce 55% risk of high-grade prostate cancer. However, this effect was not statistically significant for overall risk of prostate cancer; RR 0.75 (95% CI: 0.5, 1.11). Using a standard cup size to assess the level of coffee intake, Discacciati et al. (2013) found that consumption of six or more cups of coffee a day could reduce the risk of localised prostate cancer by 19%. This inverse association was stronger among overweight and obese men. The authors also demonstrated that each cup per day increase could also reduce the risk by 3%. The inverse relation between coffee consumption and prostate cancer risk appeared to be more prominent in the study conducted by Geybels et al. (2013a). Specifically, intake of 1 cup of coffee per day could reduce the overall prostate cancer risk. However, the effect was most prominent for those who drank four or more cups a day. Slightly different from previous studies, Li et al. (2013) reported conflicting results that drinking 1 - 2 cups of coffee a day were significantly protective (RR 0.70; 95% CI 0.50, 0.98) while drinking three or more cups a day were not (RR 0.68; 95% CI 0.42, 1.10). The two most recent studies (Table 8 (a) and (b)) provided highly consistent results. Both of them showed that at least one cup of coffee a day could be protective against prostate cancer. Russnes et al. (2014) showed that this protective effect not only for overall prostate cancer but also for advanced, lethal and high-grade prostate cancer. However, these authors did not considered the type of coffee. Tverdal (2015), in contrast, assessed the health effect of different coffee type including filtered, boiled, instant and decaffeinated coffee, and found that only boiled coffee expressed protective effects on the prostate cancer risk.

Table 8 Cohort Studies of Coffee and prostate Cancer

Reference	Study Design [Cohort Size; Cases; Follow-up]	Location	Coffee consumption assessment	Coffee Intake	Results: Relative Risk (95% CI)
a. (Tverdal, 2015)	Prospective [224,234; 5740 cases; 15 years]	Norway	Self-reported information at baseline; cups per day; type of coffee (boiled, filtered, instant and	Boiled coffee None < 1 - 4 cups per day 5 - 8 cups per day	 1.00 0.84 (0.73, 0.96) 0.80 (0.70, 0.92) 0.66 (0.55, 0.80)
b. (Russnes et al., 2014)	Prospective [47,896; 5656 cases; 22 years]	USA	Interview at baseline: cups per day	None < cup/day 1 - 3 cups per day 4 - 5 cups per day > 5 cups per day	1.00 0.79 (0.62, 0.99) 0.76 (0.61, 0.95) 0.75 (0.57, 0.98) 0.46 (0.28, 0.76)
c. (Li et al., 2013)	Prospective [18850; 318 cases; 11 years]	Japan	Interview at baseline: standard cups per day	Never Occasionally 1-2 cups per day ≥ 3 cups per day	1.00 0.81 (0.60, 1.08) 0.70 (0.50, 0.98) 0.68 (0.42, 1.10)
d. (Geybels et al., 2013a)	Prospective [630; 140 cases; 6.4 years]	USA	Interview at baseline: nine categories (never or < 1 cup/month to ≥ 6 cups per day)	≤ 1 cup/week 2-6 cups/week 1 cup/day 2-3 cups per day ≥ 4 cups per day	1.00 0.89 (0.51, 1.57) 0.44 (0.25, 0.77) 0.72 (0.46, 1.11) 0.41 (0.20, 0.81) p-trend = 0.01
e. (Discacciati et al., 2013)	Prospective [44613; 4116 cases; 13 years]	Sweden	Interview: standard cups per day	< 1 cup/day 1-3 cups per day 4-5 cups per day ≥ 6 cups per day Every one cup/day increase	1.00 1.13 (0.93, 1.37) 1.00 (0.86, 1.16) 0.93 (0.83, 1.03) 0.81 (0.69, 0.96) 0.97 (0.95, 0.99) p-trend = 0.005
f. (Bosire et al., 2013)	Prospective [288,391; 23,335 cases; 11 years]	USA	Interview: cups per day	None < 1 cup/day 1 cup/day 2-3 cups per day 4-5 cups per day ≥ 6 cups per day	1.00 0.89 (0.68, 1.16) 0.81 (0.62, 1.06) 0.87 (0.69, 1.11) 0.77 (0.58, 1.03) 0.80 (0.53, 1.18)
g. (Shafique et al., 2012)	Prospective [6017, 318, 1970 – 2007]	United Kingdom	Self-completed questionnaire	≥ 3 cups per day vs. none	0.75 (0.50, 1.11) overall 0.45 (0.23, 0.90) high-grade
h. (Wilson et al., 2011)	Prospective [47,911, 5035, 1986 – 2006]	USA	Interview at baseline, and repeated every four years during follow up	None < 1 cup/day 1 - 3 cups per day 4 - 5cups per day ≥ 6 cups per day	1.00 0.94 (0.85, 1.05) 0.94 (0.86, 1.04) 0.93 (0.83, 1.04) 0.82 (0.68, 0.98)
i. (Nilsson et al., 2010)	Prospective [32,425; 653 cases; 15 years]	Sweden	Interview: nine alternatives: never, times per year, month, week or day	< 1 time/day 1-3 times/day ≥ 4 times/day	1.00 0.92 (0.70, 1.21) 1.03 (0.77, 1.38)
j. (Kikuchi et al., 2006)	Prospective [19,561, 110 cases; 7 years]	Japan	Interview: cups per day	≥ 1 cup/day vs. none	0.67 (0.38, 1.19)
k. (Allen et al., 2004)	Prospective [18,115; 196 cases; 34 years]	Japan	Interview	Almost daily vs. < twice/week	1.02 (0.71, 1.46)
l. (Ellison, 2000)	Retrospective [3,400, 145, 1970 – 1993]	Canada		> 250 ml/day vs. none	1.4 (0.84–2.32)
m. (Lemarchand et al., 1994)	Prospective [20,316, 198, 1975 – 1989]	USA (Hawaii)		> 2.5 cups per day vs. none	1.1 (0.7–1.7)
n. (Hsing et al., 1990)	Prospective [17,633, 149, 1966 – 1986]	USA		≥ 5 cups per day vs. < 3 cups per	1.0 (0.6–1.6)

USA: the United States of America; CI: confident interval; vs.: versus; PCa: prostate cancer

Evidence of coffee consumption from reviews and meta-analysis

Table 9 summarises the most highlighted results from recent review articles and meta-analysis studies. A total of nine publications were reviewed. Overall, more recent pooled data showed protective effect of coffee consumption while previous ones showed inconsistent evidence.

The review of 4 cohort studies published before 2004 by Dagnelie et al. (2004) showed an inconsistent evidence for the protective effect of coffee. One reviewed study even showed a positive association between coffee intake and prostate cancer risk. Lee et al. (2009) reviewed 4 cohort studies and 7 case-control studies available from 1983 to 2005, and concluded that no established protective effect of coffee consumption on prostate cancer. In a subsequent meta-analysis, pooled data from 8 case-control studies suggested a slightly positive association between coffee drinking and prostate cancer, whereas pooled data from 4 cohort studies produced no association. The evidence, therefore, remained inconclusive.

Interestingly, all meta-analysis published from 2011 onward consistently showed protective effect of coffee consumption against prostate cancer; Table 9 (a) - (i). When comparing highest vs. lowest level of coffee intake, pooled data from 5 cohort studies showed an inverse association between coffee and prostate cancer risk (RR 0.79; 95% CI 0.61, 0.98) (Yu et al., 2011). Another meta-analysis of 12 case-control studies and 12 cohort studies has led to a conclusion that prostate cancer risk was borderline inversely associated with coffee (Zhong et al., 2014). The authors also found that every two cups per day increase could attributed to 7% decrease in prostate cancer risk. Three other meta-analysis published in 2014 (Cao et al., 2014, Discacciati et al., 2014, Lu et al., 2014) consistently showed an inverse association between coffee consumption and prostate cancer risk. Such association was observed mostly in the USA, Europe and Japan. The risks of both overall prostate cancer and individual stages were inversely associated with coffee intake. In the latest meta-analysis, pooled data from 13 cohort studies concluded that coffee intake was inversely associated with total and non-advanced prostate cancer. However, this effect was seen only after 2009, and in Europe but not in North America and Asia.

In summary, there has been increasing evidence that supports for the protective effect of coffee drinking against prostate cancer risk. Despite some conflicting findings, evidence from meta-analyses suggests that coffee consumption could be a potential protective factor for prostate cancer. However, generalisation of this evidence requires further higher quality studies, such as clinical trials, that have been identified from the literature.

Table 9 Evidence of coffee consumption from meta-analysis

Reference	Studies Reviewed	Comparison	Relative Risk (95% CI) and conclusions
a. (Liu et al., 2015)	13 cohort studies	Highest vs. lowest coffee intake	• 0.90 (0.85, 0.95) overall • 0.83 (0.75, 0.92) Europe • 0.90 (0.84, 0.96) after 2009 • 0.89 (0.83, 0.96) non-advanced PCa • 0.97 (0.96, 0.99) every 2 cups per day increment in consumption • Coffee inversely associated with total and non-advanced PCa
b. (Cao et al., 2014)	10.cohort studies	Regular vs. seldom or never drinkers	• 0.88 (0.82, 0.95) • Coffee may decrease PCa risk
c. (Discacciati et al., 2014)	3 case-control studies 5 cohort studies	increment of 3 cups per day	• 0.97 (0.92, 1.03) for low-grade PCa • 0.97 (0.94, 0.99) for localised PCa • 0.89 (0.78, 1.00) for high-grade PCa • 0.95 (0.85, 1.06) for advanced PCa • 0.89 (0.82, 0.97) for fatal PCa
d. (Lu et al., 2014)	12 case-control studies 9 cohort studies	Total prostate cancer Highest vs. lowest coffee intake	• 0.91 (0.86, 0.97) overall • 0.89 (0.84, 0.95) cohort • 0.93 (0.87, 0.99) USA • 0.87 (0.78, 0.97) Europe • 0.91 (0.85, 0.97) high quality studies • ≥ 4 cups per day associated with total, fatal and high-grade PCa
e. (Zhong et al., 2014)	12 case-control studies 12 cohort studies	Ever vs. none Moderate vs. lowest level Highest vs. lowest level Increase in every 2 cups per day	• 0.92 (0.85, 0.99) • 0.92 (0.85, 1.00) • 0.83 (0.72, 0.96) • 7% reduced PCa risk • Coffee borderline associated with reduced PCa risk
f. (Yu et al., 2011)	Meta-analysis of 5 cohort studies	High vs. non/lowest level	• 0.79 (0.61, 0.98) • Coffee associated with reduced PCa risk
g. (Park et al., 2010)	8 case-control studies 4 cohort studies	Highest vs. lowest level	• 1.16 (1.01, 1.33) • Positive association from case-control studies • No association from cohort studies • Inconclusive evidence of harmful effect
h. (Lee et al., 2009)	7 case-control 4 cohort studies	N/A	• Coffee is a safe beverage • Coffee consumption not associated with PCa risk
i. (Dagnelie et al., 2004)	Review of 4 cohort studies	N/A	• Inconsistent evidence • Positive association from one study

N/A: not available; PCa: prostate cancer; vs.: versus; CI: confident interval

2.4.4.3 Shortcomings of reviewed studies

There has been growing evidence for the association between coffee consumption and decreased prostate cancer risk. Nevertheless, the evidence remains inconclusive, and therefore, should be interpreted with caution. There are several shortcomings that could explain the inconsistency in the findings.

In relation to case-control study designs, selection and recall biases are potentially problematic. Low statistical power due to small sample size is also a weakness for most reviewed case-controls studies. As an example, Ganesh et al. (2011) recruited only 123 prostate cancer cases and 167 control participants, subgroup analysis or multivariable models consisted of much smaller number of subjects, and thus resulted in less statistical power. Inconsistency and in-comprehensiveness in assessment of coffee consumption is another problem. Some studies just simply classified participants as drinkers or non-drinkers (Chen et al., 2005, Ganesh et al., 2011), while others classified by number of cups consumed per day or week. Cumulative consumption of coffee was seldom taken into account. Furthermore, while type and brewing method can influence antioxidant capacity of coffee, most case-controls studies ignore these aspects.

Regarding cohort studies, no standardised measurement for assessment of coffee intake was the main shortcoming. The estimation of quantity of coffee intake depends on cup size, but most studies relied on the number of cups consumed. Again, lack of consideration of brewing method and coffee type also poses problem for estimation of prostate cancer risk.

2.4.4.4 Conclusion

The relationship between coffee consumption and prostate cancer risk has attracted much attention during the past 25 years. There has been increasing number of studies that show protective effect of coffee intake against prostate cancer. However, the evidence for this possible link remains inconsistent. Supporting evidence comes mainly from cohort studies, while case-control studies show more conflicting results. Cohort studies, especially ones that were published from 2011 onwards, provide

more consistently supporting evidence for the protective effect of coffee. These findings are substantiated by six meta-analyses over the last five years. In order to confirm this evidence, further observational studies and shorter term randomised controlled trials are required.

2.5 Current situation of research on epidemiology of prostate cancer in Vietnam

2.5.1 Literature search

A systematic strategy was employed in the search for publications about current situation of prostate cancer in Vietnam. An identified reference would be included in the review if it discussed or investigated incidence, prevalence, secular trend, risk factors or prevention of prostate cancer in Vietnam. The initial search resulted in 220 publications. After initial screening and removal of duplicating records, 49 articles were listed to be related to prostate cancer in Vietnam. Further assessment identified 22 studies that explored clinical aspects of prostate cancer, and ten other articles that reported on prostate cancer risk factors and screening, but none of them had been conducted in Vietnam. Subsequent removal of these references left a shortlist of 17 studies that matched with the selection criteria. However, full text version was available for only 12 articles. Figure 6 summarises the process of searching and screening eligible references for the review.

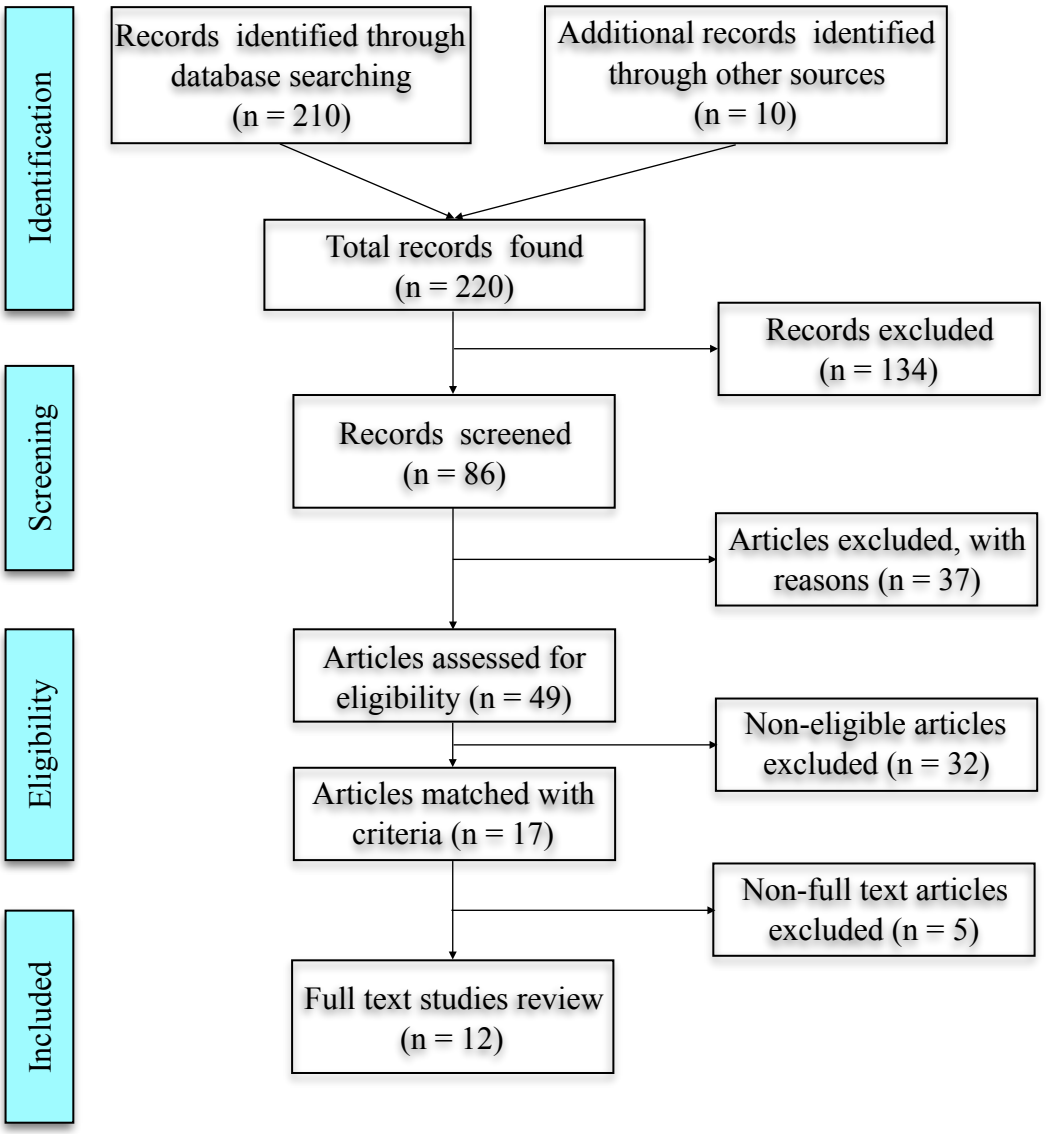

Figure 6 PRISMA flow diagram for systematic review of prostate cancer in Vietnam

2.5.2 Incidence and secular trend

Prostate cancer in Vietnam has been documented as a relatively low incidence disease. It was not until 1980s very few prostate cancer cases were diagnosed in Vietnam (Dao, 1984). Statistics from a cancer registry program in 1990 showed that the ASR of prostate cancer was 2.5 per 100,000 (Anh et al., 1993). This could be due to the poor condition of medical facility that limited the capacity of diagnosis. However, nearly two decades later, when the use of PSA test had become more

common and some advanced medical equipment has been introduced to Vietnam, the disease still remained at low prevalence. In 2010, only about 2.5% of screened men were diagnosed with the cancer at medium-grade of lesion (Gleason 7) (Vu Le et al., 2010). In this hospital-based screening program, participants mostly lived in the central urban of Ho Chi Minh City where the hospital located, and most of them had some suspicious symptoms. Therefore, the reported prevalence my not reflect the actual situation of the cancer in general population. According to report from a national project on cancer prevention, the ASR of prostate cancer was 4.7 per 100,000 men (Nguyen et al., 2010) compared to 62.0 per 100,000 men globally (Jemal et al., 2011). This rate was also much lower than that among South-East Asian countries, 15.2 per 100,000, but slightly higher than that in Middle Africa, 4.3 per 100,000 (Jemal et al., 2011).

The reported incidence of prostate cancer in Vietnam may not represent the whole country because most of the incident prostate cancer cases were observed in large cities where medical facilities are more advanced in comparison with rural areas. For instance, in 2008, the ASR for prostate cancer in Ho Chi Minh City and Hanoi City was 5.2 and 4.3 per 100,000, respectively, whereas the rate in Hai Phong, Thai Nguyen and Hue was 1.5, 1.2 and 0.9 per 100,000, respectively (Nguyen et al., 2010). This disparity might also be explained by the variations in lifestyle between urban and rural populations as well as the accessibility to diagnostic services in large cities.

