Investigating the Occupational Etiology of Prostate Cancer in Canadian Men

by

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Abstract

Prostate cancer is one of the most commonly diagnosed cancers worldwide and the etiology of prostate cancer is poorly understood. Aside from non-modifiable factors, there is limited understanding of modifiable risk factors for prostate cancer, including occupation. In epidemiological studies, job titles are generally classified into occupational or more broadly industry groupings. Previous studies have reported inconsistent findings between occupation, industry, and prostate cancer, with weak associations for farming and agriculture, rubber manufacturing, and transportation. In Canada, there have been very few large population studies that include a range of occupation and industry groups, prostate cancer outcomes, and information on non-occupational factors. The purpose of this thesis was to further investigate the occupational etiology of prostate cancer in Canadian men. By identifying occupations and industries using multiple large Canadian population based datasets, we aimed to identify consistent patterns of the multi-faceted prostate cancer – job-industry relationships. Three population based studies and one meta-analysis were conducted. Significant associations between natural resource based (agriculture, forestry, logging, wood, paper), administrative, protective services (firefighters, police, and armed forces), construction, transportation, and prostate cancer risk were observed in the three population studies. Consistent evidence for increased prostate cancer incidence and mortality among firefighting and police work was observed in the meta-analysis. Non-occupational factors including lifestyle factors and screening behaviours were also potential confounders in the

relationship between occupation and prostate cancer. Overall, the results of this work provide strong evidence associating specific occupations to prostate cancer risk. Specific occupational exposures to be considered in the future are pesticides, diesel exhaust, whole body vibrations, wood dust, wood preservative chemicals, among other factors of shift work, stress, sedentary behaviour, screening patterns. These findings indicate the need for more focused studies with better exposure assessment methods and improved understanding of related non-occupational factors. Examining these factors together will inform prevention strategies for job-specific exposure and prostate cancer risk reduction. The evidence from this thesis and proposed future directions will improve knowledge on occupational risk factors related to the etiology of prostate cancer, ultimately informing policies and programs for reduction in prostate cancer risk.

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Dedication

I would like to dedicate this thesis to my family: my parents, Sinna and Kana, my siblings, Jaline, Jeyasri, Anbhu, and Ashvinie, and my husband, Krishanth.

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List of Abbreviations

ASAP	Atypical Small Acinar Proliferation
BPA	Bisphenol A
BPH	Benign Prostatic Hyperplasia
BMI	Body Mass Index
BRCA1	Breast Cancer Gene 1
BRCA2	Breast Cancer Gene 2
CanCHEC	Canadian Census Health and Environment Cohort
CI	Confidence Interval
CCS	Canadian Cancer Society
DDT	Dichlorodiphenyltrichloroethane
DRE	Digital Rectal Exam
ED	Endocrine Disruptor
EMF	Electromagnetic Field
ERSPC	European Randomized Study of Screening for Prostate Cancer
GMR	Geometric Mean Ratio
HCB	Heptachlor Epoxide
HPC1	Hereditary Prostate Cancer Gene 1
HOXB13	Homeobox Gene13
HR	Hazard Ratio
IARC	International agency for Research on Cancer
MCPA	2-methyl-4-chlorophenoxyacetic acid
MCPP	methylchlorophenoxypropionic acid
mRE	Meta-risk estimate
MOR	Morbidity Odds Ratio
NAICS	North American Industry Classification System
NECSS	National Enhanced Cancer Surveillance System
NOC-S-2006	2006 National Occupational Classification System for Statistics
NR	Not Reported
OR	Odds Ratio
PAH	Polycyclic Aromatic Hydrocarbons

PCB	Polychlorinated Biphenyls
PCP	Pentachlorophenol
PIA	Proliferative Inflammatory Atrophy
PIN	Intraepithelial Neoplasia
PLCO	Prostate, Lung, Colorectal, and Ovarian trial
PSA	Prostate Specific Antigen
PMR	Proportional Mortality Ratio
RR	Relative Risk
SAS	Statistical Analysis System
SIC	Standard Industry Classification
SIR	Standardized Incidence Ratio
SMR	Standardized Mortality Ratio
SMOR	Standardized Morbidity Odds Ratio
STI	Sexually Transmitted Infection
SOC	Standard Occupation Classification
STATA	General Purpose Statistical Software (statistics & data)
TCDD	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin
TCE	Trichloroethylene
TURP	Transurethral Resection of the Prostate
UKAEA	United Kingdom Atomic Energy Authority
UV	Ultraviolet
UVR	Ultraviolet Radiation
WHO	World Health Organization
WSIB	Workplace Safety and Insurance Board

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Chapter 1. General Introduction

1.1 Preamble

Prostate cancer was first diagnosed in 1853 by J. Adams and was considered a rare disease among men (Denmeade & Isaacs, 2002). From the beginning, prostate cancer proved to be a complex disease as it was difficult to differentiate from other urinary conditions. As life expectancy started to increase, prostate cancer was recognized as the most rapidly growing cancer associated with age (Denmeade & Isaacs, 2002). Changes in life expectancy, diet, and the industrialization of western nations contributed to increases in prostate cancer incidence. Eventually, prostate cancer emerged as one of the most commonly diagnosed cancers in men around the world (Denmeade & Isaacs, 2002; IARC, 2016). Today, prostate cancer remains as a complex disease with few established risk factors, and unlike other common cancers, prostate cancer has no accepted preventable factors (Prostate Cancer Foundation, 2017).