Over the last decade, there has been a significant upward trend in ASR of prostate cancer. Indeed, it was one of four cancers that exhibited the highest increase in incidence rate between 2000 and 2010, with ASR doubled from 2.2 to 4.7 per 100,000. This upward trend was more rapid in Ho Chi Minh city than Hanoi, from 2.3 in 1996 to 5.2 in 2008 versus 2.5 in 1990 to 4.3 in 2008, respectively (Anh et al., 1993, Nguyen et al., 2010). Data from Binh Dan Hospital also showed that the number of annual admitted cases tripled from 117 cases in 1999 to 380 cases in 2009 (Vu Le et al., 2010). The underlying reasons for the rise in prostate cancer incidence among Vietnamese men remain unknown. Increasing awareness and knowledge of both patient and healthcare professionals, and improved diagnostic

techniques in recent years could partially explain this upward trend (Vu Le et al., 2010). Another plausible reason is the change in diet and lifestyle together with a high speed of urbanisation during the past decade (Vuong, 2005). Analyses of population-based cancer registry data found that the incidence rate among Vietnamese migrants in the USA was significantly higher than that of Vietnamese living in Hanoi over the period 1988 - 1992. In addition, differences in rates were similarly observed for other cancers, such as colon cancer and breast cancer, suggesting the influence of westernised lifestyle on cancer development for the Vietnamese population (Le et al., 2002).

2.5.3 Risk factors

Only one publication on protective factors of prostate cancer in Vietnam was found, which concerned an in vitro experiment demonstrating the inhibitory effect of garlic on the growth of prostate cancer cell line PC-3 (Nguyen, 2011). The results appeared to be consistent with other in vitro and epidemiological studies conducted in other countries. A case-control study has shown a reduced risk of prostate cancer among men who consumed garlic at least twice a week when compared to never consumers (Key et al., 1997). Another population-based study also reported similar observations (Hsing et al., 2002), while consumption of aqueous garlic extract lowered both total and free prostate-specific antigen among patients in a clinical trial (Yılmaz et al., 2003). Although garlic is a popular herb in Vietnam, no epidemiological study has been undertaken to ascertain its effect on the prostate cancer risk. Similarly, agent orange has been demonstrated to be a carcinogen associated with increased risk of prostate cancer (Chamie et al., 2008). However, information was lacking on its impact on prostate cancer in Vietnamese men, despite documents of heavy use of agent orange during the Vietnam war (Brodsky et al., 2009). The current evidence for agent orange came from studies on American and Australian veterans of the war (Ansbaugh et al., 2013, Frumkin, 2003). Besides agent orange exposure, pesticides that have been wildly and unsafely used in agriculture production, are also major environmental risk factors in Vietnam (Phung et al., 2013, Van Toan et al., 2013). Current evidence has indicated that pesticides are positively

associated with the risk of prostate cancer (Doolan et al., 2014). However, no publication about this issue has been found for Vietnamese men. A recent meta-analysis of pooled data from Asian countries showed an association between diabetes mellitus and increased risk of prostate cancer (Long et al., 2012). If this relation is confirmed among Vietnamese men, it will have important implication in early detection and prevention of the disease because diabetes has been increasingly prevalent in Vietnam (Nguyen et al., 2015).

Apart from the single reference (Nguyen, 2011), our review did not find any other study that investigated the role of lifestyle modifiable risk factors or dietary habits on the development of prostate cancer in Vietnam.

2.5.4 Conclusion

This review found little information on the epidemiology and risk factors for prostate cancer in Vietnam, with existing publications mainly concerned with clinical aspects. Despite the significant upward trend in the incidence rate of prostate cancer, lack of epidemiological evidence on risk and protective factors specifically for the Vietnamese population poses as a major barrier for the formulation of prevention strategies. It is recommended to undertake more research particularly population-based observational studies in order to understand the aetiology of prostate cancer in Vietnam.

Chapter 3: Methodology

3.1 Overview

This chapter presents the methodology of the research project. In brief, the study was conducted to address the objectives 2, 3 and 4, namely: 2) To describe the consumption pattern of tea and coffee among Vietnamese older men; 3) To evaluate the association between tea consumption and the risk of prostate cancer in Vietnam; 4) To evaluate the association between coffee consumption and risk of prostate cancer in Vietnam. The methods to address these objectives and the expected outcomes are summarised as follows:

Research question	Measurement	Method of analysis	Outcome
Pattern of tea and coffee consumption	Interview of participants for their habitual tea and coffee drinking	Descriptive analysis, results presented as mean (standard deviation) and counts (%).	- Prevalence - Frequency and amount consumed per day/week - Years of drinking - Trend in drinking habit
Association between tea consumption and prostate cancer risk Association between coffee consumption and prostate cancer risk	Interview of cases and controls for their past habitual tea drinking and exposure to potential confounders Interview of cases and controls for their past habitual coffee drinking and exposure to potential confounders	Logistic regression analysis, results presented as odds ratio (95% confident interval) Test for linear trend Subgroup and sensitivity analysis	- Odds for having prostate cancer, and associated 95% confident interval - p value for linear trend

Detail methods are presented in 6 subsequent sections. Section 3.2 gives rational for the adopting the case-control study design. Some strengths and weaknesses are also discussed in comparison to other common study designs regarding assessment of

association between dietary factors and chronic diseases. Section 3.3 describes the study location of the study. Section 3.4 defines participants of the study, and describes the estimation of sample size, and sampling method. This section also discusses the justification of the cut-off value of PSA used in this study for early screening of prostate cancer cases to minimise misclassification bias. Section 3.5 presents study instruments and procedure of data collection. Section 3.6 presents data management and statistical analysis. Finally, section 3.7 discusses some ethical considerations.

3.2 Study design

Three common study designs, including ecological, case-control and cohort study, can be used to assess association between dietary factors and chronic diseases (Freudenheim, 1999), but this research project employed a case-control study design. Basically, ecological study design uses data from the whole population to assess a correlation, whereas, case-control and cohort studies use data from individuals to assess an association between an exposure and a specific outcome. Case-control and cohort designs can better control for potential confounders, meanwhile the ecologic design cannot. Therefore, ecologic study design produces the less convincing evidence compared to the other two study designs. Case-control study relies on memory of participants about their past exposures to assess an association. Therefore, information on such exposure is prone to recall error or bias. Cohort study, on the other hand, follows up the participants for their future outcome based on their baseline exposures, and thus, can collect unbiased recall information (Colditz, 2010). Regarding the hierarchical level of evidence, cohort study design produces more convincing evidence than case-control and ecological study designs. However, this design is expensive, and requires a large number of participants, with a long follow-up period. In contrast, case-control study design is cheaper, and requires smaller number of participants since it focuses on those who already have disease of interest. Therefore, it is appropriate for low prevalent diseases. Although case-control study design is subjected to recall errors or bias, it was considered the most appropriate for this research project since prostate cancer is a low prevalent disease

in Vietnam, and the time frame for carrying out the study is limited. In addition, bias or errors in a case-control study can be minimised through careful design and meticulous implementation. Indeed, this design had been employed by a large number of studies to investigate the role of dietary factors on the development of chronic diseases (Freudenheim, 1999).

To minimise potential recall bias and errors in this study, the following measures were used:

- Apply strict selection criteria, with particular emphasis on prostate cancer patients who were diagnosed within four weeks prior to their interview, and who had not been on a long term diet modification. Indeed, almost all cases were interviewed shortly after availability of a positive biopsy result. Control subjects who were on a long term modified diet were also excluded from the study.
- Prostate cancer cases were recruited from all urology services at the two selected hospitals, and controls were also recruited from 22 wards of a district located in the same catchment area as the cases to minimise recruitment bias.
- Unique structured questionnaire was used for both cases and controls. A picture booklet was used to help participants in estimation of portion size.
- Interviewers were well trained and were blinded with the aim and objective of the study. In addition, interview was carried out shortly after appointment to minimise any potential information bias. When available, next of kin of participants were encouraged to help participant to recall their past dietary habits.
- Multivariate statistical analyses were used to control for the effects of potential confounders.

3.3 Location of the study

Vietnam is a lower middle income country, located in the Southeast Asia. It covers an area of 330,967 square kilometres, and has a population of 90.73 million people. The country lies along a coastal line, with the length of nearly 2,000 kilometres. This case-control study was conducted in Ho Chi Minh City, located in Southern Vietnam

(Figure 7). The City covers an area of 2,095.6 square kilometres, and has a population of 7.98 million people (General Statistics Office of Vietnam, 2014). Ho Chi Minh City is the second largest, but the most dynamic city in Vietnam, in terms of socioeconomic development (Burghardt and Storch, 2013). Compared to other cities in Vietnam, prostate cancer in Ho Chi Minh city is the highest incident, with ASR of 5.2 per 100,000 (Nguyen et al., 2010). Binh Dan hospital and Medic Medical Center are the two medical facilities for cases recruitment. Both of these medical institutions are affiliated with Pham Ngoc Thach Medical University.

Figure 7 Location of the study
(Department of Survey and Mapping Vietnam, 2008)

3.4 Participants, sample size calculation and sampling method

3.4.1 Selection criteria for participants

Selection of cases

Inclusion criteria:

- Newly diagnosed prostate cancer patients (diagnosis was made within 4 weeks prior to interview, with date of diagnosis written in patient's medical record)
- Confirmation of diagnosis by positive biopsy result
- Stable health condition (suitable for a 40 minute face-to-face interview)

Exclusion criteria:

- Patients who were too weak, or had memory problems which prohibited him to recall past events
- Patients who were in long term modification of diet
- Patients who have other malignant conditions
- Patients who were non-Vietnamese residents (e.g. tourists)

Selection of controls

Inclusion criteria:

- Healthy community dwelling men or male-patients who were hospitalised not for prostate cancer
- PSA level < 4 ng/ml
- At the same age group as cases (± 3 years old)

Exclusion criteria:

- In severe health conditions, and/or had memory problems
- Person who were diagnosed with any malignant disease
- Person who were non-Vietnamese residents

Justification of PSA cut-off value

A fixed threshold of serum PSA level for prostate cancer screening has been a controversial issue. This cut-off value can change with age. Among men aged 45 to 59 years, the cut-off value is 2.5 ng/ml. Among men aged 60 to 74 years, and over 75 years, the cut-off values are 3.0 ng/ml and 4.0 ng/ml, respectively. In Vietnamese

men, the PSA blood level less than 4 ng/ml is considered normal. Without suggestive symptoms, such as abnormality on digital rectal examination, a serum level of PSA from 4 - 10 ng/ml usually leads to a watchful waiting indication. Biopsy is often administered to those who have PSA greater than 10 ng/ml (Tran and Do, 2008). Among prostate cancer patients who require a surgery, blood level of PSA is expected to be 81.24 ± 71.96 ng/ml (Do, 2003). In some rare cases, prostate cancer has been reported with a very low level of 0.6 ng/ml (Nguyen et al., 2008). As aforementioned, only about 40% of men with PSA from 4 - 10 ng/ml are diagnosed with prostate cancer (Fang et al., 2015), and a positive biopsy is still the gold standard for confirmation of prostate cancer in Vietnam (Tran and Do, 2008).

Although about 3.2% of men with PSA less than 4 ng/ml can be diagnosed with prostate cancer (Randazzo et al., 2015), prevalence is small. In Vietnam, where prostate cancer is very low incident, the possibility of prostate cancer found in men with PSA less than 4 ng/ml would be much lower. To maximise the chance of recruitment of controls, as well as to minimise the possibility of misclassification of case recruitment, serum PSA level was set at 4 ng/ml in this study.

3.4.2 Sample size

Assessment of the association between tea consumption and the risk of prostate cancer was one of the main objectives of this study. Assuming that at least 75% of Vietnamese men were tea drinkers, and this prevalence is similar for coffee drinkers, the required sample size was determined to attain 90% power and 5% level of significance. For a 1:2 case-control ratio, a sample of at least 175 cases and 350 controls was required to achieve an odds ratio of 0.5 for tea drinkers versus non-drinkers in prostate cancer risk. The sample size was calculated using the formula below:

$$\mathbf{N} = \frac{(\mathbf{1}+r)^2 \mathbf{C}}{\mathbf{r}(lnOR)^2\, p(\mathbf{1}-p)}$$

Where: r (ratios of controls to cases) = 2

C (for $\alpha = 0.05$ and $\beta = 0.10$) = $\left(\frac{z_{\frac{\alpha}{2}} + z_b}{2}\right)^2$ =10.51

P (prevalence of tea or coffee drinkers) = 0.75

OR (expected) = 0.5

Application of the formula above, the total number of participants required for this study was 525, i.e. 175 cases and 350 controls:

$$N = \frac{(1+2)^2 10.51}{2(\ln 2)^2\ 0.9 * 0.1}$$

3.4.3 Sampling method

A convenient sampling procedure was applied as prostate cancer was a low prevalent disease in Vietnam. All eligible cases from the participating medical facilities were consecutively approached and invited for participation in the study. Due to possibility of refusal and withdrawal, 275 eligible prostate cancer patients from the two selected hospitals were approached and invited to participate. Most of the cases were approached before undergoing a biopsy test.

Controls were mainly recruited from the community in the same catchment areas as the cases. Eligible men from 22 wards of Binh Thanh District, Ho Chi Minh City, were identified based on health check lists available at ward health stations. Eligible men were then invited to participate in the study via mail. To supplement the recruitment of community-based controls, a number of hospital-based controls were also recruited among patients who attended hospital for non-malignant conditions. Most of the hospital-based controls were from urology services. Due to strict selection criteria, almost all eligible men were invited. Participants were tested for total PSA, then face-to-face interviewed.

3.5 Questionnaire and exposure measurements

3.5.1 Overview of questionnaire

A structured questionnaire was used in the face-to-face interview of participants. The questionnaire consisted of 4 main sections, namely demographic and life-style

characteristics, medical and family history, clinical information, and habitual consumption of tea, coffee and other dietary habits (Appendix 5). This questionnaire was developed in reference to and adopted from previous assessment tools including:

- Manual of the World Health Organisation for "STEPwise approach to chronic disease risk factor surveillance" (World Health Organisation, 2012).
- A food frequency questionnaire that had been validated with adolescents in Ho Chi Minh City, Vietnam (Hong et al., 2010).
- A food frequency questionnaire that had been validated with older adults in the North of Vietnam (Tran et al., 2013).
- An international prostatic symptom score table that had widely been used at urology services in Vietnam (Binh Dan Hospital, 2012).

The first section covers information on residential address, age, marital status, age of marriage, number of children, education level, physical activity, smoking history and alcohol consumption. Questions on physical activity, smoking and drinking habits were adapted from the stepwise instrument developed by the World Health Organisation (2012). The second section included questions on history of prostatic conditions, infections and surgical operation of urinary tract, chronic diseases (e.g. diabetes) and prostate cancer in first-degree relatives. The third section collected information on symptoms of lower urinary tract related to prostate conditions (e.g. frequency or intermittency of urination), height, weight, measurement of waist and hip circumference, arterial blood pressure, serum PSA, biopsy result and diagnosis. The final section included questions on habitual consumption of tea, coffee and other foods and beverages.

3.5.2 Measurement of habitual tea and coffee consumption

Four types of tea including dried green tea, fresh green tea leaves, Oolong tea and black tea were included in the questionnaire. For each type of tea, participants were asked for their frequency (times per day, week, month or year), quantity (number of standardised cups) and total years of tea drinking. Participants were also asked

whether they had changed their habit of tea drinking within three years prior to the interview. If a change reported, participants were requested to tell the reasons of change. Similarly, participants were asked about their habitual drinking of black coffee, instant coffee and milk coffee (black coffee added with sweetened condensed milk). The same questions asked for tea were applied for coffee consumption. To assist participants in estimation of amount of consumption, a picture of standardised cups was presented. These questions were designed based on the approach of food frequency questionnaire that had widely been used for investigation of the relationship between dietary factors and the risk of cancers (Hjartaker et al., 2007). A number of previous studies have employed this approach to assess the association between tea, coffee consumption and the risk of prostate cancer (Table 3 and 4). Below are questions used for measurement of habitual tea and coffee drinking in this study:

- *Now, I would like to ask you about your habit of drinking tea within the last three years, please recall your habit within the last three years. For each type of tea bellow, how often do you drink (times per day, week, month or year), and how many cups do you drink each time? Please look at the picture of these cups.*
- *In your life, can you please estimate the total years for which you have drank tea?*

	tea type	Frequency (**Y**ear/**M**onth/**W**eek/**D**ay)	Cup size	number of cups	Total years
1	Dried green tea	_____times/[ ]Y [ ]M [ ]W [ ]D	Cup-100ml		
2	Fresh green tea	_____times/[ ]Y [ ]M [ ]W [ ]D	Cup-200ml		
3	Oolong tea	_____times/[ ]Y [ ]M [ ]W [ ]D	Cup-100ml		
4	Black tea	_____times/[ ]Y [ ]M [ ]W [ ]D	Cup-100ml		
5	Within the last three year, have you changed your habit of drinking tea?			0 [ ] No 1 [ ] Yes	
6	If yes, how did you change, and please give the reasons for this change? …… ……				

- *Now, I would like to ask you about your habit of drinking coffee, with the same questions for tea, within the last three years, please recall your habit within the last three years. For each type of coffee bellow, how often do you drink (times per day, week, month or year), and how many cups do you drink each time? Please look at the picture of these cups.*
- *In your life, can you please estimate the total years for which you have drank coffee?*

	Coffee type	Frequency (**Y**ear/**M**onth/**W**eek/**D**ay)	Cup size	number of cups	Total years
1	Black coffee	_____times/[ ]Y [ ]M [ ]W [ ]D	Cup-150ml		
2	Instant coffee	_____times/[ ]Y [ ]M [ ]W [ ]D	sachet-16gr		
3	Milk coffee	_____times/[ ]Y [ ]M [ ]W [ ]D	Cup-150ml		

4	Within the last three year, have you changed your habit of drinking coffee?	0 [ ] No 1 [ ] Yes
5	If yes, how did you change, and please give the reasons for this change? …… ……	

3.5.3 Dietary habit of other food and beverage items

In assessment of dietary habit in relation to chronic diseases, food frequency questionnaire (FFQ) is a reliable and commonly used method (Pereira and Koifman, 1999). Questionnaires for assessment of dietary habits in this study were adapted from a previous version of FFQ developed and validated by a group of Vietnamese nutritionists (Hong et al., 2010). Apart from tea, coffee and alcoholic beverages, the FFQ used in this study consisted of 79 other food and beverage items, and 8 dietary supplements such as vitamins and minerals (Appendix 5). A version of this FFQ has also been validated for its reliability among Vietnamese old men. The habitual consumption of tea and coffee reported by the participants appeared to be reliable (intra-class correlation coefficient for tea and coffee consumption was 0.52 and 0.73, respectively (Tran et al., 2013). Food and beverage items covered in this instrument were the most commonly consumed in Vietnam. For each these food/beverage items, participants were asked for frequency (times per day, week, month or year), estimated portion size, and the number of portions consumed each time. The recall period for dietary habits was set within three years before the interview of participants. A picture booklet was used to help participants estimate the amount of food intake for each food item.

In summary, main information collected by the questionnaire include:

- Demographic and lifestyle characteristics: age, residential address, marital status, age of marriage, number of children, education level, lifetime physical activity, smoking history and habit of alcohol consumption.
- Medical and family history: prostatic conditions, infections and surgical operation of urinary tract, chronic diseases and prostate cancer first degree relatives.

- History of cancer, diabetes, cardiovascular diseases, sexual transmitted diseases, family's history of cancer.
- Clinical information: symptoms of lower urinary tract related to prostate conditions (e.g. frequency or intermittency of urination), height, weight, waist and hip circumferences, arterial blood pressure, serum PSA, biopsy result and diagnosis.
- Dietary habit: tea, coffee and other beverages (e.g. canned beverages or fruit juice), fruits, vegetables, soy foods, meats, seafoods, cereals, egg, dairy products, and supplementary dietary supplements.

3.5.4 Interview procedure

For prostate cancer participants and hospital-based controls, an appointment for interview was arranged with the assistance from nursing staff to avoid interference with treatment of patients. All hospital-based participants were interviewed during their hospitalisation. Before interview, participants were briefed about the study purpose and interview procedure. They were also informed that they could withdraw at any time during the interview process with no negative consequences to their treatment at hospital. Informed consent form with signature of participants was obtained from all interviewed subjects. Interview was conducted face-to-face by research assistants who were also medical staff of the selected hospitals. Each interview took about 40 minutes on average. During the interview, next-of-kin of the subjects were invited to help participants to recall their past dietary habit, or to provide additional information.

For community-based controls, eligible men were invited to visit the Centre of Preventive Medicine of Binh Thanh District, Ho Chi Minh City for PSA testing and interview. At the Centre, eligibility of participants was reconfirmed before briefing about the study. Only men who had signed the informed consent form were interviewed and tested for PSA. The interview was conducted by well-trained nursing staff, in a private room. Blood specimens were taken at the Centre, by

experienced nursing staff, and then sent to Medic Medical Center laboratory for PSA testing.

All research assistants were thoroughly trained by the principle investigator following a standardised protocol that was approved by the Human Research Ethics Committee of Curtin University (approval number: HR 109/2012, see Appendix 1). Interview and access to medical records of patients were permitted by the participating medical facilities.

3.6 Data management and statistical analysis

Data from the completed questionnaires were coded and first entered into an Ms Access database. The dataset was then transferred to Stata version 14.0 for cleaning and statistical analysis. All variables were explored to identify illogical information, coding and data entry errors. Review of original questionnaires and appropriate correction were then applied to any out-of-range values.

After data cleaning, univariate descriptive statistics were first applied to examine the characteristics of the sample. The distributions of clinical and demographic characteristics, lifestyle (physical activity, cigarette smoking and alcohol consumption), diet regime, total energy intake, tea and coffee consumption were described. The results were presented as mean and SD for normally distributed variables, as median and percentile values (LQ, UQ) for non-normally distributed variables, and as counts and percentage for categorical variables. Comparisons of sample characteristics between cases and controls were made, using independent t test or Wilcoxon rank-sum test for continuous variables, and chi-square test for categorical variables.

Dietary exposures, including tea, coffee and alcohol, were measured in terms of amount consumed per day. Firstly, frequency of yearly, monthly and weekly consumption of individual food or beverage items were converted into daily frequency of consumption by dividing by 365, 30 and 7, respectively. Then, daily amount of consumption for each food or beverage item was estimated using the following:

$Q = F \times P \times S$

in which:

- Q: amount of food or beverage consumed per day (in gram)
- F: frequency of consumption for each food or beverage item
- P: number of portion consumed each time
- S: portion size of each food or beverage item

Measurement of several main exposures were further defined below:

- Tea consumption measured in terms of amount of tea (mls per day), frequency (cups per day), years of tea-drinking and cumulative tea drinking (number of cup-years). The number of cup-years of tea drinking was calculated by the product of tea cups per day and years of drinking tea.
- Coffee consumption was measured in terms of frequency (cups per week), years of coffee drinking and cumulative coffee drinking (number of cup-years). Weekly coffee consumption was estimated by dividing yearly and monthly consumption by 52 and 4.5, respectively, and by multiplying daily consumption by 7. Number of cup-years of coffee drinking was calculated by the product of coffee cups consumed per week and the total years of drinking coffee.
- Alcohol consumption was measured in terms of gram ethanol consumed per day, which was the sum of all types of alcohol consumed per day (in gram).
- Total energy intake was measured in terms of Kcal per day, which was the sum of total energy of individual food and beverage items consumed per day (in Kcal). The energy intake of each food or beverage item was estimated using Food composition table for Vietnamese population (National Institute of Nutrition, 2007).
- Cigarette smoking was measured in terms of prevalence and number of pack-years which was defined as number of pack (20 cigarettes) used per day multiply by total years of smoking.

The association between habitual tea and coffee drinking and the risk of prostate cancer was assessed using logistic regression. Continuous variables for habitual tea and coffee drinking (e.g. cups per day or years of drinking) were tested regarding prostate cancer risk. These variables were then categorised into tertiles or quartiles depending on distribution of controls to facilitate statistical analysis. Lowest level of tea or coffee consumption (or non-drinkers) was used as reference category in logistic regression analyses. Both crude and adjusted odds ratios were computed in separate multivariate logistic regression models to assess the risk of prostate cancer. In assessment of habitual tea and coffee drinking regarding prostate cancer risk, odds ratios were adjusted for age (year), cigarette smoking (pack-years), alcohol consumption (gram/day), body mass index (kg/m^2), marital status (never married/ separated, married), total energy intake (Kcal/day), education level (primary, high school, tertiary), family history of prostate cancer, physical activity (never/past active, regularly active) and age at marriage (years). The results reported both crude and adjusted odds ratios (OR) and associated 95% confidence intervals (CI). Dose-response relationship was also assessed using test for linear trend, where the exposure was treated as a continuous variable in the test for linear trend.

Subgroup analysis was applied to assess the variation in association of tea consumption with prostate cancer risk at different grades (i.e. high and low-medium-grades based on Gleason score). Sensitivity of association between tea consumption and prostate cancer risk was also assessed by comparing cases to community-based controls for the odds of having prostate cancer, i.e. removing hospital controls.

3.7 Ethical considerations

The research project protocol was approved by the Human Research Ethics Committee of Curtin University, Australia. The reference number of the approval letter is HR 109/2012 (Appendix 1). Data collection was also approved by the selected hospitals/medical facility in Vietnam (Appendix 2). Some ethical considerations include consent, confidentiality and potential risk and benefits for the study participants.

3.7.1 Consent

Subjects were informed about the aims and assured confidentiality of their participation in the study. An information sheet together with a consent form was provided to each subject (Appendix 3 and 4). Written agreement to participate was obtained from each consented participant. The participation of the subjects was fully voluntary, and they were able to terminate the interview or withdraw from the study at any time without any negative consequences. An appointment for the hospital-based interview was made after obtaining formal consent from each subject and/or their next-of-kin. For community-based controls, they were interviewed at the Center of Preventive Medicine after agreement.

3.7.2 Confidentiality

The confidentiality of all information obtained was maintained throughout the study and data analysis. The completed questionnaires and personal data gathered were identified by an identity number code known only to the investigators. Aggregated data rather than individual data were being reported for statistical and publication purposes. Electronic data records are kept and will be archived at Curtin University network drive for 5 years. All original questionnaires were stored at National Institute of Hygiene and Epidemiology, Vietnam.

3.7.3 Potential benefit and risk

Data collection was based on face-to-face interview of participants, using a structured questionnaire, and thus, no risk would be concerned. Regarding PSA testing, the blood sampling was undertaken by experienced nurses, at a preventive medicine centre to minimise any possible risk. Indeed, no complication was recorded. In contrast, community-based controls received benefits from their participation in the study. They received free of charge PSA screening test. Based on their PSA test result, appropriate advices were given to individual participants, such

as referring participants to an urologist if the PSA was high. To encourage their participation, community-based controls also received a small incentives as compensation of their travel expense.

Chapter 4: Results

4.1 Overview

The results chapter comprises five sections addressing participant recruitment and response rates, sample characteristics, consumption pattern of tea and coffee in older Vietnamese men, and the association of tea and coffee consumption with prostate cancer risk. First, subject enrolment and response rates for cases, community-based and hospital-based controls are summarised (section 4.2). Second, demographic, lifestyle and clinical features of the cases and controls are compared (section 4.3). Mean (SD) for continuous variables, and number of participants (n) [percentage (%)] for categorical variables are presented. Third, section 4.4 presents the patterns of tea and coffee consumption in old Vietnamese men (descriptive statistics were for controls only). Findings of the association between tea consumption and prostate cancer risk from bivariate and multivariate analyses are shown in section 4.5. Finally, the apparent relationship between coffee consumption and prostate cancer risk is investigated (section 4.6).

The results are presented in the order of the objectives of the study, namely:

- To describe the consumption pattern of tea and coffee among Vietnamese men.
- To evaluate the association between tea consumption and risk of prostate cancer in Vietnam.
- To evaluate the association between coffee consumption and risk of prostate cancer in Vietnam.

4.2 Response rates

Prostate cancer patients were recruited between March 2013 and September 2015. Only men who had been diagnosed with prostate cancer within one month prior to the interview were approached and invited to participate in the study. Community-based controls were recruited among healthy men who resided in the same catchment area as the enrolled prostate cancer patients. The recruitment and interview of

community controls was carried out between April and September 2015. To supplement community-based controls, hospital controls were also recruited from urology departments, in parallel with recruitment of prostate cancer cases.

Figure 8 presents the flowchart of participant recruitment and response numbers. Initially, 275 eligible cases, 700 eligible community-based and 120 hospital-based controls were consecutively approached. Cases selected from hospitals were briefed about the study face-to-face. Seventeen patients declined to attend the interview due to time constraints. Of the 258 consented cases, 23 patients were excluded as they did not meet the selection criteria, resulting in 235 cases for the interview, giving a response rate of 85.4%.

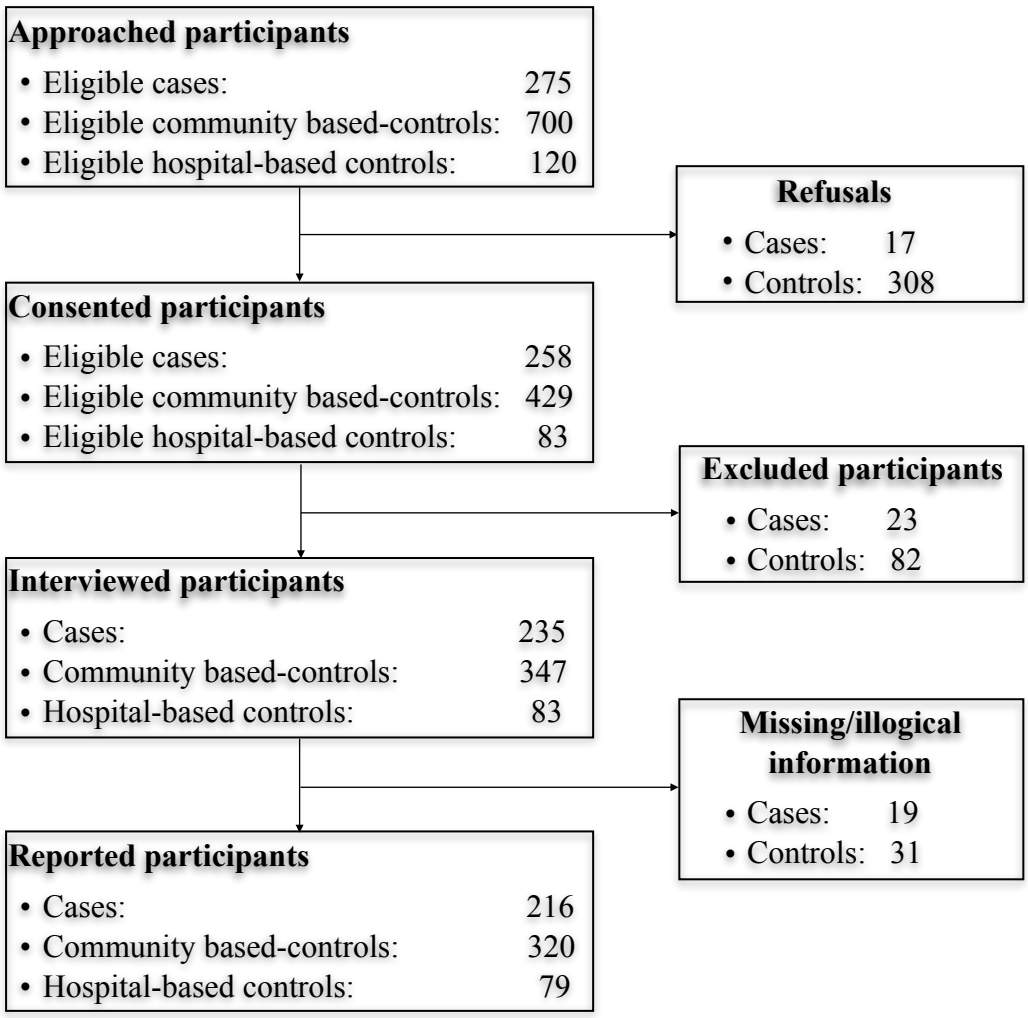

Figure 8 Flowchart of participant recruitment

While cases were recruited from hospitals, controls were selected from both community and hospitals. For community-based controls, 700 letters were sent to eligible men residing in 22 wards of Binh Thanh District - Ho Chi Minh City, the same catchment area as the cases. As a result of these letters, 429 men agreed to participate in the study. Of these potential controls, 82 men were excluded because they did not meet the selection criteria or declined to give their blood samples for a PSA test, leaving 347 men for the interview (response rate 49.5%). Similar to the selection of cases, hospital-based eligible controls (n = 120) were briefed on the study procedure, and were invited to participate in the study. After initial screening,

83 agreed to attend a face-to-face interview (response rate 69.1%). Additionally excluded subjects were 27 community-based controls, 4 hospital-based controls and 19 cases due to illogical or missing data on their questionnaires. Finally, a total of 399 controls (80.2% community-based and 19.8% hospital-based) and 216 prostate cancer patients remained for statistical analyses.

4.3 Characteristics of participants

Table 10 summarises major clinical characteristics of cases. Median level of total blood PSA was 85.0 ng/ml (IQR 25.9, 150.0 ng/ml). Most cases of prostate cancer were diagnosed at medium (31.5%) or higher grade (55.1%) based on Gleason scores. Regarding medical history, nearly half (46.2%) of the cases had history of either benign prostate hyperplasia (BPH, 18.9%) or prostatitis (27.3%). Renal calculi was also relatively common as reported by about 8% of cases. About 13.4% of cases reported ever undergoing surgical procedures. Among them, transurethral resection of prostate was the most prevalent (6.5%), followed by appendectomy (2.3%). Among the reported chronic diseases, hypertension was the most frequent (15.3%). Other chronic diseases including diabetes, coronary heart diseases and hepatitis B were much less frequent. A small number of cases reported having a family history of prostate cancer in their first-degree relatives (n = 7).

Table 10 Clinical characteristics of prostate cancer (n = 216)

	n (%)
Total PSA level (ng/ml)	
Mean ± SD	182.8 ± 338.3
Median (IQR)	85.0 (25.9, 150.0)
Gleason score, Mean ± SD[a]	4.9 ± 1.5
Low-grade	29 (13.4)
Medium-grade	68 (31.5)
High-grade	119 (55.1)
Medical history	
Benign prostate hyperplasia[b]	41 (18.9)
Prostatitis	59 (27.3)
Syphilis	1 (0.5)
Renal calculi	17 (7.9)
Urinary infection	1 (0.5)
Other kidney diseases	2 (1.0)
Surgical history	29 (13.4)
Transurethral resection of prostate[c]	14 (6.5)
Removal of kidney stone	2 (1.4)
Appendectomy	5 (2.3)
Coronary stent	1 (0.5)
Gastrectomy	1 (0.5)
Goitre	1 (0.5)
Gallbladder removal	1 (0.5)
Leg fracture	2 1.0
Hernia	1 (0.5)
Sinusitis	1 (0.5)
Chronic disease	
Diabetes	3 (1.4)
Hypertension	33 (15.3)
Coronary heart diseases	2 (1.0)
Hepatitis B	1 (0.5)
Prostate cancer in first degree relatives	7 (3.2)

PSA: prostate specific antigen; SD: standard deviation; IQR: interquartile range

[a] Low-grade: a Gleason score (GS) of ≤ 6; medium-grade: a GS of 7; high-grade: a GS ≥ 8

[b] Most benign prostate hyperplasia (BPH) cases were diagnosed within 3 years prior to the diagnosis of prostate cancer. A small number of BPH cases were diagnosed longer than 5 years before the prostate cancer diagnosis was made.

[c] Surgery undertaken as treatment of BPH

Table 11 shows clinical characteristics of controls. The mean ± SD and median (IQR) level of total blood PSA in the control group were 3.98 ± 15.5 ng/ml and 1.12 (95% CI 0.99, 2.47) ng/ml, respectively. The most frequent medical history was renal calculi as reported by nearly 13% of controls. Surgical history was reported by 20.6% of controls, of which digestive operations were the most frequent, followed by urinary tract operations. The data also showed that nearly 30% of controls suffered from at least one chronic disease, and the most common condition was hypertension (20.1%).

Table 11 Clinical characteristics of controls (n = 399)

	n (%)
Total PSA level (ng/ml)	
Mean ± SD	3.98 ± 15.5
Median (IQR)	1.12 (0.99, 2.47)
Medical history	
Benign prostate hyperplasia	12 (3.0)
Prostatitis	7 (1.75)
Syphilis	2 (0.5)
Gonorrhoea	5 (1.3)
Gall bladder stone	1 (0.25)
Renal calculi	51 (12.8)
Urinary infection	11 (2.8)
Urinary retention	2 (0.5)
Other urinary obstruction	5 (1.3)
Surgery history	82 (20.6)
Digestive tract surgery	42 (10.5)
Respiratory surgery	2 (0.5)
Urinary tract surgery	19 (4.8)
Transurethral resection of prostate	1 (0.2)
Other surgery	18 (4.8)
Chronic disease	116 (29.6)
Hypertension	80 (20.1)
Diabetes	8 (2.0)
Digestive diseases	3 (0.8)
Respiratory	6 (1.5)
Osteoarthritis	5 (1.3)
Other	16 (4.0)

SD: standard deviation; IQR: interquartile range

Table 12 compares demographic and lifestyle factors between hospital-based and community-based controls. There were no differences between the two control groups regarding age at interview, marital status, age at marriage, education, BMI, waist to hip ratio and history of family smoking. Alcoholic beverages were categorised into three groups, namely strong (containing 39% ethanol), light (containing 12% ethanol) and beer (containing 4.5% ethanol), and converted into grams of ethanol per day (National Institute of Nutrition, 2007). About 65% of community controls and 52% of hospital controls reported drinking less than 10 grams of ethanol per day, and there was no significant difference in drinking patterns between the two groups ($p = 0.07$).