1.2 Thesis Outline

This thesis is organized as a multiple paper format to reflect the existing literature related to the occupational etiology of prostate cancer and to understand new and different investigations, ultimately leading to future directions. Chapter 2 encompasses a wide review of epidemiological studies that investigate the relationship between occupation and prostate cancer. The literature review describes trends and the burden of prostate cancer, diagnosis and screening, non-modifiable and modifiable risk factors linked to prostate cancer, occupations and related exposures, mechanisms of carcinogenic action, and the justification of this thesis work. Chapter 3 outlines the specific research aims and hypotheses of this thesis. Chapters 4, 5, and 6 present population based research that address the specific research objectives of this thesis. Each of these population based study chapters present self-contained manuscripts, both published and currently in press. Chapter 7 presents a meta-analysis, combining the findings from Chapter 4, 5, and 6, among other studies and is also a self-contained manuscript accepted for publication. Chapter 8 provides a thorough discussion that compliments the short discussions presented in the manuscripts from Chapters 4-7. Chapter 9 provides concluding remarks and a discussion on future directions.

Chapter 2. Literature Review

2.1 Secular Trends and Burden of Prostate Cancer

Prostate cancer rates vary more than 25-fold around the world with the highest rates in North America, Western and Northern Europe, Australia, and New Zealand (Lassed et al, 2016; Bashir, 2015). There are also relatively high rates in areas of the Caribbean, South America, and South Africa and lower rates across Asia and Eastern Europe (Lassed et al, 2016). In Canada, prostate cancer is the most commonly diagnosed cancer in men, after skin cancer, and it is the third leading cause of cancer related death in men (Canadian Cancer Society, 2015). In 2016, 21,600 Canadian men were diagnosed with prostate cancer, representing 21% of all new cancer cases, and 4,000 men died from prostate cancer, presenting 10% of cancer deaths (Canadian Cancer Society, 2017). It is expected that prostate cancer will continue to be the most commonly diagnosed cancer in Canadian men (Figure 1) (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2015).

In Canada, prostate cancer incidence rates have shown substantial increases in the early 1990s and early 2000s (Dickinson et al, 2016). These patterns coincide with the emergence and use of prostate specific antigen (PSA) testing in Canada. With the introduction of PSA testing, prostate cancer mortality rates began to decline and incidence rates continued to rise due to early detection (Dickinson et al, 2016). Mortality rates declined as a result of prostate cancer having a high survival rate, as most men do not die from this disease (Canadian Cancer Society, 2015). The patterns observed in Canada are similar to other industrialized nations (Potosky et al, 2001). Because of the PSA era, resulting in a rapid increase in diagnoses, the economic burden of prostate cancer has become substantial. In the United States there was a 30% increase in expenditure for prostate cancer treatment in 2000 from 1994 (Fradet et al, 2009). However, in recent years, large randomized trials showed conflicting findings for mortality reduction from increased PSA testing, which resulted in inconsistent screening recommendations put forth by different organizations in industrialized nations (Andriole et al, 2012; Schroder et al, 2014). Given the financial burden and current uncertainty surrounding PSA testing, there is a need to focus on prevention efforts (Fradet et al, 2009). For most of the major cancers in industrialized nations, there are established preventable risk factors, except for prostate cancer (Cogliano, 2011; Cancer Research UK, 2011). Research efforts on preventable risk factors for prostate cancer show some convincing evidence, but further evaluation is needed. It is important to assess possible preventable risk factors to provide evidence for effective prevention strategies as prostate cancer continues to be a complex disease and as more men than ever are being diagnosed with prostate cancer.