However, there were significant differences between the two groups in terms of numbers of children, smoking habits, lifetime physical activity, tea consumption, coffee consumption and total energy intake ($p < 0.05$). Hospital-based controls have more children than community subjects (4.1 children versus 3.5 children, on average, $p < 0.05$). While hospital controls tended to quit smoking, community controls tended to continue the habit. Hospital controls seemed to be more active in terms of participation in regular physical activity. In general, the community subjects consumed more tea and coffee than their hospital counterparts ($p < 0.01$). Finally, mean total energy intake among community controls was significantly higher than that of hospital controls ($p < 0.01$).

Table 12 Characteristics of hospital and community controls

	Community controls (n = 320)	Hospital controls (n = 79)	p value[a]
	Mean ± SD	**Mean ± SD**	
Age (year)	68.0 ± 5.5	67.4 ± 5.3	0.34
Age at marriage (year)	27.5 ± 4.9	26.5 ± 5.0	0.10
Waist to hip ratio	0.91 ± 0.06	0.9 ± 0.1	0.81
Tea drinking (ml per day)	323.8 ± 374.9	153.8 ± 221.3	< 0.01
Coffee drinking (cups per day)	1.08 ± 1.16	0.63 ± 0.77	< 0.01
Total energy intake	1989 ± 664	1743 ± 527	< 0.01
	n (%)	**n (%)**	
BMI (kg/m^2)			
< 18.5	49 (15.3)	10 (12.7)	
18.5 - 22.9	147 (45.9)	44 (55.7)	0.46
23.0 - 24.9	70 (21.9)	13 (16.5)	
≥ 25	54 (16.9)	12 (15.2)	
Number of children			
≤ 2	112 (35.0)	21 (26.3)	
3 - 4	132 (41.2)	28 (35.4)	0.03
> 4	76 (23.7)	30 (38.0)	
Marital status			
Married	296 (92.5)	71 (89.9)	0.44
Single	24 (7.5)	8 (10.1)	
Education			
Primary	55 (17.2)	16 (20.3)	0.35
High school	203 (63.4)	53 (67.1)	
Tertiary	62 (19.4)	10 (12.7)	
Smoking			
Never	75 (23.4)	32 (40.5)	
Former	128 (40.0)	37 (46.8)	< 0.01
Current	117 (36.6)	10 (12.7)	
Pack-years[b]			
0	76 (23.7)	32 (40.5)	
< 15	107 (33.4)	28 (35.4)	0.06
15 - 30	96 (30.0)	13 (16.5)	
> 30	41 (12.8)	6 (7.6)	
History of family smoking			
No	178 (55.6)	46 (58.2)	
Yes	137 (42.8)	30 (38.0)	0.36
Unknown	5 (1.6)	3 (3.8)	
Physical activity participation			
Never or past active	236 (73.8)	48 (60.8)	0.02
Regular	84 (26.3)	31 (39.2)	
Alcohol drinking (g per day)			
0	61 (19.1)	17 (21.5)	
< 10	147 (45.9)	24 (30.4)	0.07
10 - 25	51 (15.9)	19 (24.1)	
> 25	61 (19.1)	19 (24.1)	

[a] p value from t-test or chi-square test

[b] One pack-year is smoking 20 cigarettes per day for one year

Table 13 compares major demographic characteristics between cases and controls. There was no significant difference in the mean age between cases and controls, 68.4 (SD 6.9) years and 67.9 (SD 5.5) years, respectively. The two groups were also similar in marital status, height, weight, BMI, waist to hip ratio and consumption of alcohol. Cases tended to get married at a slightly younger age than the controls (25.2 years in cases versus 27.3 years in controls, $p < 0.01$). The average number of children among cases was significantly higher than that among controls. Around 42% of cases had 4 children or more, compared with about 26% of controls. The overall education level appeared to be higher in the control group when compared to the cases ($p = 0.04$).

Table 13 Demographic characteristics of cases and controls

	Cases (n = 216)	Controls (n = 399)	p value (t-test/ chi-square test)
	Mean ± SD	Mean ± SD	
Age (year)	68.4 ± 6.9	67.9 ± 5.5	0.38
Age at marriage (year)	25.2 ± 4.7	27.3 ± 4.9	< 0.01
Waist circumference (cm)	78.4 ± 10.5	84.0 ± 9.6	< 0.01
Hip circumference (cm)	85.6 ± 9.3	92.1 ± 7.7	< 0.01
Waist to hip ratio	0.92 ± 0.06	0.91 ± 0.07	0.16
Height (cm)	163.4 ± 6.1	163.4 ± 5.8	0.93
Weight (kg)	58.7 ± 9.0	58.6 ± 9.1	0.89
	n (%)	n (%)	
BMI (kg/m^2)			
< 18.5	26 (12.0)	59 (14.8)	0.03
18.5 - 22.9	122 (56.5)	191 (47.9)	
23.0 - 24.9	27 (12.5)	83 (20.8)	
≥ 25	41 (19.0)	66 (16.5)	
Marital status			
Never married or separated	9 (4.2)	32 (8.0)	0.06
Married	207 (95.8)	367 (92.0)	
Number of children			
≤ 2	49 (22.7)	133 (33.3)	< 0.01
3 - 4	76 (35.2)	160 (40.1)	
> 4	91 (42.1)	106 (26.6)	
Education			
Primary	56 (25.9)	71 (17.8)	0.04
High school	119 (55.1)	256 (64.2)	
Tertiary	41 (19.0)	72 (18.0)	

BMI: body mass index

Table 14 presents the overall score of prostate symptoms in cases and controls using the International prostate symptom scores. The mean score in the former and in the latter was 13.1 and 4.3, respectively ($p < 0.01$). Most of controls had mild symptoms (total score < 7). Only 2.6% of controls reported severe symptoms, but were found to be benign prostate hyperplasia (BPH) after confirmation by biopsy. In contrast, most (70%) of the cases reported moderate or severe symptoms. About 30% of the cases presented with mild symptoms.

Table 14 International prostate symptom scores in cases and controls

	Controls (n = 399)	Cases (n = 216)	p value (t-test/ chi-square test)
Total score, presented with mild symptoms, Mean ± SD	4.3 ± 5.3	13.1 ± 8.1	< 0.01
Prostate symptoms, n (%)			
Mild symptom (< 7)	321 (82.3)	65 (30.1)	
Moderate symptom (7 - 19)	59 (15.1)	106 (49.1)	< 0.01
Severe symptom (20 - 35)	10 (2.6)	45 (20.8)	

SD: standard deviation

Table 15 presents and compares several lifestyle features in the past three years prior to the interview between cases and controls. Smoking appeared to be more common in cases than in the controls. However this was true for former and never smokers, but not current smokers. When duration and frequency of smoking were considered using "pack-years", the smoking history was not significantly different between the case and control groups ($p > 0.05$). Cases were less physically active than the controls. While more than 90% of cases reported to be 'never' or 'past active' in terms of physical activity, only about 70% of controls participated in the same level of physical activity as the cases. In contrast, there were more controls than cases who regularly participated in physical activity (28.8% of controls versus 8.8% of cases). Regarding total energy intake, control subjects consumed more energy than cases (Mean 2025 [SD 818] Kcal/day in controls versus Mean 1672 (SD 644) Kcal/day in cases, $p < 0.01$).

Table 15 Main lifestyle characteristics of participants by case and control status

	Cases (n = 216) n (%)	Controls (n = 399) n (%)	p value (t-test/ chi-square test)
Smoking			
Never	54 (25.0)	107 (26.8)	
Former	111 (51.4)	165 (41.4)	0.04
Current	51 (23.6)	127 (31.8)	
Years of smoking, Mean ± SD	22.8 ± 18.8	22.3 ± 19.2	0.77
Total number of pack-years			
0	54 (25.0)	108 (27.1)	
< 15	73 (33.8)	135 (33.8)	
15 - 30	52 (24.1)	109 (27.3)	0.29
> 30	37 (17.1)	47 (11.8)	
History of family smoking			
No	132 (61.1)	224 (56.1)	
Yes	80 (37.0)	167 (41.9)	0.49
Unknown	4 (1.9)	8 (2.0)	
Physical activity			
Never or past active	197 (91.2)	284 (71.2)	< 0.01
Regular	19 (8.8)	115 (28.8)	
Alcohol drinking (g per day)			
0	33 (15.3)	78 (19.5)	
< 10	101 (46.8)	171 (42.9)	0.56
10 - 25	36 (16.7)	70 (17.5)	
> 25	46 (21.3)	80 (20.1)	
Total energy (Kcal per day), Mean ± SD	1672 ± 644	2025 ± 817	< 0.01

SD: standard deviation

Table 16 shows the percentage of study subjects who changed their dietary habits and habitual alcohol drinking within three years before recruitment. Only 6.5% of controls changed their diet within the past three years. The percentage of cases who changed their diet was double that of controls (p = 0.04). For those cases who changed their diet, they tended to eat less (44.8%), reduce intakes of salt, fat and sugar (24.1%), and eat more fruit and vegetables (17.2%). Some of them became vegetarians (13.8%). Most of the controls, who changed their diets, tended to consume less fat, salt and sugar (69.2%). Change in habitual alcohol consumption was reported by 31% of cases and 17.3% of controls. Of the subjects who changed their habitual alcohol drinking (beer, spirit and wine) 56.7% (cases) and 46.4%

(controls) tended to quit, and 38.8% (cases) and 44.9% (controls) tended to drink less (p = 0.54).

Table 16 Changes in diet regime and alcohol drinking habits within 3 years prior to interview

	Cases (n = 216) n (%)	Controls (n = 399) n (%)	p value (chi-square test)
Change in diet regime			
No	187 (86.6)	373 (93.5)	0.04
Yes	29 (13.4)	26 (6.5)	
Tendency in diet change†			
Less salt, fat and sugar	7 (24.1)	18 (69.2)	< 0.01
Vegetarian	4 (13.8)	3 (11.5)	
Eat less	13 (44.8)	0 (0)	
More fruits and vegetables	5 (17.2)	5 (19.2)	
Change in alcohol consumption			
No	149 (69.0)	330 (82.7)	< 0.01
Yes	67 (31.0)	69 (17.3)	
Tendency in alcohol consumption change†			
Drink more alcohol	1 (1.5)	3 (4.3)	0.54
Switch to herbal alcohol	2 (3.0)	3 (4.3)	
Drink less alcohol	26 (38.8)	31 (44.9)	
Quit alcohol drinking	38 (56.7)	32 (46.4)	

(†) percentage was the number of subjects in each category out of the total number of subjects who had changed their diet regime of alcohol consumption habit within three years prior to their interview

4.4 Tea and coffee consumption pattern in older Vietnamese men

Table 17 describes the pattern of habitual tea drinking in Vietnamese men (controls only). Overall, 87% of Vietnamese older men drank tea. Mean and median amount of tea drank per day was 290 ± 356 ml and 140 (P25 30, P75 420) ml, respectively. These are equivalent to a mean of 4.2 ± 5.1 cups of tea per day. The mean duration of tea drinking habit was 22.8 ± 18.1 years. In terms of cumulative tea drinking, Vietnamese older men had a mean cup-years of 108.7 ± 171.8.

Within three years prior to the interview, only 20 men (5.0%) had changed their habits of tea drinking. Among them, 13 men (65%) stopped drinking tea, and 5 men

(25%) drank tea more often (25.0%). The other two men (10%) continued their habit, but drank less tea than three years ago.

Table 17 Tea consumption pattern among controls, aged 50-81 years

	n = 399
Tea drinking[a], n (%)	
No	52 (13.0)
Yes	347 (87.0)
Frequency of drinking (cups per day), n (%)	
< 1	114 (28.6)
1 - 3	129 (32.3)
3 - 6	57 (14.3)
> 6	99 (24.8)
Amount of drinking (ml per day)	
Mean ± SD	290.2 ± 356.2
Median (LQ, UQ)	140 (30, 420)
Years of tea drinking	
Mean ± SD	22.8 ± 18.1
Median (LQ, UQ)	20 (5, 40)
Cumulative tea drinking (cup-years)	
Mean ± SD	108.7 ± 171.8
Median (LQ, UQ)	32 (4, 120)
Changes in tea drinking habit, n (%)	
No	379 (95)
Yes	20 (5)
Directions of change in tea drinking[b], n (%)	
Drink more tea	5 (25.0)
Drink less tea	2 (10.0)
Quit tea drinking	13 (65.0)

LQ: lower quartile at 25%; UQ: upper quartile at 75%; SD: standard deviation
([a]) ever drink green tea, green tea leaves, black tea or Oolong tea. The majority of participants drank green tea.
([b]) percentage was the number of subjects in each category out of the total number of subjects who had changed their habit of tea drinking within three years prior to their recruitment.

Table 18 presents the pattern of habitual coffee drinking among older men (controls) in Vietnam. In general, 81.7% of interviewees reported to be habitual coffee drinker. The mean number of cups of coffee drank per week was 6.9 ± 7.8. They had kept their habit of coffee drinking for on average 20 ± 17.5 years. In terms of cumulative coffee drinking, older Vietnamese men drank on average 24.9 ± 34.9 cup-years. 35

men (8.8%) reported to have changed their habit within three years before their interview. Among those who had the habit changed, 14 men (40%) tended to drink more coffee, while the same number of men tended to drink less. Only 7 men (20%) reported to have stopped drinking coffee.

Table 18 Coffee consumption pattern among controls, aged 50-81 years

	n = 399
Coffee drinking[a], n (%)	
No	73 (18.3)
Yes	326 (81.7)
Frequency of drinking (cups per day), n (%)	
< 1	171 (42.9)
1 - 3	215 (53.9)
> 3	13 (3.3)
Years of coffee drinking	
Mean ± SD	20 ± 17.5
Median (LQ, UQ)	16 (4, 33)
Cumulative coffee drinking (cup-years)	
Mean ± SD	24.9 ± 34.9
Median (LQ, UQ)	10 (0.6, 40)
Changes in coffee drinking, n (%)	
No	364 (91.2)
Yes	35 (8.8)
Directions of change in coffee drinking[b], n (%)	
Drink more coffee	14 (40.0)
Drink less coffee	14 (40.0)
Quit coffee drinking	7 (20.0)

LQ: lower quartile at 25%; UQ: upper quartile at 75%; SD: standard deviation
([a]) ever drink black coffee, instant coffee or milk coffee (black coffee added with condensed milk). The majority of participants drank black coffee.
([b]) percentage was the number of subjects in each category out of the total number of subjects who had changed their habit of coffee drinking within three years prior to their recruitment.

4.5 Tea consumption and prostate cancer risk

The association between tea drinking and the risk of prostate cancer was evaluated by comparing the level of tea consumption between the cases and the controls without and with consideration of potential confounders. Tea consumption was classified in terms of the amount of tea (ml per day), frequency (cups per day), years

of tea-drinking and cumulative tea drinking (number of cup-years). Daily tea drinking was estimated by dividing tea consumption on yearly, monthly and weekly basis by 365, 30 and 7, respectively. The number of cup-years of tea drinking was calculated by the product of tea cups per day and years of drinking tea. In Vietnam, habitual drinking of mixed tea (e.g. green tea, black tea and oolong tea) is popular. Green tea, including dried and fresh tea leaves, is the most popular type of tea. Both dried and fresh tea leaves can be brewed with hot water for drinking. Given the small number of participants who only drank black and oolong tea, the present study investigated the association between total tea drinking and the risk of prostate cancer, without differentiating the type of tea they drank.

Table 19 compares tea drinking between cases and controls. Overall, the proportion of tea drinkers was lower in the former than in the latter, albeit the difference was not significant ($p = 0.65$). In terms of quantity, however, controls drank a larger amount of tea compared to cases (290.2 ± 356.2 ml per day in controls versus 148.6 ± 206.1 ml per day in cases, $p < 0.01$). Similar results were noted when the number of cups of tea per day was used. On average, controls drank 4.2 ± 5.1 cups per day, while cases drank 2.1 ± 2.9 cups of tea per day. In the case group, nearly 64% drank less than 2 cups of tea per day, whereas around 45% of the controls group drank tea at the same level. For 2 cups or more, however, controls drank tea more often than cases ($p < 0.01$). Mean years of tea drinking in the control group were greater than the case group, albeit statistically non-significant ($p = 0.25$). When cumulative lifetime tea drinking (cup-years) was considered, cases tended to consume less than controls, regardless of tea drinking being treated as either a continuous or categorical variable ($p < 0.01$).

Table 19 Comparison of tea drinking between cases and controls

	Controls (n = 399)	Cases (n = 216)	p value (t-test/ chi-square test)
	n (%)	n (%)	
Tea drinking[a]			
No	52 (13.0)	31 (14.4)	0.65
Yes	347 (87.0)	185 (85.6)	
Amount of drinking (ml per day), Mean ± SD	290.2 ± 356.2	148.6 ± 206.1	< 0.01
< 100	174 (43.6)	134 (62.0)	< 0.01
100 - 500	141 (35.3)	63 (29.2)	
> 500	84 (21.1)	19 (8.8)	
Frequency of drinking (cups per day), Mean ± SD	4.2 ± 5.1	2.1 ± 2.9	< 0.01
< 2	181 (45.4)	138 (63.9)	< 0.01
2 - < 4	69 (17.3)	36 (16.7)	
4 - 6	50 (12.5)	22 (10.2)	
> 6	99 (24.8)	20 (9.3)	
Years of tea drinking, Mean ± SD	22.8 ± 18.1	20 ± 16.4	0.05
< 15	162 (40.6)	97 (44.9)	0.25
15 - 35	118 (29.6)	68 (31.5)	
> 35	119 (29.8)	51 (23.6)	
Cumulative tea drinking (cup-years), Mean ± SD	108.7 ± 171.8	48.4 ± 84.9	< 0.01
≤ 20	152 (38.1)	109 (50.5)	< 0.01
20 - 60	93 (23.3)	60 (27.8)	
60 - 150	69 (17.3)	30 (13.9)	
≥ 150	85 (21.3)	17 (7.9)	

SD: standard deviation

([a]) ever drink green tea, green tea leaves, black tea or Oolong tea. The majority of participants drank green tea.

Table 20 shows the association between tea drinking and prostate cancer risk from logistic regression analyses. Compared with non-drinkers, tea drinkers appeared to have lower odds for having prostate cancer, albeit statistically non-significant (adjusted OR: 0.75; 95% CI: 0.44, 1.29). Subjects drinking between 100 - 500 ml of tea per day had 43% significantly lower odds for having prostate cancer relative to those drinking < 100 ml per day. The negative association was much stronger when comparing individuals drinking > 500 ml per day versus those drinking < 100 ml per (adjusted OR: 0.33, 95% CI 0.18, 0.59). Overall, the risk of prostate cancer was

reduced by 9% for an increment of 50 ml of tea drunk per day, after adjusting for the effects of confounding variables.

Table 20 Association between tea consumption and prostate cancer risk

Frequency	Control (n = 399)	Case (n = 216)	Crude OR	95% CI	Adjusted OR†	95% CI
Tea drinking						
No	52 (13.0)	31 (14.4)	1	-		
Yes	347 (87.0)	185 (85.6)	0.89	(0.55, 1.44)	0.75	(0.44, 1.29)
Amount of drinking (ml per day)						
< 100	174 (43.6)	134 (62.0)	1	-		
100 - 500	141 (35.3)	63 (29.2)	0.58	(0.40, 0.84)	0.57	(0.38, 0.85)
> 500	84 (21.1)	19 (8.8)	0.29	(0.17, 0.51)	0.33	(0.18, 0.59)
					p for trend = 0.01	
Frequency of drinking (cups per day)						
< 2	181 (45.4)	138 (63.9)	1	-	1	-
2 - 4	69 (17.3)	36 (16.7)	0.68	(0.43, 1.08)	0.71	(0.43, 1.16)
4 - 6	50 (12.5)	22 (10.2)	0.58	(0.33, 0.99)	0.53	(0.29, 0.95)
> 6	99 (24.8)	20 (9.3)	0.26	(0.16, 0.45)	0.29	(0.17, 0.52)
					p for trend < 0.01	
Duration of drinking (years)						
< 15	162 (40.6)	97 (44.9)	1	-	1	-
15 - 35	118 (29.6)	68 (31.5)	0.96	(0.65, 1.42)	0.84	(0.54, 1.29)
> 35	119 (29.8)	51 (23.6)	0.72	(0.47, 1.08)	0.59	(0.37, 0.94)
					p for trend = 0.02	
Cumulative tea drinking (cup-years)						
< 20	152 (38.1)	109 (50.5)	1	-	1	-
20 - 60	93 (23.3)	60 (27.8)	0.9	(0.61, 1.35)	0.84	(0.54, 1.31)
60 - 150	69 (17.3)	30 (13.9)	0.61	(0.37, 0.99)	0.59	(0.34, 1.00)
> 150	85 (21.3)	17 (7.9)	0.28	(0.16, 0.50)	0.25	(0.13, 0.48)
					p for trend = 0.01	

p for trend: p-value from test of linear trend

(†) Adjusted for age (years), smoking habit (pack-years), alcohol consumption (gram/day), body mass index (kg/m^2), marital status (never married/separated, married), total energy intake (Kcal/day), education level (primary, high school, tertiary), family history of prostate cancer, physical activity (never/past active, regularly active) and age at marriage (years)

Table 21 presents the association between tea consumption and the risk of low- or medium-grade prostate cancer defined as Gleason score ≤ 7. There was a lack of association between tea drinking and prostate cancer risk (OR: 1.17; 95% CI: 0.55,

2.50). However, when tea drinking was classified by quantity, frequency, duration of drinking and cumulative consumption, we observed an inverse association between tea drinking and prostate cancer. Specifically, compared with subjects drinking less than 80 ml per day, individuals drinking 400 ml of tea per day had significantly lower risk of prostate cancer (95% CI: 0.12, 0.55, p for trend = 0.01). Similarly for participants drinking 4 cups per day or more (95% CI: 0.10, 0.45, p for trend < 0.01).

Table 21 Association between tea consumption and low- or medium-grade prostate cancer†

Frequency	Control (n = 399)	Case (n = 97)	Crude OR	95% CI	Adjusted OR††	95% CI
Tea drinking						
No	52 (13.0)	10 (10.3)	1	-		
Yes	347 (87.0)	87 (89.7)	1.3	(0.64, 2.67)	1.17	(0.55, 2.50)
Amount of drinking (ml per day)						
< 80	170 (42.6)	58 (59.8)	1	-		
80 - 400	112 (28.1)	29 (29.9)	0.75	(0.45, 1.25)	0.7	(0.40, 1.20)
> 400	117 (29.3)	10 (10.3)	0.25	(0.12, 0.51)	0.26	(0.12, 0.55)
					p for trend = 0.01	
Frequency of drinking (cups per day)						
< 1	114 (28.6)	38 (39.2)	1	-	1	-
1 - 4	146 (36.6)	48 (49.5)	0.98	(0.63, 1.61)	0.86	(0.51, 1.47)
> 4	139 (34.8)	11(11.3)	0.24	(0.12, 0.49)	0.21	(0.10, 0.45)
					p for trend < 0.01	
Duration of drinking (years)						
< 15	162 (40.6)	44 (45.4)	1	-	1	-
15 - 35	118 (29.6)	32 (33.0)	0.99	(0.59, 1.66)	0.92	(0.53, 1.59)
> 35	119 (29.8)	21 (21.6)	0.65	(0.37, 1.15)	0.64	(0.34, 1.19)
					p for trend = 0.01	
Cumulative tea drinking (cup-years)						
< 20	152 (38.1)	47 (48.5)	1	-	1	-
20 - 60	93 (23.3)	32 (33.0)	1.11	(0.66, 1.87)	1.05	(0.65, 1.82)
60 - 150	69 (17.3)	14 (14.4)	0.66	(0.34, 1.27)	0.63	(0.30, 1.29)
> 150	85 (21.3)	4 (4.1)	0.15	(0.05, 0.44)	0.16	(0.05, 0.46)
					p for trend < 0.01	

p for trend: p-value from test of linear trend

(*) Defined as a Gleason score of 7 or less (**) Adjusted for age (years), smoking habit (pack-years), alcohol consumption (gram/day), body mass index (kg/m^2), marital status (never married/separated, married), total energy intake (Kcal/day), education level (primary, high school, tertiary), family history of prostate cancer, physical activity (never/past active, regularly active) and age at marriage (years)

In addition, longer duration of tea drinking tended to reduce the risk of low/medium grade prostate cancer (p for trend = 0.01; the odds ratio for prostate cancer among subjects drinking tea over 35 years versus those drinking less than 15 years was 0.64 (95% CI: 0.34, 1.19). When cumulative tea drinking (cup-years) was used, there was a significant inverse association; the odds ratio for low/medium grade prostate cancer for individuals drinking over 150 cup-years versus those drinking less than 20 cup-years was 0.16 (95% CI: 0.05, 0.46; p for trend < 0.01).

Table 22 shows the relationship between tea consumption and the risk of high-grade prostate cancer defined as Gleason score of 8-10. There was an inverse association between, daily tea drinking and the risk of high-grade prostate cancer; the odds ratio for tea drinkers versus non-drinkers was 0.58 (95% CI: 0.3, 1.1). Drinking 100 - 500 ml of tea per day was associated with 49% decreased odds of having high-grade prostate cancer. The odds was further decreased by 62% among those who drank more than 500 ml of tea per day compared to those who drank less than 100 ml of tea per day (p < 0.01; p for trend < 0.01). Similarly, there was an inverse association between daily tea drinking (the number of cups) and the risk of high-grade prostate cancer. Compared to subjects drinking less than 2 cups per day, the odds ratios for high-grade prostate cancer among individuals drinking 2 to 6 cups per day and over 6 cups per day were 0.57 (95% CI 0.34, 0.98) and 0.36 (95% CI0.18, 0.72), respectively. In addition, there was a borderline significant, inverse association between duration of tea drinking and prostate cancer risk; the odds ratios were 0.57 (95% CI 0.32, 1.03) for participants drinking over 35 years relative to those drinking less than 15 years (p for trend < 0.01). Besides, cumulative tea drinking (number of cup-years) was significantly associated with a decreased risk of high-grade prostate cancer. This association was observed among those with 15 cup-years or more (OR: 0.56, 95% CI: 0.33, 0.96). Among those with more than 100 cup-years, the odds of high-grade prostate cancer were reduced by 61 % (95% CI: 0.21, 0.70, p for trend < 0.01).

Table 22 Association between tea consumption and high-grade prostate cancer†

Frequency	Control (n = 399)	Case (n = 119)	Crude OR	95% CI	Adjusted OR††	95% CI
Tea drinking						
No	52 (13.0)	21 (17.6)	1	-		
Yes	347 (87.0)	98 (82.4)	0.7	(0.40, 1.26)	0.58	(0.30, 1.11)
Amount of drinking (ml per day)						
< 100	174 (43.6)	74 (62.2)	1	-	1	-
100 - 500	141 (35.3)	32 (26.9)	0.53	(0.33, 0.85)	0.51	(0.30, 0.86)
> 500	84 (21.1)	13 (10.9)	0.36	(0.19, 0.69)	0.38	(0.19, 0.78)
					p for trend < 0.01	
Frequency of drinking (cups per day)						
< 2	181 (45.4)	75 (63.0)	1	-	1	-
2 - 6	119 (29.8)	30 (25.2)	0.61	(0.38, 0.98)	0.57	(0.34, 0.98)
> 6	99 (24.8)	14 (11.8)	0.34	(0.18, 0.63)	0.36	(0.18, 0.72)
					p for trend < 0.01	
Duration of drinking (years)						
< 15	162 (40.6)	53 (44.5)	1	-	1	-
15 - 35	118 (29.6)	36 (30.3)	0.93	(0.57, 1.51)	0.86	(0.50, 1.48)
> 35	119 (29.8)	30 (25.2)	0.77	(0.46, 1.27)	0.57	(0.32, 1.03)
					p for trend < 0.01	
Cumulative tea drinking (cup-years)						
< 15	141 (35.3)	59 (49.6)	1	-	1	-
15 - 100	126 (31.6)	35 (29.4)	0.66	(0.40, 1.07)	0.56	(0.33, 0.96)
> 100	132 (33.1)	25 (21.0)	0.45	(0.27, 0.76)	0.39	(0.21, 0.70)
					p for trend < 0.01	

p for trend: p-value from test of linear trend

(†) Defined as a Gleason score of 8 - 10

(††) Adjusted for age (years), smoking habit (pack-years), alcohol consumption (gram/day), body mass index (kg/m^2), marital status (never married/separated, married), total energy intake (Kcal/day), education level (primary, high school, tertiary), family history of prostate cancer, physical activity (never/past active, regularly active) and age at marriage (years)

Table 23 displays the association between daily tea drinking and the risk of prostate cancer, using only community-based controls. Although there was a statistically non-significant lower risk of prostate cancer among tea drinkers relative to non-drinkers, we observed consistent inverse associations for tea drinking in terms of quantity (ml per day), frequency (cups per day), duration and cumulative exposure with the

prostate cancer risk. The odds ratios for prostate cancer among subjects drinking at least 500 ml per day or 6 cups per day compared with those drinking less than 100 ml per day or 2 cups per day were 0.28 (95% CI 0.15, 0.51) and 0.25 (95% CI 0.14, 0.46), respectively (p for trend < 0.01). Likewise, individuals drinking tea for over 35 years had 44% significantly lower odds of having prostate cancer (95% CI: 0.35, 0.92) compared with those drinking tea less than 15 years. In other words, each additional year of habitual tea drinking was associated with a 1.4% reduced risk of the cancer (p for trend = 0.005). In addition, cumulative tea drinking (cup-years) was inversely associated with prostate cancer; odds ratios for subjects drinking 10 - 70 and > 70 cup-years versus those drinking < 10 cup-years were 0.58 (95% CI 0.36, 0.91) and 0.34 (95% CI 0.21, 0.56), respectively (p for trend < 0.01).

Table 23 Association between tea consumption and prostate cancer risk among community-based controls

Frequency	Control (n = 320)	Case (n = 216)	Crude OR	95%	Adjusted OR†	95% CI
Tea drinking						
No	39 (12.2)	31 (14.4)	1	-	1	-
Yes	281 (87.8)	185 (85.6)	0.83	(0.50, 1.37)	0.69	(0.38, 1.23)
Amount of drinking (ml per day)						
< 100	130 (40.6)	134 (62.0)	1	-	1	-
100 - 500	112 (35.0)	63 (29.2)	0.54	(0.36, 0.80)	0.55	(0.36, 0.85)
> 500	78 (24.4)	19 (8.8)	0.23	(0.14, 0.41)	0.28	(0.15, 0.51)
					p for trend < 0.01	
Frequency of drinking (cups per day)						
< 2	134 (41.9)	138 (63.8)	1	-	1	-
2 - 4	48 (15.0)	36 (16.7)	0.72	(0.44, 1.19)	0.76	(0.44, 1.29)
> 4 - 6	46 (14.4)	22 (10.2)	0.46	(0.26, 0.81)	0.46	(0.25, 0.86)
> 6	92 (28.7)	20 (9.3)	0.21	(0.12, 0.36)	0.25	(0.14, 0.46)
					p for trend < 0.01	
Duration of drinking (years)						
< 15	133 (41.6)	97 (44.9)	1	-	1	-
15 - 35	88 (27.5)	68 (31.5)	1.06	(0.70, 1.60)	0.89	(0.56, 1.40)
> 35	99 (30.9)	51 (23.6)	0.71	(0.46, 1.08)	0.56	(0.35, 0.92)
					p for trend < 0.01	
Cumulative tea drinking (cup-years)						
< 10	94 (29.4)	96 (44.5)	1	-	1	-
10 - 70	104 (32.5)	75 (34.7)	0.71	(0.46, 1.06)	0.58	(0.36, 0.91)
> 70	122 (38.1)	45 (20.8)	0.36	(0.23, 0.56)	0.34	(0.21, 0.56)
					p for trend < 0.01	

p for trend: p-value from test of linear trend
(†) Adjusted for age (years), smoking habit (pack-years), alcohol consumption (gram/day), body mass index (kg/m^2), marital status (never married/separated, married), total energy intake (Kcal/day), education level (primary, high school, tertiary), family history of prostate cancer, physical activity (never/past active, regularly active) and age at marriage (years)

4.6 Coffee consumption and prostate cancer risk

The association of habitual coffee drinking and the risk of prostate cancer was assessed by comparing frequency (cups per week), years of drinking and cumulative coffee drinking (number of cup-years) between cases and controls. The association was investigated using both univariate and multivariate logistic regression models. Weekly number of cups of coffee was estimated by dividing coffee consumption on yearly and monthly basis by 52 and 4.5, respectively, and multiplying daily consumption by 7. Number of cup-years of coffee drinking was calculated by the product of cups consumed per week and the total years of drinking coffee. In Vietnam, black coffee (85.6%) was more popular than instant (48.1%) and milk coffee (56.0%). However, Vietnamese adults can drink two types of coffee or even three types coffee as a habit. Given the popularity of mixed habitual drinking of coffee, the present study evaluated the association of total coffee drinking and the risk of prostate cancer.

Table 24 compares the coffee drinking between cases and controls. Overall, the prevalence of coffee drinkers among case subjects was similar to that among control subjects ($p = 0.2$). Also, mean years and cup-years of coffee drinking were similar between the two groups ($p = 0.7$). Stratification by frequency of coffee drinking (cups per week) showed a significant difference between cases and controls ($p < 0.01$). At the level of 3-7 cups per week, the prevalence of coffee drinkers among cases and controls was 31.1% and 14.4%, respectively. In contrast, at consumption level of 7 or more cups of coffee per week, the prevalence of coffee drinkers among controls (43.5%) was greater than that in cases (31.1%).

Table 24 Comparison of coffee drinking between cases and controls

	Controls (n = 399)	Cases (n = 216)	p value (t-test/ chi-square test)
	n (%)	n (%)	
Coffee drinking†			
No	73 (18.3)	31 (14.4)	0.20
Yes	326 (81.7)	185 (85.6)	
Frequency of drinking (cups/ week), Mean ± SD	6.9 ± 7.8	7.2 ± 8.6	0.30
< 3	151 (37.8)	91 (42.1)	< 0.01
3 - 7	124 (31.1)	31 (14.4)	
7 - 15	93 (23.3)	74 (34.2)	
> 15	31 (7.8)	20 (9.3)	
Years of coffee drinking (years), Mean ± SD	20 ± 17.5	21.4 ± 17.6	0.30
< 5	101 (27.7)	49 (24.4)	0.70
5 - 20	106 (29.1)	56 (27.9)	
20 - 40	100 (27.5)	61 (30.3)	
> 40	57 (15.7)	35 (17.4)	
Cumulative coffee drinking (cup-years), Mean ± SD	24.9 ± 34.9	28.4 ± 47.1	0.50
< 5	157 (39.3)	83 (38.4)	0.70
5 - 20	92 (23.1)	43 (19.9)	
20 - 45	77 (19.3)	47 (21.8)	
> 45	73 (18.3)	43 (19.9)	

(†) ever drink coffee

Table 25 summarises the results of logistic regression analyses in relation to coffee drinking. The risk of the cancer was not associated with coffee consumption. When compared to non-coffee drinkers, coffee drinkers had 20% higher odds of having prostate cancer. But the elevated risk was not significant (95% CI 0.73, 1.99). Compared with participants drinking less than 3 cups of coffee per week, those drank 3 - 7 cups per week had lower odds of having prostate cancer (adjusted OR: 0.37; 95% CI: 0.22, 0.63). However, at higher level of coffee consumption (> 7 cups per week), the odds of having prostate cancer were not significantly different between high and low consumption levels. Similarly, both years of and cumulative coffee drinking (cup-years) were not associated with the risk of prostate cancer ($p > 0.05$). Further analysis found no association between coffee consumption and high-grade prostate cancer.

Table 25 Crude and adjusted odds ratios and associated 95% confidence intervals of prostate cancer risk for coffee consumption

	Control (n = 399) n (%)	Case (n = 216) n (%)	Crude OR	95% CI	Adjusted OR†	95% CI
Coffee drinking						
No	73 (18.3)	31 (14.4)	1	-	1	-
Yes	326 (81.7)	185 (85.6)	1.34	(0.85, 2.11)	1.2	(0.73, 1.99)
Frequency of drinking (cups/week)						
< 3	151 (37.8)	91 (42.1)	1	-	1	-
3 - 7	124 (31.1)	31 (14.4)	0.41	(0.26, 0.66)	0.37	(0.22, 0.63)
7 - 15	93 (23.3)	74 (34.2)	1.32	(0.88, 1.97)	1.17	(0.75, 1.81)
> 15	31 (7.8)	20 (9.3)	1.07	(0.57, 1.98)	0.98	(0.49, 1.96)
					p for trend = 0.60	
Years of coffee drinking (years)						
< 5	101 (27.7)	49 (24.4)	1	-	1	-
5 - 20	106 (29.1)	56 (27.9)	1.08	(0.68, 1.74)	1.13	(0.67, 1.90)
20 - 40	100 (27.5)	61 (30.3)	1.25	(0.78, 2.00)	1.03	(0.61, 1.73)
> 40	57 (15.7)	35 (17.4)	1.26	(0.73, 2.17)	1.01	(0.55, 1.87)
					p for trend = 0.71	
Cumulative coffee drinking (cup-years)						
< 5	157 (39.3)	83 (38.4)	1	-	1	-
5 - 20	92 (23.1)	43 (19.9)	0.88	(0.56, 1.38)	0.75	(0.45, 1.23)
20 - 45	77 (19.3)	47 (21.8)	1.15	(0.73, 1.81)	0.96	(0.58, 1.58)
> 45	73 (18.3)	43 (19.9)	1.11	(0.70, 1.76)	0.9	(0.53, 1.52)
					p for trend = 0.68	

p for trend: p-value from test of linear trend

(†) Adjusted for age (years), smoking habit (pack-years), alcohol consumption (gram/day), body mass index (kg/m^2), marital status (never married/separated, married), total energy intake (Kcal/day), education level (primary, high school, tertiary), family history of prostate cancer, physical activity (never/past active, regularly active) and age at marriage (years)

Chapter 5: Discussion

5.1 Overview of the chapter

The main aim of this study was to investigate the association between tea, coffee consumption and the risk of prostate cancer in Vietnam. The study focused on four objectives, namely, assessing the epidemiology of prostate cancer in Vietnam, the pattern of tea and coffee consumption in Vietnamese men, investigation of association between tea consumption, coffee consumption and the risk of prostate cancer among Vietnamese men. The discussion over the findings in Chapter 4 will be presented in this chapter. It also discusses some limitations of the present study. The chapter begins with a brief discussion on the setting of the study location in relation to incidence and trend of prostate cancer in Vietnam, section 5.2.1. The next section, 5.2.2 focuses on the pattern of habitual consumption of tea and coffee among Vietnamese men. The relation between tea consumption and the risk of prostate cancer in Vietnam will be discussed in section 5.2.3. The discussion will summarise results of the present study in comparison with previous studies, and potential molecular mechanism of the effect of tea consumption on the development and progression of prostate cancer. Similarly, section 5.2.4 will present the discussion on the relation between habitual coffee consumption and the risk of prostate cancer in Vietnam. Section 5.3 and section 5.4 discusses some strengths and limitations of the study, respectively.