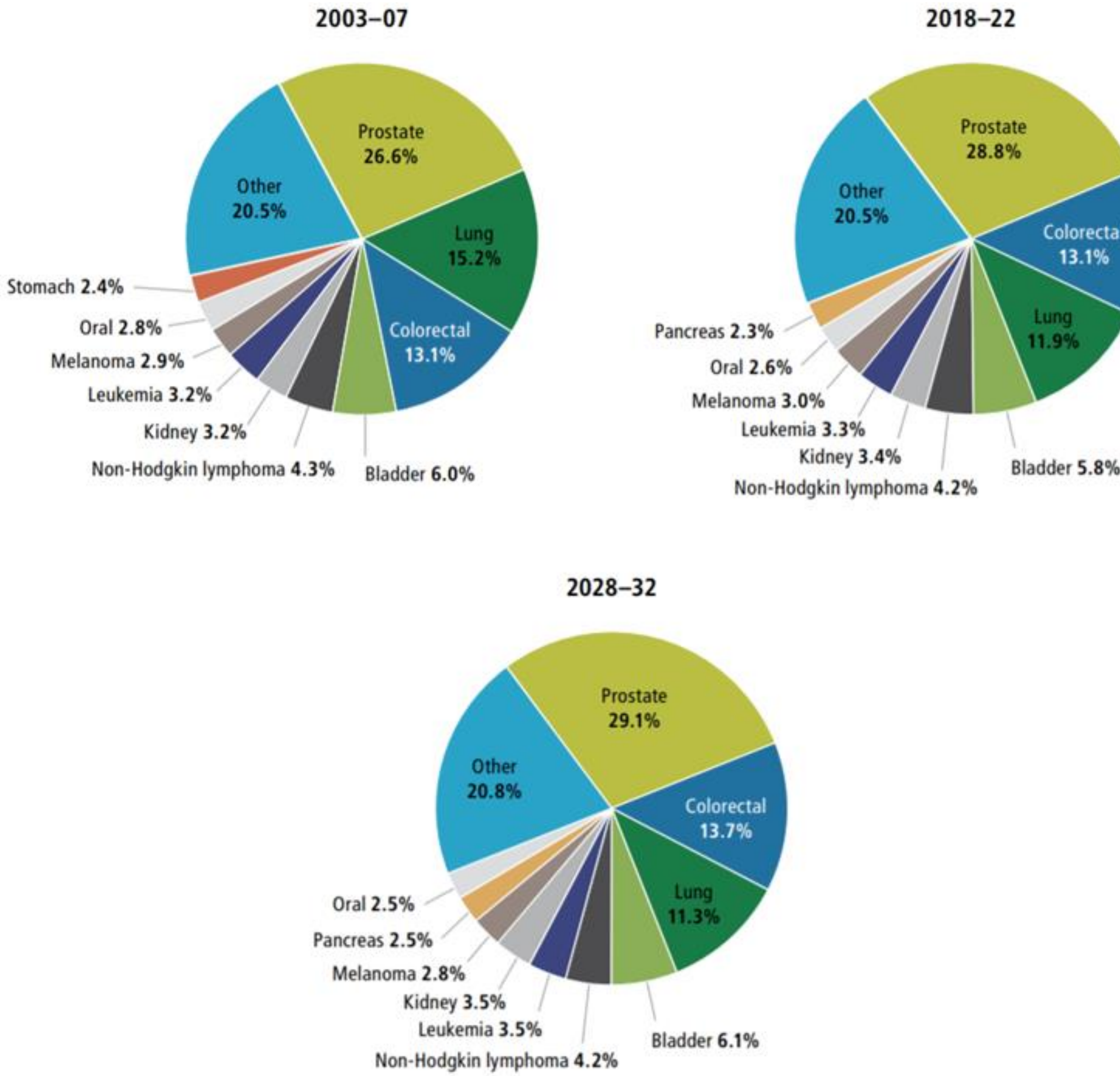

Figure 1. Projected distribution of cancers in males in Canada from 2003-2007, 2018-2022, 2028-2032. The distribution of prostate cancer is projected to remain as the most commonly diagnosed cancer in Canadian men in the following years to come: 2018-2022 and 2028-2032. This image is reproduced from the Canadian Cancer Society’s Advisory Committee on Cancer Statistics, 2015, and permission was not required as per report guidelines (Canadian Cancer Society, 2015).

2.2 Anatomy and Histopathology

The prostate is a part of the male genitourinary system and sits below the bladder and in front of the rectum (Figure 2). It aids with fluid secretion contributing to seminal fluid and nourishment of sperm. The size of the prostate varies with age and is normally the size of a walnut in younger men and can be larger in older men. The growth of the prostate is dependent on androgenic hormones such as testosterone (Platz, 2010; American Cancer Society 2015; Canadian Cancer Society, 2016).

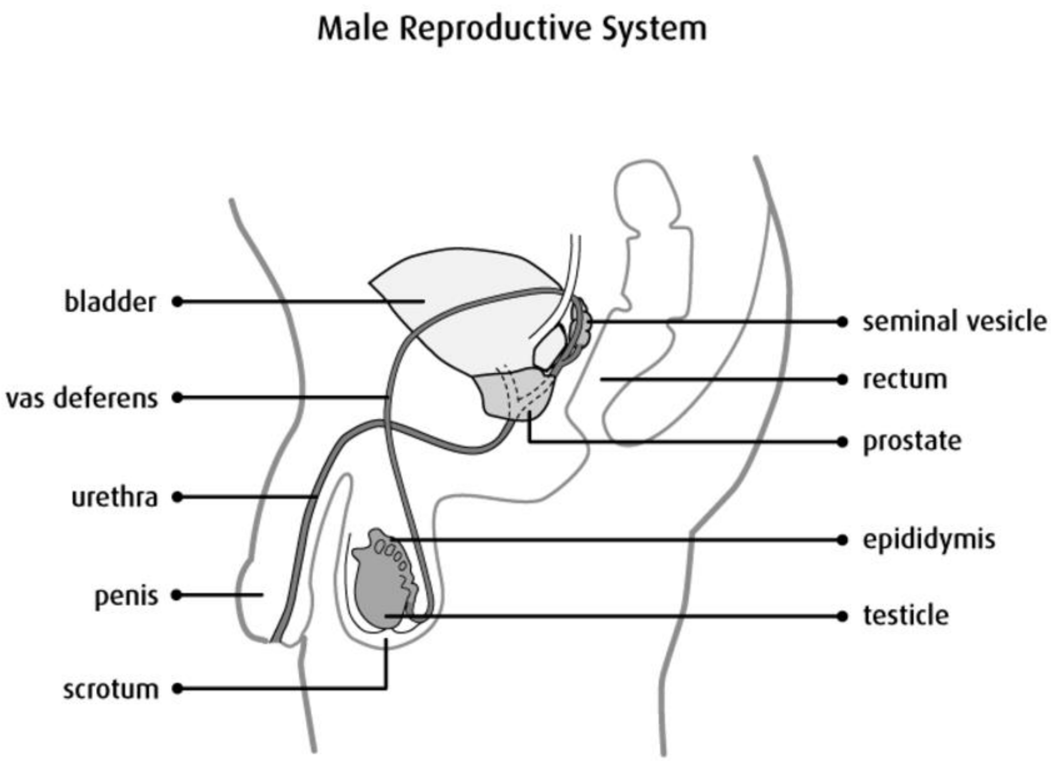

Figure 2. Description of the male reproductive system.
This image demonstrates where the prostate gland is located in the male reproductive system. Image reproduced from the Canadian Cancer Society with permission (http://www.cancer.ca/en/cancer-information/cancer-type/prostate/prostate-cancer/the-prostate/?region=on) (Canadian Cancer Society, 2017).

Adenocarcinomas are the most common form of prostate cancer accounting for 95% of cases and usually begin in the glandular cells of the prostate (Canadian Cancer Society, 2016). Rare types of prostate cancer include transitional cell carcinoma and sarcoma which account for <5% of cases. Prostate cancer can grow and spread quickly, but in most cases, adenocarcinomas grows very slowly over time (Canadian Cancer Society, 2016). Sometimes the changes in cells in the prostate lead to precancerous conditions that can later develop into prostate cancer. These precancerous conditions are known as prostatic intraepithelial neoplasia (PIN), proliferative inflammatory atrophy (PIA), and atypical small acinar proliferation (ASAP) (Canadian Cancer Society, 2016). In many cases, men die from other causes rather than from prostate cancer, and only during post-mortem it is discovered that these men had prostate cancer without any indicators. From the early stages of prostate cancer to the advancement of this disease there may be no signs or symptoms making it difficult to identify by affected men. However, there are some common symptoms or indicators that can be experienced such as interrupted urine flow, inability to stop or start urine flow, frequent urination, pain or sense of burning during urination, blood in the urine or semen, or painful ejaculation. The challenge with these indicators is that they are not unique to prostate cancer and also can be indicative of other conditions.