5.2 Discussion

5.2.1 Trends in the incidence of prostate cancer in Vietnam

Over the last two decades, there has been a steady increase in the life expectancy of the Vietnamese population. It has increased from 69.1 years in 1990 to 76.3 years in 2013 (Gapmider, 2013). Since age is the main established risk factor of prostate cancer, the increase in life expectancy is believed to result in increase in incidence and prevalence of prostate cancer. A report from Australia showed that 25% of men are diagnosed with prostate cancer by the age of 85 years (Cancer Council of

Australia, 2011). This is also the experience in Vietnam where there has been an upward trend in the incidence of prostate cancer. The age standardised rate for prostate cancer has nearly doubled from 2.5 per 100,000 in 1990 (Anh et al., 1993)to 4.7 per 100,000 in 2010 (Nguyen et al., 2010). The most recent report from a screening program showed that the cancer was diagnosed in 2.5% of men aged 50 years and over (Vu Le et al., 2010). Along with the ageing population, changes to Westernised lifestyle could also be a plausible factor leading to the upward trend in the incidence of prostate cancer in Vietnam. The popularity of 'fast food' chains such as Kentucky Fried Chicken, McDonald's and Lotteria in Vietnam has increased in recent decades (Euromonitor, 2014). The influence of a Western diet on prostate cancer risk is partly demonstrated by a study that compared the incidence rate of prostate cancer in Vietnamese men who lived in Hanoi (Hanoi-Vietnamese) and their counterparts living in the United States of America (US-Vietnamese). It showed that the rate of prostate cancer among US-Vietnamese was 4 times higher than that among Hanoi-Vietnamese (Le et al., 2002).

5.2.2 Pattern of tea and coffee consumption in Vietnam

5.2.2.1 Tea consumption pattern in Vietnamese older men

Tea drinkers were highly prevalent in Vietnam (87% of older men). This prevalence in Vietnam was higher than several other Asian countries. A baseline survey of nearly 28,000 Singaporean men showed that tea drinkers accounted for 66.7% of the study population (Montague et al., 2012). In China, personal interview of 274 hospital in-patients who were involved in a case-control study found 79.9% to be tea drinkers (Jian et al., 2004). On average, 71.4% of Vietnamese men drank at least one cup of tea per day. This prevalence is similar to that in Japan. A baseline survey of 49,566 Japanese men showed that 74% of these men drank at least one cup of green tea per day (Kurahashi et al., 2009).

Among four types of tea, i.e. green tea, fresh green tea leaves, black tea and oolong tea, green tea is far more popular among Vietnamese men than the other three types. According to Food Agriculture Organisation of the United Nations (2015), Vietnam

ranked second in green tea export worldwide in 2013, after China. In Vietnam, green tea can be found in almost every household, food court, restaurants or at street vendors. Green tea is also predominant in other Asian countries such as China, Singapore and Japan (Jian et al., 2004, Kurahashi et al., 2008, Montague et al., 2012). Black tea, on the other hand, is less common in Vietnam. An ecological study of 50 countries on the association between black tea consumption and health indicators showed that Vietnam's yearly consumption of black tea in kg per capital was among the lowest. In contrast, black tea is far more popular in Western countries (Beresniak et al., 2012).

Drinking tea is a lifetime habit for most Vietnamese men. On average, our sample of Vietnamese older men drank tea for 22.8 ± 18.1 years, and 55% of them drank tea for at least 15 years in their life. This habit is comparable to that in China. Jian et al. (2004) reported that about 64.6% of Chinese men drank tea for at least 20 years. The habit of tea drinking among Vietnamese men appeared to be persistent as 95% of them did not change their habitual tea drinking within the past three years.

5.2.2.2 Coffee consumption pattern in Vietnamese men

Similar to tea, coffee is one of the most popular beverages in Vietnam, especially in Southern Vietnam. The prevalence of coffee drinkers in this study was 81.7%, which was higher than other Asian countries. According to a survey in Japan, 69.9% of 49,566 Japanese men were coffee drinkers (Kurahashi et al., 2009). Our prevalence of coffee drinkers in Vietnam was similar to the United States (83.5%) (Wilson et al., 2011), but lower than Sweden (94.6%) where men drank at least one cup of coffee per day (Hallström et al., 2014).

Regarding the total number of cups of coffee consumed per day, Vietnamese men drank much less than Western men. In this study, very few Vietnamese men (3.3%) drank more than three cups of coffee per day. Most of them drank 1 to 3 cups per day, whereas, 41.4% of Swedish men drank at least 4 cups of coffee per day (Hallström et al., 2014). Similarly, a cohort study of 224,234 Norwegian men, including 5,740 prostate cancer patients, showed that 40.2% of the men drank 5 to 8

cups of coffee per day, while 11.2% of other patients even drank at least 9 cups of coffee per day. In that study, drinking coffee was found to be a protective factor against prostate cancer risk (Tverdal, 2015). However, drinking more cups of coffee may not necessarily mean consuming more caffeine or other bioactive compounds. The intake of coffee's bioactive compounds depends on the concentration of coffee liquid and the method of preparation (Perez-Martinez et al., 2010). Unlike Western culture, in which people drink light coffee with milk such as latte or flat white, Vietnamese men typically drink condensed filtered black coffee, without milk. However, consumption of excessive amount of caffeine could result in discomfort such as headache and dizziness (Winston et al., 2005), or even harmful health effects such as atrial fibrillation (Ciszowski et al., 2014). This could be the reason why Vietnamese men drink fewer cups of coffee per day than men in Western countries.

Similar to habitual tea consumption, coffee drinking is also a lifetime habit among Vietnamese men. On average, the total years of daily coffee drinking among Vietnamese men was 20 ± 17.5. This duration appeared to be shorter in comparison to Western men. According to a population-based case-control study in Canada (Sharpe and Siemiatycki, 2002), 91.2% of Canadian men drank coffee for at least 20 years.

5.2.3 Association between tea consumption and prostate cancer risk in Vietnamese men

An extensive review of literature in Chapter 2 found insufficient evidence for the protective effect of habitual tea drinking against prostate cancer risk (Table 6), due to inconsistency of findings between studies in the existing epidemiological evidence. A number of factors could be involved, such as variations in pattern of tea drinking, type of tea drank or other potential confounding factors. Thus, to further evaluate the relation between habitual tea drinking and prostate cancer risk, more epidemiological studies are required. One of the main objectives of the present study was to investigate the association between habitual tea drinking and the risk of prostate cancer in Vietnam, where the cancer was low incident, and where tea was the most

popular beverage. To the best of my knowledge, the present study was the first attempt to investigate such association in Vietnam.

The results of this study revealed that habitual tea drinking was significantly associated with lower odds of having prostate cancer in Vietnamese men. This inverse association was observed for higher levels of tea consumption when compared to the lowest one (< 100 ml of tea per day). At the level of 100 - 500 ml per day, tea consumption was found to be associated with 42% reduction in risk of prostate cancer (OR: 0.58, 95% CI: 0.40, 0.84). Such inverse association became more apparent after adjustment for confounding factors. Furthermore, the inverse association was found to be dose responsive (p for trend ≤ 0.01), and significant for all grades of prostate caner, but more apparent for high-grade (Gleason score > 7). Sensitivity analysis by control groups also confirmed this association. Overall, the results of this study support the hypothesis of an inverse association between habitual tea drinking and the risk of prostate cancer among Vietnamese men. Together with existing evidence from previous epidemiological studies, these findings suggested that regular tea consumption may have a protective effect against prostate cancer, which have important implications in prevention of the cancer.

Our findings were consistent with a number of, but not all, observational studies on the same topic. For example, in a recent case-control study, Hu et al. (2014)compared the habit of tea drinking between 108 patients and 242 healthy men in China. The authors reported an association of drinking four or more times of tea per week with 42% reduction in the risk of the cancer, when compared to seldom or never drinking tea. Another case-control study in Hangzhou, China, which included 130 prostate cancer patients and 274 hospital controls, also indicated an inverse association between tea consumption and prostate cancer risk. In that study, Jian et al. (Jian et al., 2007)reported a reduction of 55% in the odds of having prostate cancer for the highest relative to the lowest quartile of tea consumption (OR: 0.45, 95% CI: 0.25, 0.82). Epidemiological studies from several Western countries, such as the United States, Uruguay, Canada and Netherlands, also support the present findings (see Table 3 and Table 4 in Chapter 2: Literature review). For example, in a population-based case-control study in the United States, Geybels et al. (2013a) included 892

prostate cancer cases and 863 controls, and found an association of drinking at least two cups of tea per day with a 27% reduction in the odds of prostate cancer, when compared to drinking less than one cup per week. Moreover, pooled data from a recent meta-analysis of 8 cohort and 13 case-control studies showed a reduction of 16% in the overall risk of prostate cancer due to tea consumption, when comparing the highest level of tea drinking versus the lowest level (Fei et al., 2014).

In contrast, in a hospital-based case-control study that included 240 prostate cancer patients and 268 controls in Singapore, no significant association with prostate cancer was found for green tea (OR: 1.45, 95% CI: 0.93, 2.27) (Chia et al., 2010a). However, it was unclear whether or not the hospitalisation of their controls could influence their tea consumption because the authors did not report the duration of habitual or cumulative tea drinking exposure. Another hospital-based case-control study in India also did not fully support our findings. Ganesh et al. (2011) simply compared tea drinking status (yes or no) between 123 prostate cancer cases and 167 controls, and concluded that being a tea drinker was not associated with the cancer risk. However, there were several flaws in the methodology of that study. For instance, the cases did not match with the controls in terms of age (the mean age of cases and controls was 64 and 46 years old, respectively). In addition, the authors did not consider the frequency and the amount of tea consumed. A recent meta-analysis of 6 cohort and 1 case-cohort studies concluded the evidence was insufficient to support the protective effect of tea drinking against prostate cancer (Yu et al., 2014). Similar to findings from 4 other meta-analysis studies, most cohort, but not case-control, studies fail to demonstrate a significant association between tea consumption and a reduced risk of prostate cancer (Fei et al., 2014, Kim and Lee, 2012, Lin et al., 2014). It should be remarked that most cohort studies used baseline information regarding habitual tea consumption, albeit the tea drinking habit could change over time. In addition, prostate cancer has a long latent development before being diagnosed clinically. Lack of information about tea consumption during the follow up could influence the strength of association.

The present study shows that cumulative consumption of tea was also associated with a lower odds of having prostate cancer. For those who had kept their habit of tea

drinking for less than 35 years, an inverse association was observed, though not statistically significant (adjusted OR: 0.84, 95% CI: 0.54, 1.29). After 35 years of tea consumption, the association became stronger (adjusted OR: 0.59, 95% CI: 0.37, 0.94). Chi-square test for linear trend was also significant(p for trend = 0.015). Our inverse association was supported by a previous case-control study conducted in China by Jian et al. (2004). In that study, drinking tea for 20 to 40 years was associated with a 68% reduction in the odds of having prostate cancer (OR: 0.32, 95% CI: 0.18, 0.59), and was also dose-responsive. To further investigate the relation between cumulative tea consumption and prostate cancer risk, the present study took into account both frequency and duration of tea consumption together in terms of number of cup-years, defined by multiplying daily number of tea cups and total years of tea consumption. Logistic regression analyses confirmed an inverse association between cumulative tea consumption and the odds of prostate cancer for men who had cumulative exposure of at least 60 cup-years compared to those who had less than 20 cup-years (p for trend = 0.01). These findings suggest that not only frequency and amount of tea drinking, but duration of tea consumption, may exert a protective effect on the development of prostate cancer. However, it would take a long duration of daily tea drinking to show a significant effect. Therefore, tea-based preventive strategy for prostate cancer should consider the cumulative consumption of tea over a long term throughout the life span.

To further investigate the potential influence of habitual tea consumption on the progression of prostate cancer, sub-group analyses were applied for high-grade (Gleason score of 8, 9 or 10) and low-grade prostate cancer (Gleason score 7 or lower), separately. The inverse association between habitual tea consumption and prostate cancer risk appeared to be stronger for the high-grade than the lower grade ones. For instance, reduced risk of prostate cancer was found to be associated with at least 150 cup-years for low-grade cancer, but with only at least 15 cup-years for high-grade cancer. Our findings were consistent with several previous studies. For example, Geybels et al. (2013c) followed up 58,279 Dutch men for 17.3 years, and found an inverse association between tea consumption and the risk of stage III/IV prostate cancer (RR: 0.67, 95% CI: 0.5, 0.91), but not stage I/II nor overall prostate

cancer. In an earlier case-control study of 892 prostate cancer patients and 863 controls conducted in the United States, inverse association with habitual tea consumption was stronger in metastasised prostate cancer (OR: 0.4, 95% CI: 0.18, 0.90) than the localised ones (OR: 0.68, 95% CI: 0.47, 0.97) (Geybels et al., 2013a). The present research findings were further supported by several clinical trials. For instance, in a open label, phase II, randomised-controlled trial involving 113 prostate cancer patients prior to radical prostatectomy, Henning et al. (2014) demonstrated an antineoplastic ability of green tea extract. Specifically, treatment with six cups of tea a day was associated with a reduced level of serum PSA and reduced activity of systemic antioxidant. The authors also found the presence of tea polyphenols in prostate tissue. In view of these findings, habitual tea consumption may have a protective effect on the progression of prostate cancer. It is unknown about the mechanism for this effect. Nevertheless, these findings also indicate a possibility for chemo-preventive treatment of prostate cancer.

It remains unclear about the underlying mechanism for the effect of tea consumption on the risk of prostate cancer. However, evidence from experimental studies have shown that tea, especially green tea, is an important source of antioxidants, and possesses protective effects against the development and progression of prostate cancer cells (Carlsen et al., 2010). Among the variety of tea flavonoids, epigallocatechin gallate (EGCG) is the most important compound in terms of both quantity and antioxidant activity (Bhagwat et al., 2014). Indeed, tea polyphenols can inhibit the proliferation of prostate cancer cells. Such effect becomes stronger when combining EGCG with quercetin, another flavonol in tea (Wang et al., 2012b). Most recent experiments with cancer mice showed that oral administration of EGCG with nano-technology can significantly inhibit the growth of tumour and secretion of PSA (Khan et al., 2014). There are several possible mechanistic effects of tea EGCG to explain its protective effects against the growth of prostate cancer cells. EGCG is believed to induce apoptosis and cell cycle arrest through mitochondria in multiple cell lines. It also acts as a sensitising agent, which is an important constituent of the extrinsic pathway of apoptosis. In addition, EGCG down regulates pro-inflammatory pathway, the insulin like growth factor axis and multiple kinases, which results in the

inhibition of tumour growth. It also reduces the effects of androgens on the progression of prostate cancer cells (Johnson et al., 2010).

5.2.4 Association between coffee consumption and prostate cancer risk in Vietnamese men

Despite the fact that coffee is a rich source of antioxidant, and possesses anticarcinogenic properties, review of the literature showed that existing evidence remains inconclusive in terms of the association between coffee consumption and the risk of prostate cancer. Investigation into the association between habitual coffee drinking and prostate cancer risk was another main objective of the present case-control study. Similar to the investigation into the association between tea consumption and prostate cancer risk, this was the first attempt to ascertain the potential association between coffee consumption and the risk of prostate cancer in Vietnamese men.

As described in Section 5.2.2.2, coffee consumption was highly prevalent in Southern Vietnam. However, results of this study did not show any association between habitual coffee consumption and prostate caner risk in Vietnamese men. At the level of 3 - 7 cups of coffee per week, drinking coffee was associated with a reduced odds of prostate cancer (OR: 0.41, 95% CI: 0.26, 0.66), compared to those who drank less than 3 cups per week. However, no association was found for higher levels of coffee consumption. Test for linear trend also did not exhibit any significant association (p for trend = 0.60). The relationship between coffee consumption and the odds of prostate cancer was not changed after inclusion of potential confounding factors into the logistic regression model. The findings of this research provide limited evidence to support the hypothesis that regular consumption of coffee is associated with a reduced risk of prostate cancer.

The present study was consistent with 5 out of 8 case-control studies on habitual coffee consumption and prostate cancer risk, since 2000 (Arab et al., 2012, Ganesh et al., 2011, Geybels et al., 2013a, Sharpe and Siemiatycki, 2002, Sonoda et al., 2004). Sonoda et al. (2004) compared the habit of daily coffee drinking between 140

Japanese prostate cancer patients and 140 controls, and found that habitual coffee drinking was not associated with the prostate cancer risk (OR: 0.92, 95% CI: 0.40, 2.11). Their findings did not change after adjustment for cigarette smoking and total energy intake. In a more recent study, Geybels et al. (2013a) included 892 prostate cancer cases and 863 population-based controls in their study, but did not find any association between coffee consumption and prostate cancer risk. Their results were consistent for both overall and subgroups (defined by Gleason grade or stage) of prostate cancer. In the present study, logistic regression analyses for Gleason score-based subgroups (low or medium-grade: Gleason score of 7 or lower, high-grade: Gleason score of 8-10) also led to similar results. In both strata, the adjusted odds ratios were not stable, and the association was not significant (data not presented for brevity). It may be argued that prostate cancer risk may be affected by a long-term consumption of coffee. However, in a population-based study of 399 prostate cancer cases and 476 controls in Canada, Sharpe and Siemiatycki (2002) measured the cumulative coffee consumption by total years of daily coffee drinking and total number of drink-years, but failed to confirm any association for both total years and total number of drink-years with the prostate cancer risk. Similarly, the present study measured cumulative coffee exposure by cup-years, yet did not observe any association between total number of cup-years and the risk of prostate cancer (p for trend = 0.68).

In contrast to the present study, a population-based case-control study of 1,499 Swedish prostate cancer patients and 1,112 controls suggested that coffee consumption was associated with a reduced risk of prostate cancer (Wilson et al., 2013). However, the association was not significant for overall or localised prostate cancer. Furthermore, men need to drink at least five cups of coffee a day to reduce the cancer risk. In the two earlier case-control studies, drinking coffee was even associated with an increased risk of prostate cancer, 88% higher risk in Taiwanese men (Chen et al., 2005), and 90% higher risk in Italian men (Gallus et al., 2007). However, there are several issues that should be taken into account when interpreting the results of these two studies. For instance, the prevalence of coffee drinkers was low, 13.1% for the former and 45.5 - 47% for the latter, while the prevalence of

coffee drinker in the present study of Vietnamese men was well over 81%. Moreover, in the former study, the authors simply assessed the association between prostate cancer risk and coffee drinking status (yes or no). In the latter study, it was unclear about the duration of the participants' coffee consumption. Potential influences of food or beverage on the cancer risk depend on various parameters, such as frequency, amount and duration of its consumption.

The present study was not consistent with 4 recent prospective cohort studies (Discacciati et al., 2013, Geybels et al., 2013b, Russnes et al., 2014, Tverdal, 2015), which showed protective effects of coffee drinking against the prostate cancer risk. For example, in one recent study, 224,234 Norwegian men were followed up for 15 years, and among them, 5,740 prostate cancer cases were identified. Tverdal (2015) used baseline information on coffee consumption to assess its association with the prostate cancer risk. The authors reported that prostate cancer risk could be reduced by 16% for men who drank 1 - 4 cups, and 24% for men who drank 9 or more cups of boiled coffee a day, respectively. In those cohort studies, coffee consumption was found to be a protective factor for both localised and advanced prostate cancer. However, the assessment of exposure to coffee was taken at baseline only, despite a long follow-up period (at least 13 years, except for one study which was 6.4 years of follow-up). As pointed out by Lee and Binns (2011), using baseline information on coffee consumption is insufficient to assess its association with the prostate cancer risk, because the habit of coffee drinking could change over time before and after diagnosis of the cancer. Moreover, lack of cumulative exposure to coffee would be problematic in assessment of association with the risk of prostate cancer. Finally, the contradictory findings between those studies and the present study could be attributed to differences in pattern of coffee consumption across the various study populations (Vietnamese versus North American). These differences could also be related to the brewing method (e.g., boiling, filtering or using instant coffee), brand of coffee and cup size. In Vietnam, coffee is usually filtered with much stronger concentration than Western styles such as latte or flat white. Finally, another plausible explanation is the smaller sample size (216 cases and 399 controls) used in comparison to those cohort studies.

5.3 Strengths of the study

This is the first time the association between habitual tea and coffee drinking and the risk of prostate cancer being investigated in Vietnam. This study has made some important contributions in view of several gaps in the current understanding about the protective effects of tea and coffee against prostate cancer. As mentioned previously, Vietnam has a low incidence of prostate cancer, albeit it has experienced an upward trend in the incident cases over the last decade. However, prostate cancer has received little attention so far, especially its risk factors. This study attempts to provide information about the relationship between tea, coffee consumption and the risk of prostate cancer.

There are several strengths of study. Firstly, the statistical analysis was based on a validated method of assessment of tea and coffee exposure as well as other dietary habits. The habitual consumption of tea and coffee was assessed in detail, namely through number of standard cups per day, week, month or year; the number of years of consumption; and whether or not a change in the habit within three years prior to interview. The availability of duration of tea and coffee consumption allowed us to assess for cumulative exposure to tea and coffee drinking in relation to the risk of prostate cancer. Furthermore, the questionnaire used in the study included all plausible confounding factors such as cigarette smoking, physical activity and total energy intake. The questions to obtain information on these factors were adapted from validated questionnaires, such as “STEPwise approach to chronic disease risk factor surveillance” (World Health Organisation, 2012),and the Vietnamese version of a food frequency questionnaire that had been developed and validated in Southern Vietnam (Hong et al., 2010). In particular, the food frequency questionnaire used had been piloted and validated for older Vietnamese adults (Tran et al., 2013) before its application in this study. The food items used were selected from previous questionnaires developed and validated in Vietnam, and also taken from a book of 400 most popular dishes in Vietnam (Hung, 2001). All food items were quantifiable. During the interview, family members who were in the same household as the study subjects were also involved to help in recalling or providing additional information on dietary habits. Therefore, recall error was minimised.

Another strength of the study is the rapid ascertainment of cases. Most of the cases were approached shortly before their biopsy operation. Interview was undertaken within one or two days after histological confirmation. Consequently, the recall ability of the cases were less likely to be affected. Furthermore, their dietary habits or lifestyle were also less likely to be changed due to treatment or advice from doctors, therefore, there is little chance for recall bias. Moreover, all identified cases were approached and enrolled into the study without any loss due to severity or mortality of the cancer.

Finally, the present study was designed to minimise misclassification case-control status. For case recruitment, the histological confirmation was the first criteria. Therefore, there could be some false negative cases, but very small probability of false positive cases. This mean, all the recruited cases were actual cases. For controls recruitment, almost all of the eligible controls were tested for serum PSA level. Only men with serum PSA less than 4 ng/ml were recruited. Admittedly, there might be some cases diagnosed with prostate cancer at serum PSA level of less than 4 ng/ml. However, the chance was small. In addition, prostate cancer in Vietnam is low incident and low prevalent. Therefore, if some cases were indeed misclassified as controls, the percentage should be very small. Even though, such misclassification, if existed, would weaken the actual strength of the inverse association between tea consumption and the risk of prostate cancer. In other words, the actual protective effect of habitual tea drinking would be even stronger than that observed in the present study (i.e in favour of the alternative hypothesis).

5.4 Limitations of the study

Despite the above strengths, several limitations should be considered when interpreting the results. Firstly, due to the nature of case-control study design, recall about past events is subjected to bias, particularly when comparing cases with controls. Cases tend to recall more precisely than the controls about their exposures related to a particular health condition. However, in the present case-control study, participants were asked about their habit of drinking tea and coffee, which are the

most popular beverages in Vietnam. Moreover, prostate cancer is low in both incidence and prevalence, and no epidemiological study about risk factors of prostate cancer has ever been undertaken in Vietnam. Therefore, tea and coffee are quite "neutral" in terms of association with prostate cancer as perceived by participants. In addition, the interview was carried out with help from their next of kin to recall the past dietary habits. Thus, there should be little difference between cases and controls in terms of recalling their habit of tea and coffee drinking.

One might argue that the three-year time frame was too long to recall, and therefore, the information about tea and coffee consumption might not be precise. The focus of this study was not on the exact quantity of the beverages consumed at a particular point of time, but on the habit of drinking tea and coffee. Moreover, such habit is mostly daily or weekly which should not be difficult to recall. In addition, questions about tea and coffee drinking habit had been demonstrated to be reliable and valid for old adults in Vietnam (Tran et al., 2013).

It could also be argued that green tea is a proxy for a healthy lifestyle, and that a lower risk of prostate cancer may not be associated with tea consumption but with a general healthy lifestyle instead. This argument is not convincing for several reasons. Firstly, there is no evidence to suggest that regularly green tea drinking implies a healthier lifestyle. In Vietnam, men tend to drink more tea than women, and they can drink tea at any time, even while smoking. Also, men attend alcoholic meals more often than women, and they usually drink tea after the meal. Secondly, both univariate and multivariate logistic regression models showed a significant association between tea drinking and decreased risk of prostate cancer. In the multivariate logistic regression model, plausible and established protective and risk factors have been accounted for. Therefore, it is unlikely that inverse association observed in the present study was due to chance or confounding. Nevertheless, there was still the possibility of residual confounding effect.

Reserve causation is another concern, albeit small. It is possible for a change in diet and habit of tea drinking after onset of cancer symptoms or after diagnosis of the cancer. However, this possibility is unlikely due to several reasons. Firstly, prostate cancer is a latent disease and there are no specific symptoms. Late symptoms are

usually related to the obstruction of lower urinary tract that usually leads to medical examination and treatment. Almost all cases were recruited immediately after histological confirmation was made. Some cases were even interviewed before their diagnosis. Also, no adverse effect of tea on prostate cancer has been reported. Therefore, it is less likely that the tea drinking habit had been changed because of the cancer. In fact, only 6.5% of cases reported a change in tea drinking habit. This low proportion and the pattern of change in tea consumption were similar between cases and controls (see Table 17).

Lack of detailed clinical information poses another weakness of this study. It was unable to access the patients' medical records. After being confirmed with histological examination, cases went to different hospitals for their treatment. Therefore, we were unable to collect information about their stage of the cancer, the status of metastasis and other biochemical test results. The histological result can only provide information about Gleason score, which is more important for prostate cancer diagnosis.

Another weakness of the present study is the lack of histological confirmation for all controls. However, serum PSA level plus total score of prostate symptoms (see Table 15) were used to screen potential cases. As explained before, prostate cancer is a low incident disease in Vietnam, if happened, only a few cases would be misclassified as controls. Such misclassification bias usually leads to underestimation of the strength of the association. In other words, the actual association between tea consumption and reduced risk of prostate cancer could be even stronger. Furthermore, The assessment of diet is can be inaccurate and unreliable based on FFQ, because of inherent measurement errors can bias the results towards the null hypothesis.

Finally, the control group might include some men benign prostate hyperplasia due to a high prevalent of this condition at the age of recruitment. Since there is some evidence to suggest that benign prostate hyperplasia is a precursor of prostate cancer, albeit not conclusive, inclusion of these controls may alter the apparent association between tea and coffee consumption and the risk of prostate cancer. However, if it

was indeed the situation, the strength of the association would be weakened, while the inverse association would be stronger.

Chapter 6: Conclusion and recommendation

6.1 Prostate cancer in Vietnam

Prostate cancer is low incident in Vietnam. It ranked 9th among the most common cancers. In the global map of prostate cancer incidence, Vietnam has been recognised as one of the lowest countries in the world. Despite an upward trend in the past decade, the age standardised rate of incident cases remains low compared to the overall global rate (4.7 per 100,000 versus 31.1 per 100,000). On average, prostate cancer patients in Vietnam are diagnosed at 68.4 years old, and at medium (30.6%) and high (56.0%) grade of the cancer. Late diagnosis of prostate cancer in Vietnam could be due to lack of attention to the disease from both patients and general practitioners. In particular, there has been no practice of early screening in Vietnam for the disease. Most patients only visit a medical facility when they have problem with their urination that they cannot postpone.

6.2 Tea and prostate cancer

The association between habitual tea drinking and the risk of prostate cancer in Vietnam was investigated in this case-control study. The findings of the study confirm the inverse association between daily tea drinking and the risk of prostate cancer in Vietnamese men. Specifically, drinking above 100 ml of liquid tea per day could reduce the risk by at least 43%. However, the duration of habitual tea drinking needs to be long enough to exhibit an protective effect. The results showed the inverse association between tea drinking and prostate cancer risk became apparent after 35 years of consumption. In addition, the dose-response relationship was found to be significant. This held for both frequency and duration of tea drinking, and cumulative tea consumption in particular.

The protective effect of daily tea consumption appears to be stronger in high-grade prostate cancer than medium or lower grade prostate cancer for Vietnamese men. This finding is consistent with previous studies which suggested that the inverse association between habitual tea drinking and prostate cancer risk was more apparent

in higher grade prostate cancer. Some studies even reported the inverse association being only observed in the advanced stage of the cancer.

Findings of this study have important implications towards the prevention of prostate cancer, with tea being the second most popular beverage worldwide, after water. Nevertheless, further investigations are required before generalising the findings from Vietnam to other populations or to make recommendation for public health practice.

6.3 Coffee and prostate cancer

Unlike tea consumption, habitual coffee drinking appears not to be associated with the risk of prostate cancer. This case-control study found little association between regular consumption of coffee and the risk of prostate cancer. Neither frequency of coffee drinking (number of cups per week) nor the duration of the habit (number of years of drinking coffee) was significantly associated with prostate cancer risk. The association was not apparent even after taking cumulative coffee consumption (number of cup-years) into account. The results of this study about coffee drinking and prostate cancer risk are consistent with previous reports supporting the null hypothesis. Admittedly, some recent studies reported a protective effect of coffee drinking against the prostate cancer risk. However, there are great variations in cultures and the way of drinking coffee between countries. Therefore, any significant association observed in one population might not be able to carry over to another population. Further investigations should be undertaken to obtain conclusive evidence to confirm the relationship between habitual coffee drinking and the risk of prostate cancer.

6.4 Recommendations

Despite a growing body of evidence on the protective effect of regular tea consumption on the risk of prostate cancer, it remains inconclusive to generalise any recommendation for the public in terms of the prevention of prostate cancer.

Therefore, further research into the issue is recommended to establish stronger epidemiological and clinical evidence. There are several areas that futures studies should consider:

- Biomarkers of tea and coffee in human body, such as EGCG: How is tea or coffee involved in the development and progression of prostate cancer cells?
- Study of other dietary and nutritional factors such as tomato lycopene, soy food isoflavones, and lifestyle factors such as alcohol consumption, physical activity and so on.
- New approach to measure tea and coffee exposure in relation to the prostate cancer risk. Recall of past dietary habits is subjected to bias and error. Alternative approaches, such as repeated measures over time or using a food diary, could provide useful information in addition to the baseline food frequency questionnaire.
- Higher level of study designs should be employed, such as prospective cohort study or clinical trial. Although the case-control study design is more feasible in the setting of Vietnam, the level of evidence is not strong enough to be conclusive.
- Impact of regular tea and coffee drinking on survival of prostate cancer. There is evidence suggesting that the protective effect of tea consumption on prostate cancer risk is stronger in advanced stage than early stage. However, its effect on the survival of the cancer is unknown. Using the present case-control study as baseline data, a prospective cohort study is recommended to assess the effect of tea consumption on survival of prostate cancer and mortality due to this cancer.
- To account for the different outcomes (no prostate cancer, low- or medium-grade prostate cancer and high-grade prostate cancer), a multinomial logistic regression model incorporating the three different levels can be fitted.

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Appendices

Appendix 1 Ethics approval letter

Curtin University

Memorandum

To	Professor Andy Lee, School of Public Health
From	Professor Stephan Millett, Chair, Human Research Ethics Committee
Subject	Protocol Approval **HR 109/2012**
Date	18 October 2012
Copy	Mr Van Dong Hoang School of Public Health Professor Colin Bins School of Public Health

Office of Research and Development
Human Research Ethics Committee

TELEPHONE 9266 2784
FACSIMILE 9266 3793
EMAIL hrec@curtin.edu.au

Thank you for providing the additional information for the project titled "*Tea, coffee and prostate cancer: a case-control study in Vietnam*". The information you have provided has satisfactorily addressed the queries raised by the Committee. Your application is now **approved**.

- You have ethics clearance to undertake the research as stated in your proposal.
- The approval number for your project is **HR 109/2012.** *Please quote this number in any future correspondence.*
- Approval of this project is for a period of twelve months **16-10-2012** to **16-10-2013**. To renew this approval a completed Form B (attached) must be submitted before the expiry date **16-10-2013**.
- It is your responsibility, as the researcher, to meet the conditions outlined above and to retain the necessary records demonstrating that these have been completed.

Applicants should note the following:

It is the policy of the HREC to conduct random audits on a percentage of approved projects. These audits may be conducted at any time after the project starts. In cases where the HREC considers that there may be a risk of adverse events, or where participants may be especially vulnerable, the HREC may request the chief investigator to provide an outcomes report, including information on follow-up of participants.

The attached **FORM B** should be completed and returned to the Secretary, HREC, C/- Office of Research & Development:
When the project has finished, or

- If at any time during the twelve months changes/amendments occur, or
- If a serious or unexpected adverse event occurs, or
- 14 days prior to the expiry date if renewal is required.
- An application for renewal may be made with a Form B three years running, after which a new application form (Form A), providing comprehensive details, must be submitted.

Yours sincerely

Professor Stephan Millett
Chair Human Research Ethics Committee

Appendix 2 Approval letter from Binh Dan Hospital

Binh Dan Hospital
371 Dien Bien Phu Street, Ward 4, District 3
Ho Chi Minh City, Vietnam
Tel: (84) 8394747 – (84) 8325154, Fax: (84) 8391315
Email: bvbinhdan@hcm.vnn.vn
Website: http://www.bvbinhdan.com.vn

HCM, February 12th, 2012

School of Public Health
Faculty of Health Sciences, Curtin University
GPO Box U1987
Perth, Western Australia 6845

To whom it may concern,

In response to the request from Dr. Hoang Van Dong, PhD candidate from Curtin University, for the implementation of the research study "Tea, coffee and prostate cancer: A case-control study in Vietnam", Binh Dan Hospital allows Dr. Hoang Van Dong to conduct all necessary field work and data collection at the hospital for a 3-year period (tentatively starting from October 2012). The proposed project to be conducted has been approved by the Director Board of this hospital. Our hospital will provide assistance in the recruitment of prostate cancer patients and access to medical records.

Please feel free to contact us for any further information.

Yours sincerely,

Associate Prof. Chuyen Vu Le, MD, PhD

Vice director and Chief of Urology Department

Email: vulechuyen@hotmail.com

Appendix 3 Information letter

School of Public Health
GPO Box U 1987
Perth, WA 6845, Au

PARTICIPANT INFORMATION SHEET

PROJECT: Tea, coffee and Prostate Cancer: A Case-Control Study In Vietnam

My name is Hoang Van Dong. I am a medical and public health researcher, and have a Degree of General Medical Doctor from Vietnam and a Master of Public Health degree from Curtin University, Australia. I am investigating the lifestyle factors relating to the development of prostate cancer in Vietnamese men. In this research project, I will interview men with and without prostate cancer. I am interested to find out what you eat and drink as well as your lifestyle habits such as smoking and alcohol consumption. I will also ask you several questions regarding your health status and demographic details. Each face-to-face interview will take about 40 minutes to complete.

Your participation in this project is completely voluntary. You can refuse any specific question that you are uncertain or find it difficult to answer. During the interview, if you decide to withdraw from the project, please feel free to do so because there will be no negative consequences, especially with respect to the treatment you are receiving at this hospital. I can assure you that your treatment or therapy will not be affected at all by participation in this research project.

After you have signed the enclosed consent form, I will assume that you have agreed to participate, and you allow me to use your data in this research project. The information you provided will be kept strictly confidential, and your identity will remain anonymous. Only aggregated data from all participants will be analysed and reported.

Please be assured that your information will only be accessed by the chief investigators of this project, and not anyone else. In particular, it will not be released to the medical staff and authority of this hospital. Your completed questionnaire and other documents will be kept in a locked cabinet for five years at Curtin University before being destroyed.

This study has been approved by the Curtin University Human Research Ethics Committee (Approval Number HR109/2012). The Committee is comprised of members of the public, academics, lawyers, doctors and pastoral carers. If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University, GPO Box U1987, Perth 6845 or by telephoning 92662784 or by emailing hrec@curtin.edu.au.

If you require further information about this study, please do not hesitate to contact me.

Thank you very much for your participation in this research project. Your contribution is important and greatly appreciated.

Yours sincerely,

Hoang Van Dong

Phone: +61 451984088; Email: vandong.hoang@student.curtin.edu.au

Appendix 4 Consent form

CONSENT FORM

for

PROJECT: Tea, coffee and Prostate Cancer: A Case-Control Study In Vietnam

I, _____, have read the information on the attached sheet, and have been informed about the purpose of this research project.

I agree to participate in this project, but have the option to change my mind and withdraw at any time.

I agree to take part in an face-to-face interview where my answers will be transcribed onto a questionnaire.

I understand that all information provided by me will be treated as confidential and that my identity will remain anonymous.

I understand that no individual data will be used except in aggregated form for subsequent reporting purpose.