In the later stages of prostate cancer, signs and symptoms can include significant bone pain, weight loss, fatigue, anemia, weakness in extremities, and loss of bowel or bladder control (American Cancer Society 2015; Canadian Cancer Society, 2016). A condition known as benign prostatic hyperplasia (BPH) can also cause similar symptoms to prostate cancer, specifically prostate enlargement. BPH is often treated with medication but can also be treated by the transurethral resection of the prostate (TURP), which is the surgical removal of part of the prostate gland (American Cancer Society 2015; Canadian Cancer Society, 2016). If there is significant blockage of urine flow from prostate cancer, TURP may also be recommended to help enlarge the urinary passageway but this will not eliminate the cancerous prostate gland (Prostate Cancer Canada, 2017).

2.2.1 Diagnosis and Screening Methods

Diagnosis of prostate cancer involves different diagnostic and staging tests. First, a physical examination and medical history would be initiated. During this examination, the primary health care provider will perform a digital rectal exam (DRE) to physically feel the prostate and locate any lumps or abnormalities. The human prostate contains three zones – the central, transition, and peripheral zones. Over 75% of prostate tumors occur in the peripheral zone and can be identified during a DRE. Family history of prostate cancer would also be assessed within the medical history examination. Following these examinations, the next step would be a prostate specific antigen (PSA) blood test to examine PSA levels which can indicate abnormalities with the prostate (Canadian Cancer Society, 2016). Both the DRE and PSA screening tests are used to detect prostate cancer before symptoms appear. It is common to observe small concentrations of PSA in the blood but higher levels of PSA can be an indicator of prostate related conditions. The PSA test can detect an abnormality with the prostate gland but cannot guarantee if the abnormality is prostate cancer, thus making it a sensitive but non-specific screening method (Canadian Cancer Society, 2016).

Standards vary in terms of appropriate cut off levels for what are considered high levels of PSA in the blood. A PSA level of >4ng/L is often considered abnormal in Canada and the United States (Ontario Ministry of Health and Long-Term Care, 2012). However, this cut off is interpreted with age in mind as PSA levels increase with increased age. As the PSA test is non-specific, elevated levels of PSA can emerge from other non-cancerous conditions. With such a non-specific test, PSA levels in older men are often monitored over time to observe any abrupt increases in PSA levels (Canadian Cancer Society, 2016). Both the DRE and PSA tests are recognized as minimally invasive and are the only existing screening tests for prostate cancer.

In recent years, large research trials including the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial have had a profound impact on the understanding of prostate cancer screening. Both trials are recognized as using high quality methodologies to perform complex analyzes with high patient compliance. The ERSPC trial assessed data from seven European countries with a total of 72,952 men in a screening group and 89,245 men in a control group (Schroder et al, 2009). The study had a varying PSA cut off between 3 and 4 ng/mL to define prostate cancer and it was not clear how much prostate cancer screening took place in the control group (Schroder et al, 2009). It was concluded that PSA screening reduced mortality from prostate cancer by 20% in this trial. The authors also acknowledged the risk of over-diagnosis that is common with prostate cancer screening (Schroder et al, 2009). With follow-up to 13 years, the ERSPC trial observed a significant reduction in mortality (21-27%) from prostate cancer based on PSA testing (Schroder et al, 2014).

The PLCO trial included 10 USA study centers and included 38,343 men in the screening group and 38,350 men in the control group (Andriole et al, 2009). Randomization was performed by factors of age, sex, and study center and the PSA cut off in this trial was >4 ng/mL (Andriole et al, 2009). Annual screening was provided to men in the screening group whereas men in the control group were sometimes screened outside of the study. The PLCO trial concluded that there was no significant difference in prostate cancer mortality between the screening and control groups (Andriole et al, 2009). With 13 years of follow-up, findings remained consistent with no evidence of mortality reduction from annual screening compared to opportunistic screening (Andriole et al, 2012).

The conflicting evidence presented by two complex trials led to controversy surrounding the role of PSA testing as a useful screening tool for prostate cancer and mortality reduction (Shelke & Mohile, 2011). Based on these findings, recommendations for screening in Europe and North America have been inconsistent (NCI, 2009). In Canada, the Canadian Task Force on Preventative Health Care provides specific recommendations by age group and has recommended overall that men not be screened with the PSA test. (CTFPHC, 2014). On the other hand, Prostate Cancer Canada has recommended that men in their 40s have a PSA test to achieve a baseline level and further testing should be based on risk factors and discussions with healthcare providers. (Prostate Cancer Canada, 2016). The Canadian Urological Association provides similar recommendations that PSA testing should be selective among favourable risk cases or among high risk individuals (Izawa et al, 2011). These varying recommendations are not only unique to Canada but also across most industrialized nations. The concern is that over-diagnosis of non-aggressive prostate cancers results in excessive treatment and unfavourable adverse side effects which can be more harmful than the disease itself (Andriole et al, 2012; Schroder et al, 2014). The conflicting evidence of the effectiveness of screening to reduce mortality and the over-diagnosis and overtreatment leading to more harm than benefit caused inconsistencies in PSA testing recommendations across industrialized nations. Because of these conflicting issues, there is a significant need to understand risk factors of prostate cancer and put efforts towards prostate cancer prevention.

The Gleason grading system is commonly used to grade prostate biopsies to determine the prognosis of prostate cancer. Based on the microscopic appearance of the prostate cancer, a Gleason score is provided. Two scores are used to grade the most common or dominant cell morphology and the second is based on the non-dominant pattern (Canadian Cancer Society, 2016). The two grades are scored between a Gleason score of 1 to 5, with 1 being highly differentiated and least aggressive and 5 being poorly differentiated and most aggressive. The scores of each grade are then combined together for a total Gleason score between 2 and 10. Generally, a combined Gleason score of ≤6 is considered a low grade prostate cancer, well-differentiated, and less aggressive (Canadian Cancer Society, 2016). A Gleason score of 3 and 4, resulting in a combined score of 7 is considered a low to intermediate grade prostate cancer, whereas a Gleason score of 4 and 3, with also a combined score of 7 is recognized as a high to intermediate grade prostate cancer. This is because the first score indicates the more dominant grade of the tumor, which is higher in the latter example. A Gleason score of 8 to 10 is considered a high grade prostate cancer, poorly differentiated, and highly aggressive (Canadian Cancer Society, 2016).

2.3 Established Non-Modifiable Risk Factors of Prostate Cancer

Few well-established non-modifiable risk factors for prostate cancer are age, family history of prostate cancer, and ethnicity (Bashir, 2015). These factors are non-modifiable (cannot be changed) and established risk factors, making it necessary to consider them in all prostate cancer studies.

2.3.1 Age, Family History & Ethnicity

Prostate cancer incidence increases faster with age than any other major cancer in men (Fradet et al, 2009). It is often termed an old man's disease as there is an increasing risk of prostate cancer with increasing age and it is more common in men over the age of 50 years than in younger men. Men over the age of 55 years have an almost 17 fold higher risk than men below the age of 55 years (Canadian Cancer Society, 2016; Bashir, 2015). In Canada, the rate of prostate cancer diagnosis significantly increases with age group – 100 per 100,000 men (aged 50-54), 500 per 100,00 men (aged 60-64) and 700 per 100,000 men (aged 70-74) (Fradet et al, 2009). As life expectancy increases in westernized countries, there is a subsequent increase in the proportion of older individuals in these countries which makes diseases such as prostate cancer a prominent concern (Shelke & Mohile, 2011). Although prostate cancer is rare in younger men (<50 years), cases tend to be more aggressive and high grade resulting in increased risk mortality (Lin et al, 2009).

Over half of the men diagnosed are known to have reported family history with prostate cancer (Canadian Cancer Society, 2016; Bashir, 2015). Men who have a family history (first degree relative, father, brother, son who has been diagnosed with prostate cancer) have a 2-fold or more increased risk for prostate cancer (Albright et al, 2015; Canadian Cancer Society, 2016). The more first-degree relatives that are diagnosed with prostate cancer, the higher the risk is for the related male. Having second-degree or third-degree relatives diagnosed with prostate cancer also increases a man's risk of developing prostate cancer (Albright et al, 2015). Some studies have shown that inherited genetic mutations increase the risk for prostate cancer, but these mutations only account for 5-10% of prostate cancer cases. Research is underway to understand genetic factors associated with prostate cancer, inherited gene mutations that have been linked to prostate cancer include: HPC1, BRCA1 and BRCA2, DNA mismatch repair genes, and HOXB13 (American Cancer Society, 2016; Canadian Cancer Society, 2016). The age of diagnosis in men with hereditary prostate cancer was 6 years younger than men who did not have hereditary prostate cancer. This is a small difference, given that other common cancers (e.g. breast colon) see up to a 20 year difference by hereditary influence (Fradet et al, 2009). As only a small percentage of cases stem from genetic mutations (5-10%), it is important to consider other possible risk factors for prostate cancer that may have a greater impact on risk.

Men of African American/Black ethnicity have the highest risk of developing prostate cancer and men of Asian ethnicity have the lowest risk of developing prostate cancer when compared to Caucasian men (Canadian Cancer Society, 2016; Bashir, 2015). Men of African American ethnicity are likely to be diagnosed at a younger age and have aggressive forms of prostate cancer when compared to any other ethnic group (Canadian Cancer Society, 2016). Diagnosis of prostate cancer by ethnic group can also be influenced by a number of factors such as genetic predisposition, socioeconomic status, comorbidity, and accessibility to health care and cancer screening (Hoffman et al, 2000).

With immense diversity in Canada, it is important to understand prostate cancer differences by ethnic group. Canada has experienced a growth in visible minority populations over the past decades. Visible minority populations accounted for 19% of the Canadian population in 2011, growing from only 2% in 1971 (Khan et al, 2015). South Asian, Chinese, and Black visible minority populations make up the largest group of minorities in Canada (Statistics Canada, 2009). Although there is clear diversity in Canada, there continues to be limited provincial or national representation of visible minorities in health research. In previous Canadian population studies, there have been gaps in addressing cancer risk differences by ethnicity (Khan et al, 2015). Even though not all cancer types are associated with ethnicity, it is an important risk factor for prostate cancer (Canadian Cancer Society, 2016). As there are recognized differences for prostate cancer across different ethnic groups, ethnicity needs to be accounted for in population studies examining prostate cancer. Age, family history of prostate cancer, and ethnicity differences are important established risk factors that will be accounted for in each population study of this thesis.

2.4 Modifiable Risk Factors of Prostate Cancer

Aside from the three well-established modifiable risk factors, there are other modifiable risk factors with less established evidence for prostate cancer. Based on the existing literature, dietary factors, obesity and physical activity, vasectomies and sexually transmitted diseases, exogenous androgens, and occupation are a few of the suspected risk factors.