Name of participant	Signature of participant	Date
_____	_____	_____
Name of witness	Signature of witness	Date
_____	_____	_____

Patient's medical record number:	

Appendix 5 Questionnaire (English version)

Questionnaire
Case-Control Study on Risk and Protective Factors of Prostate Cancer in Vietnam

The interviewee is:	**[ ] Case**	**[ ] Control**
Questionnaire ID:	CA/____/____ *Case/"hospital number"/ "case number"*	CO/____/____/____ *Control/"hospital number"/"control number"*
Diagnosis:		
Medical record ID:		
Department :		
Hospital:	[ ] Binh Dan [ ] Medic center [ ] Binh Thanh PMC	
Date of interview:	_____/_____/_____ *(dd/mm/yyyy)*	
Date of completion:	_____/_____/_____ *(dd/mm/yyyy)*	
Interviewer ID:		

Structure of the questionnaire:

A. Demographic information and lifestyle characteristics
B. Medical and family history
C. Clinical information (interview and extract from medical record)
D. Tea and coffee consumption and other dietary habits (Food frequency questionnaire)

A. Demographic information and life-style characteristics		
1	Name of interviewee:	
2	Resident address	
	Number: ; Street: commune/ward:	
	District: ; Province:	
3	*Contact address*	*[ ] As above [ ] Different*
	Number: ; Street: commune/ward:	
	District: ; Province:	
4	Contact number (home phone/ mobile)	[...../.....]
5	Date of Birth	____/___/ ____ *(dd/mm/yyyy)* Or age: .....years
6	Marital status	0 [ ] Never married 1 [ ] Married 2 [ ] Widowers/divorced/separated
7	Age at marriage	.....years
8	Number of children	.....children
9	What is the highest level of education you have completed?	0 [ ] No formal education 1 [ ] Primary school 2 [ ] Secondary school 3 [ ] High school

Physical activity		
Before the disease, how long, on the average, <u>in a day (/week)</u> did you spend in the following <u>sitting</u> activities?		
10	Sitting in car or bus	…..hrs…....mins/day **Or** : …..hrs…....mins/week
11	Riding on motorbike	……hrs…....mins/day **Or** : ..…hrs…....mins/week
12	Sitting at work (e.g. sewing, at office or factory…)	……hrs…....mins/day
13	Other sitting activities (e.g. watching TV, eating meals, reading, playing cards, listening radios, sufing the internet…)	……hrs…....mins/day
14	Sleeping time (including afternoon naps)	……hrs…....mins/day
15	*Lifelong physical activity involvement was defined as '(doing) active sports or vigorous exercise or work long enough to get sweaty, at least twice a week'*	
	How would you describe your physical fitness activity over your entire life course?	0 [ ] Never been much involved 1 [ ] Previously active but not any more 2 [ ] Active just recently 3 [ ] Intermittently active 4 [ ] Always been involved

Before the disease, how long, on the average, <u>in a day (/week)</u> did you spend in the following <u>physical</u> activities?		
16	Strenuous sports (i.e. jogging, bicycling on hills, tennis, badminton, swimming, aerobics)	:……hrs…....mins/week
17	Vigorous work (i.e. moving heavy furniture, shovelling, weight lifting, loading/ unloading trucks, or equivalent manual labour)	……hrs…....mins/week
18	Moderate activity (i.e. housework, brisk walking, golfing, bowling, bicycling on level ground, gardening, walking, Taichi)	….....hrs…....mins/day **Or** : ….....hrs…....mins/week

Exposure to cigarette smoking and indoor pollutants			
19	Are you a	0 [ ] never smoker? 1 [ ] former smoker? 2 [ ] current smoker?	*If not, => F13*
20	On average, how many of the following tobacco products do you smoke per day?	Manufactured cigarettes? Hand-roll cigarettes? Pipes full of tobacco? Cigars, cheroots or cigarillos? Number of water pipe sections? Any others? Specify……..	..... per day ..... per day ..... per day ..... per day ..... per day ..... per day ..... per day
21	How many years have (had) you been smoking?	……. years	
22	Are your relatives/people living with you smoking at home?	0 [ ] No 1 [ ] Yes	

B. Personal medical and family history		
1	Have you had any health problem related to prostate gland?	0 [ ] No 1 [ ] Yes
2	*Benign prostate hyperplasia?*	0 [ ] No 1 [ ] Yes If yes, year of diagnosis:.....
3	*Prostatitis?*	0 [ ] No 1 [ ] Yes If yes, year of diagnosis:.....
4	Have you ever had gonorrhoea or syphilis?	0 [ ] No 1 [ ] Gonorrhoea 2 [ ] Syphilis
5	Have you had any disease related to urinary tract, such as?	0 [ ] No 1 [ ] Kidney stone 2 [ ] Bladder infection 3 [ ] Urinary tract infection 4 [ ] Urinary retention 5 [ ] Other urinary obstructions
6	Have you undergone any surgery, such as?	1 [ ] Vasectomy 2 [ ] Prostectomy 3 [ ] Emasculation 4 [ ] Other:…….

7	Currently, have you had any chronic disease, such as?	0 [ ] No 1 [ ] Hypertension 2 [ ] Cardiovascular diseases 3 [ ] Hypercholesteron 4 [ ] Diabetes 5 [ ] Other, ……
8	In your family, is there anyone who has suffered from prostate cancer?	0 [ ] No 1 [ ] Yes
9	*If yes, is he your?*	1 [ ] father 2 [ ] brother 3 [ ] uncle 4 [ ] cousin

International prostate symptom score (IPSS)								
		Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your score
1	**Incomplete emptying** Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
2	**Frequency** Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
3	**Intermittency** Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4	**Urgency** Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5	
5	**Weak stream** Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
6	**Straining** Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
7	**Nocturia**	None	1 time	2 times	3 times	4 times	5 times or more	Your score
	Over the past month, many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5	

8	**Quality of life due to urinary symptoms**	Delighted	Pleased	Mostly satisfied	Mixed – about equally satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Terrible
	If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

C. Clinical information		
1	Diagnosis at hospital:	1 [ ] prostate cancer (PCa) 2 [ ] Benign prostate hyperplasia (BPH) 3 [ ] other, _____
2	Date of diagnosis	...../ …../ …. *(dd/mm/yyyy)*
3	*Digital rectal examination (if C1=PCa or BPH):*	……
4	*Ultrasonographic result (if C1=PCa or BPH):*	……
5	*Biopsy test result (if C1=PCa or BPH):*	……
6	*PSA level (if available):*	*Total PSA: ..... ng/ml; Free PSA:.....ng/ml or ……..%*
7	Fasting blood glucose	……mmol/l
8	Triglycerides	……mmol/l
9	LDL cholesterol	……mmol/l
10	HDL cholesterol	……mmol/l
11	Total cholesterol	……mmol/l

Anthropometric measurements			
I would now like to measure your blood pressure, pulsatile, height, weight, and your hip and waist circumferences. To do so, I would like you to follow my instructions so as we can obtain more exact measurements.			
1	Blood pressure (I will measure 2 times your arterial blood pressure and your pulse rate at your left arm)		
1.a	Measurement time 1	Systolic Diastolic Pulse rate/minute	……..mmHg ……..mmHg ……
1.b	Measurement time 2	Systolic Diastolic Pulse rate/minute	……..mmHg ……..mmHg ……
2	Height	___ ___ ___.___	Centimetres
3	What is your weight three years ago?	___ ___ ___.___	Kilograms
4	Current weight	___ ___ ___.___	Kilograms
5	Waist circumference	___ ___ ___.___	Centimetres
6	Hip circumference	___ ___ ___.___	Centimetres

D. Food frequency questionnaire

(Please tell us about your dietary habits 3 years ago)

General dietary habit – please recall your habit three years ago

No	Questions	Answer
1	Are you on a special diet listed below now or 3 years ago?	0 [ ] No 1 [ ] Vegetarian 2 [ ] Low fat 3 [ ] Low salt 4 [ ] other: ……
2	Do you have meals regularly (having 3 meals per day)	1 [ ] Regularly 2 [ ] Occasionally irregular 3 [ ] Sometime irregular 4 [ ] Often irregular
3	Your eating habit *Eating breakfast:* 1 [ ]everyday 2 [ ]frequently 3 [ ]occasionally 4 [ ] never *Take-away food or eating out:* 1 [ ]everyday 2 [ ]frequently 3 [ ]occasionally 4 [ ] never *Eating snacks (Biscuits):* 1 [ ]everyday 2 [ ]frequently 3 [ ]occasionally 4 [ ] never *Eating sweet food (candy. ...):* 1 [ ]everyday 2 [ ]frequently 3 [ ]occasionally 4 [ ] never	
4	Did you or any of your family members feel your food was salty?	0 [ ] never 1 [ ] sometimes 2 [ ] usual
5	When you eat meat, did you trim off all the fat?	0 [ ] never 1 [ ] sometimes 2 [ ] usual
6	When you ate chicken, did you eat the skin	0 [ ] never 1 [ ] sometimes 2 [ ] usual
7	How often do you eat the following types of food? *(times per **Y**ear/**M**onth/**W**eek/**D**ay?)* *Fried food:* ..... times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D** *Smoked food:* ..... times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D** *Cured food:* ..... times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D** *Grilled food:* ..... times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	
8	How often do you use vegetable cooking oil?	..... times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**
9	How often do you use pork lard?	..... times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**
10	When you eat, how often do you use the following seasonings? *Fish sauce:* ..... times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D** *Salt:* ..... times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D** *Soybean sauce:* ..... times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D** *Tomato sauce:* ..... times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	
11	*Within the last 3 years, have you changed you diet habit*	0 [ ] No 1 [ ] Yes
12	*If yes,please specify:* *- How you have changed: ……* *- The reasons for this change: ……*	

Consumption of beverage - *How often/what amount of/ when did you eat the following alcohol? – Please tell us about your dietary habits 3 years ago.*

No	40	Frequency Per **Y**ear/**M**onth/**W**eek/**D**ay	Unit (PS: portion size)	Quantity/ each time (PS)	For how many years?
13	Beer	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	*300ml cup*		
14	Home-made rice	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	*30ml cup*		
15	Home-made herbal	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	*30ml cup*		
16	Strong bottled liquor	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	*30ml cup*		
17	Light bottled liquor	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	*30ml cup*		
18	Red wine	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	*100ml cup*		
19	White wine	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	*100ml cup*		
20	Within the last 3 years, have you changed your drinking habit for any type of liquor above?			0 [ ] No 1 [ ] Yes	
If yes, please tell us the reasons for that change?					
21	Green tea (dried)	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	*100ml cup*		
22	Green tea leave	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	*200ml cup*		
23	Black tea	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	*100ml cup*		
24	Oolong tea	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	*100ml cup*		
25	Within the last five years, have you changed your drinking habit for any type of tea above?			0 [ ] No 1 [ ] Yes	
If yes, please tell us the reasons for that change?					
26	Black coffee	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	*150ml cup*		
27	Instante coffee	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	*Bag* *5gr spoon*	*.....bag* *....spoon*	
28	Milk coffee	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	*150ml cup*		
29	Within the last 3 years, have you changed your drinking habit for any type of coffee above?			0 [ ] No 1 [ ] Yes	
	If yes, please tell us the reasons for that change?				
30	Water	_____times/day	*250ml cup*	_____cup	
31	Soy milk	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	*250ml cup*	_____cup	
31	Lemon water	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	*250ml cup*	_____cup	
33	Orange water	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	*250ml cup*	_____cup	
34	Coconut juice	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	*250ml cup*	_____cup	
35	Fruit shake juice	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	*250ml cup*	_____cup	
36	*What type of fruits did you drink the most?*	1 [ ] mango 2 [ ] guava 3 [ ] water melon	4 [ ] avocado 5 [ ] custard apple 6 [ ] paw paw		
37	Soft drink (coke,	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	*250ml cup*	_____cup	
38	*What type of soft drinks did you drink the most?*	1 [ ] Coca cola 2 [ ] Pepsi 3 [ ] Fanta	4 [ ] Nestea 5 [ ] Icetea 6 [ ] Other canned soft drink		
39	Did you add sugar into your drinks, such as tea, coffee or orange juice? *If yes, how many spoons (5g) did you add?*		0 [ ] No 1 [ ] Yes, …….spoons		

Consumption of soy bean products, vegetables and fruits - *How often do you eat soy bean products?*				
No	**Food item**	**Frequency** (per month/week/day)	**Unit (PS)**	**Quantity/meal?** (½ PS, 1PS, 1.5PS...)
40	Fried tofu	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Piece (**I**)	_____PS
41	Raw tofu	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Piece (**I**)	_____PS
40	Soybean curd with sweet syrup	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small bowl (**J**)	_____PS
Vegetables- *How often/what amount of/ when did you eat vegetables?*				
43	Tomato	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Whole	_____PS
44	Bean sprout	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small bowl (**L**)	_____PS
45	Amaranth, Jute potherb	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small bowl (**L**)	_____PS
46	Chinese vegatabes (Kai choy, Buck choy, Kai lan,...)	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small bowl (**L**)	_____PS
47	Mustard green, Chinese cabbage	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small bowl (**L**)	_____PS
48	Malabar nightshade	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small bowl (**L**)	_____PS
49	Crown-daisy	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small bowl (**L**)	_____PS
50	Chinese leek	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small bowl (**L**)	_____PS
51	Cabbage	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small bowl (**L**)	_____PS
52	French bean	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small bowl (**L**)	_____PS
53	Pumpkin	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small bowl (**L**)	_____PS
54	Gourd	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small bowl (**L**)	_____PS
55	Cucumber	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small bowl (**L**)	_____PS
56	Broccoli	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small bowl (**L**)	_____PS
57	Chinese yam	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small bowl (**L**)	_____PS
58	Ash gourd, wax gourd	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small bowl (**L**)	_____PS
59	Bitter melon	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small bowl (**M**)	_____PS
60	Capsicum	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small bowl (**N**)	
61	Carrot	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Whole (**O**)	_____PS
63	White potato	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Whole (**O**)	_____PS
64	Sweet potato	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Whole (**P**)	_____PS
Consumption of fruits - *How often/what amount of/ when did you eat fruit?*				
65	Dragon fruit	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Whole	_____PS
66	Banana	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Whole	_____PS
67	Papaya	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Piece 20x4cm (**Q**)	_____PS
68	Pomelo	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Piece (**R**)	_____PS
69	Longan	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Kg	_____kg
70	Orange	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Whole	_____PS
71	Water melon	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Piece (**S**)	_____PS
72	Pear	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Whole	_____PS
74	Grape	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Kg	_____kg
75	Guava	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Whole	_____PS
76	Apple	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Whole	_____PS
77	Lychee	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Kg	_____kg

78	Durian	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Piece (**T**)	_____PS
79	Mangoes	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Whole	_____PS

Consumption of sweet varieties - *How often/what amount of/ when did you eat sweet varieties?*				
No	**Food item**	**Frequency** (per month/week/day)	**Unit (PS)**	**Quantity/meal?** (½ PS, 1PS, 1.5PS...)
80	Sweet soup (made of glutinous rice and bean, corn…)	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	250 ml cup (**U**)	_____PS
81	Please choose 3 types that you eat the most oftenommon?		1 [ ] Glutinous soup with taro 2 [ ] Glutinous soup with corn 3 [ ] Glutinous soup with mung bean 4 [ ] Glutinous soup with black bean 5 [ ] Glutinous soup with white bean 6 [ ] Mix glutinous soup with bean 7 [ ] Other:.....	
82	Sweet cakes	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Piece (**V**)	_____PS
83	Biscuits	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Piece	_____PS
Consumption of bread and rice varieties - *How often/what amount of/when did you eat the following items?*				
84	French type bread (either plain or with meat)	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Load (**W**)	_____PS
85	sliced bread (either plain or with meat)	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Slice	_____PS
86	Rice-based noodles	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Large bowl (**X**)	_____PS
87	wheat-based noodles	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Large bowl (**X**)	_____PS
88	Instant noodle	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Bag	_____PS
89	Plain rice (at home)	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small bowl	_____PS
90	Rice comes in a serving (a plate of fried rice, broken rice…) when eating outside	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Plate	_____PS
91	Glutinous rice (either plain, with bean, or salted)	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small bowl	_____PS

Consumption of meat- *How often/what amount of/when did you eat?*				
No	**Food item**	**Frequency** (per month/week/day)	**Unit (PS)**	**Quantity/meal?** (½ PS, 1PS, 1.5PS...)
91	Pork lean	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small piece (**Y**)	_____PS
92	Pork medium fat	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small piece (**Z**)	_____PS
93	Pork rib	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small piece (**AA**)	_____PS
94	Pork lower leg	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small piece (**BB**)	_____PS

95	Pork steak	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Piece 60g (**CC**)	_____PS
96	Beef	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small bowl (**DD**)	_____PS
97	Chicken	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small piece (**EE**)	_____PS
98	Muscovy duck	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small piece (**FF**)	_____PS
99	Duck	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Small piece (**FF**)	_____PS
10	Pork heart	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	gram	_____gr
101	Pork liver	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	gram	_____gr
102	Pork kidney	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	gram	_____gr
103	Chicken heart	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	gram	_____gr
104	Chicken liver	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	gram	_____gr
105	Chicken kidney	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	gram	_____gr
Consumption of fish, egg and milk- *How often/what amount of/when did you eat?*				
106	Sea fish (Mackerel, tuna...)	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Piece 70g (**GG**)	_____PS
107	*Please check two types of sea fish that you eat the most often?*		1 [ ] Mackerel 2 [ ] Tunal 3 [ ] Mullet 4 [ ] other, specify……..	
108	Fresh water fish (Tilapia...)	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Piece 50g (**HH**)	_____PS
109	*Please check two types of fresh water fish that you eat the most often?*		1 [ ] Tilapia 2 [ ] Snake-head 3 [ ] Carp 4 [ ] Chep 5 [ ] Other, specify……..	
110	Shrimp	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	whole (**II**)	_____PS
111	Squid/octopus	times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Piece (**JJ**)	_____PS
Egg				
112	Chicken egg	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	whole	_____PS
113	Duck egg	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Whole	_____PS
Preserved food				
114	Pickle vegetable & garlic	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	gram	gr
115	Fermented soy product	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	gram	gr

116	Salted fish	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	gram	gr
117	Preserved meat (sausage…)	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	gram	gr
Milk				
118	Cow whole milk	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Cup 250ml	_____PS
118	Soya milk	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Cup 250ml	_____PS
120	Milk powder, whole	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	5gr spoon (**H**)	_____PS
121	Yogurt	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Box	_____PS
122	Condensed milk	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	ml (**C**)	_____PS

Dietary supplements - *How often/what amount of/when did you use?*

No.	**Item**	**Frequency**	**Unit**	**Quantity / time (unit)**	**Years of use**
121	Multivitamin	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Tablet		
122	Vitamin A	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Tablet		
123	Vitamin C	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Tablet		
124	Vitamin E	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Tablet		
125	Riboflavin (Vitamin B6)	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Tablet		
126	Calcium	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Tablet		
127	Selenium	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Tablet		
128	Iron	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	Tablet		
129	Ginseng	___times/[ ]**Y** [ ]**M** [ ]**W** [ ]**D**	bag		

A. 300ml cup

B. 30ml cup

C. 100ml cup

D. 150ml cup

E. 200ml cup

F. Black coffee

G. Milk coffee

H. 5gr spoon

I. Fried tofu

J. Soybean curd with sweet syrup

K. Tomato

L. Small bowl of vegetable

M. Bitter melon

N. Capsicum

O. Potato and carot

P. Sweet potato

Q. Paw paw

R. Pomelo

S. Water melon

T. Durian

U. Sweet soup

V. Sweet cakes

W. F-type bread

X. Noodle

Y. Pork lean

Z. Pork meat

AA. Pork rips

BB. Low pork leg

CC. Pork steak

DD. Beef

EE. Chicken

FF. Duck meat

GG. Sea fish (70g)

HH. Fresh water fish (50g)

II. Shrimp

JJ. Squid

KK.