2.4.1 Diet

Dietary factors associated with prostate cancer include the intake of saturated fats, trans fatty acids, red meat, and dairy products (Di Sebastiono, 2014). High intake of dietary fat may be associated with prostate cancer risk while a low-fat diet may be beneficial for both prostate cancer risk and reduced cancer recurrence in survivors (Di Sebastiono, 2014). However, there is also some evidence showing no association between fat intake and prostate cancer risk (Xu, 2015). Although the findings have been inconsistent, there is some evidence for increased risk from consumption of specific fats that include animal (red meat) and saturated fats. Red meat refers to mammalian meat that includes beef, pork, lamb, mutton, veal, horse, and goat (IARC, 2015). Increased consumption of these fats may play a role in tumor promotion and carcinogenesis. Studies examining animal fat and prostate cancer risk have shown inconsistent findings (Giovannucci et al, 1993; Fradet et al, 1999; Koutros et al, 2008; Park et al, 2007; Wallstrom et al, 2007). Some studies specifically examining red meat and prostate cancer risk have identified associations (Gann et al, 1994; Merchand et al, 1994; Michaud et al, 2001; Bashir et al 2015), while other studies have found no association (Cross et al, 2005; Sinha et al, 2009). A recent review on six cohorts examining red meat consumption and multiple cancer sites found that consumption of 50 g day of processed meat increased prostate cancer risk by 4% (Wolk, 2016), whereas another meta-analysis on 19 cohort studies found no association between red or processed meat and prostate cancer. The meta-analysis also concluded that there were no associations with meat cooking methods, heme iron, and heterocyclic amines and prostate cancer. (Bylsma, 2015).

Recently, the International Agency for Research on Cancer (IARC) evaluated the cancer risks associated with consumption of red meat and reported limited evidence for prostate cancer risk (IARC, 2015). Dietary studies have also linked dairy intake to prostate cancer risk. Although dairy products are essential for bone development and prevention of osteoporosis, some studies have shown links between increased consumption of dairy products and prostate cancer risk (Tseng et al, 2005; Mitrou et al, 2007; Kurahashi et al, 2008; Lassed et al, 2016) while other studies have observed no association (Koh et al, 2006; Huncharek et al, 2008). It is hypothesized that increased dairy consumption, primarily milk products, leads to high levels of calcium and phosphate in the plasma which may lower metabolites of vitamin D concentration leading to prostate cancer risk (Tseng et al, 2005). It is also considered that estrogen in milk products may affect hormone levels in the body affecting the prostate (Lassed et al, 2016). There are continued efforts to understand the relationship between dairy products, calcium, and vitamin D and how these factors contribute to prostate cancer.

The dietary evidence so far indicates that fruit and vegetable rich diets with reduced carbohydrates, saturated fats, and cooked meat may be protective for prostate cancer (Lin 2015). Specifically, the evidence that vegetable and fruit consumption is protective for prostate cancer is limited (Le Marchand et al, 1994; Schuurman et al, 1998; Deneo-Pellegrini et al, 1999; Meng et al, 2014; Lassed et al, 2016). It is also suggested that fish consumption may be linked to a reduced risk of prostate cancer (Chavarro et al, 2008). The Health Professionals Study examined over 47,000 men over 12 years and found that fish consumption more than three times per week was associated with reduced prostate cancer risk (Augustsson et al, 2003). However, other studies have shown no conclusive evidence that fish consumption is protective for prostate cancer risk but the findings may be due to low levels of fish consumption (Lassed et al, 2016; Szymanski et al, 2010). Prostate cancer incidence is lower in Eastern and South-Central Asia, but incidence has increased in immigrants from these regions who migrated to Western nations. It is believed that these populations that migrated to the West have adapted to western diets that may alter prostate cancer incidence patterns in their populations (Lassed et al, 2016). There may be other factors involved in migrating populations but diet continues to be an important factor among these groups.

2.4.2 Obesity & Physical Activity

Traditionally, physical activity and obesity have been studied alongside diet in cancer studies. These factors tend to be associated and are usually examined together to understand their association with cancer. It is suggested that rigorous physical activity may reduce prostate cancer risk by about 10 to 30% (Shephard, 2016). Recent reviews on physical activity and diet adherence found limited or few associations with prostate cancer risk (Shephard, 2016; Kohler, 2016; Kruk, 2013). The most recent review by Shephard et al (2016) reported on 85 analyzes looking at both occupational and leisure physical activity. There were mixed findings across the reports, 22 of which found a statistically significant reduction in prostate cancer risk. Although the reports included in the review had different findings, the authors concluded that as regular physical activity is important for other health conditions, it is also an important factor for prostate cancer prevention (Shephard et al, 2016). Due to the benefits of physical activity for other cancer types, and with some evidence of benefit for prostate cancer prevention (Young-McCaughan, 2012), further research is needed.

Obesity, often measured by body mass index (BMI), has been associated with increased prostate cancer risk based on strong evidence from the International Agency for Research on Cancer and the World Cancer Research Fund (De Pergola, 2013). A review of studies published between 1991 and 2012 also concluded that obesity appears to be associated with aggressive forms of prostate cancer incidence (Allot 2013). Although previous studies have shown mixed findings for obesity and prostate cancer, recent studies are increasingly showing that obesity is associated with aggressive forms of prostate cancer (Bashir, 2015). Physical activity and obesity are also linked to different occupational groups. White collar occupations, such as office or managerial positions, are often regarded as occupations with lower physical activity and increased sedentary behavior when compared to blue collar occupations (Krstev et al, 1998).

2.4.3 Vasectomies & Sexually Transmitted Infections (STIs)

In the 1990s, a relationship between vasectomies and prostate cancer risk was reported but more recently, studies have not confirmed these findings (Loughlin, 2016; Shang, 2015; Jacobs, 2016; Gaines, 2015). Cohort studies published between 1980 and 2015 found no significant association between having a vasectomy and risk of prostate cancer (Shang, 2015; Jacobs, 2016). Furthermore, the American

Urological Association has disputed the notion that vasectomies are linked to prostate cancer risk (Sharlip, 2012). Men who have a history of prostatitis, which involves inflammation and enlargement of the prostate, are often observed to have a higher risk for prostate cancer (Bashir, 2015). Also, sexually transmitted infections (STI) have also been linked to prostate cancer risk as there is a high incidence of both these conditions. A recent review on 47 studies looking at multiple STI conditions found only a significant association with prostate cancer risk in men with gonorrhea. No other STI conditions were associated with prostate cancer risk (Caini, 2014). The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial also examined prostate cancer risk related to serum antibodies to various STIs. No consistent associations were observed for any STI and prostate cancer, demonstrating a weak relationship overall (Huang, 2008). However, a previous meta-analysis on sexual activity and prostate cancer reported an elevated risk for prostate cancer among men who had a history of STIs (17 studies) and also among men who had increased sexual activity (12 studies) (Dennis & Dawson, 2002). Although the meta-analysis observed an increased risk of prostate cancer in men with increased sexual activity, it is often reported that increased sexual behavior and frequent ejaculation may be protective for prostate cancer risk (Kotb et al, 2015). Increased sexual activity resulting in increased ejaculation may help to release inflammatory cells that are gathered in the seminal vesicles near the prostate. Without release of these accumulating inflammatory cells, these cells may build up over time potentially increasing the risk of prostate cancer (Kotb et al, 2015).

2.4.4 Exogenous Androgens

Male sex hormones, also known as androgens, are important for the development and function of the male reproductive system. Testosterone is primarily involved and it is metabolized by the body to create dihydrotestosterone. Exposure to high levels of testosterone and dihydrotestosterone may be influential in the development of prostate cancer. In 1987, IARC reported limited evidence that androgenic steroids are carcinogenic to humans, specific to prostate cancer (IARC, 1987). IARC also identified sufficient evidence for carcinogenicity in animal studies for only testosterone exposure (IARC, 1987). Over the years, studies have shown mixed evidence with few reporting rapid prostate cancer progression in men who received testosterone, whereas most studies showed no association between testosterone, dihydrotestosterone and prostate cancer risk (Eaton et al, 1999; Roddam et al, 2008; Muller et al, 2012; Botelho et al, 2012; Klap et al, 2014). Measuring testosterone levels has been limiting in many studies because testosterone levels in the body vary throughout the day. Also, measurement of total testosterone may not be clear because of other steroids that are circulating and may interfere (Klap et al, 2014). There have been significant differences in methodology among studies examining testosterone and prostate cancer, which has led to contradictions in findings (Klap et al, 2014). Based on the available evidence, there is no clear relationship between serum concentrations of sex hormones and prostate cancer risk.

2.4.5 Occupation

Employment is integral to the human population as over half the world spends at least 30% of their adult life at work (WHO, 1994). Employment not only impacts the well-being of working individuals and their families, but also contributes to societal and economic growth. Employment can be beneficial to the health and well-being of individuals, and provides a sense of purpose for many (WHO, 1994). In Canada, on average, men spend more years employed and work longer hours than women (Statistics Canada, 2015). Similar patterns by gender are recognized worldwide and are expected to remain unchanged (International Labour Organization, 2017). As employment continues to be an important part of the human population, there is a need to understand how it impacts human health. Examining worker populations can lead to improved understanding of exposures related to disease outcomes, leading to better health and safety in the workplace.

Health and safety in worker populations has improved over the past years, but there are still occupational factors that need to be addressed to understand common disease patterns as exposure levels in the workplace tend to be higher than in other settings (WHO, 1994). This is particularly important for diseases with limited knowledge on etiology and risk factors, such as prostate cancer. By understanding disease patterns in worker populations, research can improve the health of worker populations and provide evidence on disease prevention and health promotion. In worker populations, employment is often classified by occupation and/or industry. Occupation describes the set of activities or tasks that an individual performs, whereas industry describes the broader sector of economic activity that these occupations belong to (‘t Mannetje & Kromhout, 2003). Occupation is more commonly used than industry to understand job titles and corresponding occupational exposures. Both classification methods are valuable tools for studying workplace risk factors in population-based epidemiological studies (‘t Mannetje & Kromhout, 2003).

Occupational epidemiology involves the study of workplace exposures and corresponding disease outcomes among worker populations (Checkoway et al, 2007). This area of research is focused on understanding the occurrence of diseases in exposed workers which can help improve disease prevention. Historically, occupational studies focused on workplaces with very high exposures which led to the detection of well-known carcinogens (cancer causing agents) such as asbestos, silica, metals, radon gas, and diesel exhaust (Frumkin, 2010). Over the years there have been many changes to workplace environments particularly in industrialized nations. Based on the evolution of workplace changes and the emergence of various exposures in work environments, there have been disparities in occupational exposures around the world. Occupational exposures, also referred to as workplace exposures, prove to be more difficult to examine due to the synergistic effects of mixed exposures in a work environment (Merletti et al, N/A). The general population may be exposed to similar exposures as the worker populations, but at decreased levels or different environments. Ultimately, reducing or eliminating hazards in the workplace and improving understanding on how exposures affect workers can lead to increased understanding of these hazards in the general population (Merletti et al, N/A).

Prostate cancer has been a challenging area for occupational research because of the limited understanding of prostate cancer etiology and related exogenous agents (Parent & Siemiatycki, 2001). Without well-established modifiable risk factors for prostate cancer, there is a need to continue investigating if occupational risk factors are associated with the risk of prostate cancer. Employment information and job titles, which represent specific occupations and industries, often act as surrogates for potential job-related exposures (Sun et al, 2003). Strengthening the evidence on potential exposures can be indicative of where prostate cancer prevention research should focus and can provide insight into existing evidence.

IARC, a leading research body on cancer risk factors, has been influential in quantifying and interpreting the existing evidence on risk factors for prostate cancer. IARC evaluates different agents of interest based on both human and animal published evidence in order to group agents of interest into specific classifications of carcinogenicity (IARC, 2017). Agents for review are selected based on evidence of human exposure and if there is existing evidence of carcinogenicity. Agents can be classified as the following: Group 1 (carcinogenic to humans), Group 2A (probably carcinogenic to humans), Group 2B (possibly carcinogenic to humans), Group 3 (not classifiable), and Group 4 (probably not carcinogenic to humans). Currently, there are 120 agents in Group 1, with 375 agents in Group 2A and 2B, 505 agents in

Group 3, and 1 agent in Group 4 (IARC, 2017). There are approximately 55 occupational exposures classified as known or probable carcinogens (Group 1 and 2A), with many more occupational exposures as suspected carcinogens (Siemiatycki, Richardson, Straif et al, 2004). With various occupational exposures classified as known or probable carcinogens, it is important to investigate what types of occupations are involved in these exposures, and their relationship to prostate cancer risk.

For prostate cancer, IARC concluded that there is limited evidence for the following agents: *androgenic steroids, arsenic and compounds, cadmium and compounds, malathion (insecticide), rubber production industry, thorium-232 and decay products, X- and ɣ- radiation, and consumption of red meat* (Cogliano et al, 2011). Based on IARC's findings, it is evident that associations exist primarily between occupation related agents and prostate cancer. There have been many studies that have explored occupation and cancer, but less so with prostate cancer (Cogliano et al, 2011). The following sections will provide an in depth evaluation of the evidence that exists for occupation and risk of prostate cancer.

2.5 Occupation, Industry & Prostate Cancer: Epidemiological Evidence

2.5.1 Agriculture and Pesticides

Prostate cancer risk among farming and agriculture workers has been assessed in many previous studies, with mixed findings. Multiple studies have shown increased prostate cancer incidence and mortality in men who worked in farming or agriculture occupations (Araki et al, 1983; Checkoway et al, 1987; Brownson et al, 1988; Cerhan et al, 1998; Buxton et al, 1999; Lee et al, 2002) and other studies have shown decreased risks or non-significant elevations (Levi et al, 1988; Ronco et al, 1992; Zeegers et al, 2004; Erdurak et al, 2014; Sritharan et al, 2016). The findings across studies are variable with differences in occupation and exposure. A recent Saskatchewan study found significant associations between farming work and prostate cancer and specifically observed a significant association between those who lived on a farm and prostate cancer risk, compared to those who did not live on a farm (Sharma et al, 2016). The study also observed a significant association between combined insecticide and fungicide exposure and prostate cancer risk but not for each exposure individually (Sharma et al, 2016).

Pesticides are the primary exposure identified in agriculture occupations. Pesticides can act as endocrine disruptors and may affect hormone levels in the body, influencing the development of hormonal cancers (Lewis-Mikhael et al, 2016). A 2015 review of 15 studies that included a meta-analysis of 10 of the studies reported positive non-significant associations for multiple organochlorine pesticides. However the findings were not clear enough to support the hypothesis that specific organochlorine pesticides are linked to increased prostate cancer incidence (Lewis-Mikhael et al, 2015). A more recent review of 52 studies and meta-analysis of 25 studies observed no association between low occupational pesticide exposure and prostate cancer but observed a significant association between high occupational pesticide exposure and prostate cancer (pooled OR 1.33, 95% CI 1.02-1.63; p=0.024) (Lewis-Mikhael et al, 2016). The association between high occupational exposure and pesticides was significant for men with a family history of prostate cancer which is consistent with findings from the Agriculture Health Study publications (Lewis-Mikhael et al, 2016).

The Agriculture Health Study was a large prospective cohort study that took place in 1993 and addressed health outcomes in pesticide applicators in Iowa and North Carolina. There were over 89,000 farmers and their spouses involved in this study. A number of published studies came out from this study, with important findings related to prostate cancer risk. Findings showed associations between organochlorine pesticides and aggressive prostate cancer. When comparing the highest quartile of exposure to those non-exposed, fonofos (RR 1.63, 95% CI 1.22-2.17), malathion (RR 1.43, 95% CI 1.08-1.88), terbufos (RR 1.29, 95% CI 1.02-1.64) were all also associated with aggressive prostate cancer (Koutros et al, 2013). This study observed only a suggestive increased risk for aggressive prostate cancer and diazinon exposure. A follow-up study of Koutros et al (2013) observed a similar finding of a non-significantly elevated risk for aggressive prostate cancer among the highest category of diazinon use (Jones et al, 2015). Methyl bromide use among pesticide applicators was assessed from 1993 to 2007 and no association with prostate cancer was observed for the full follow-up time. However, in the early period of 1993 to 1998, there was an association between high methyl bromide exposure and prostate cancer but this association attenuated over time (Barry et al, 2012). There was also some evidence that showed pesticide applicators with a family history of prostate cancer had elevated prostate cancer risks when compared to those without a family history of prostate cancer (Barry et al, 2012).

Other AHS studies assessed coumaphos and DDVP (2, 2-dichloroethenyl dimethlyphosphate) exposures and prostate cancer risk, with no associations identified. But these studies did observe a relationship between exposure and prostate cancer risk when examining men who have a family history of prostate cancer (Christensen et al, 2010; Koutros et al, 2008). Agriculture studies are continuing to show a strong association for pesticide exposure and some association for diesel exhaust exposure (Parent et al, 2009). It is important to assess agriculture occupations and prostate cancer across studies to understand if the relationship is persistent, while addressing pesticide exposures among other possible exposures. It is also important to understand how non-occupational factors (e.g. age, family history of prostate cancer) are involved in these associations.

2.5.2 Forestry, Logging, and Wood Working

There are limited research efforts in understanding prostate cancer risk in forestry, logging, and wood-working occupations. Common exposures among these occupations include pesticides, wood dust, polycyclic aromatic hydrocarbons (PAHs), diesel exhaust, and whole-body vibrations (Sauve et al, 2016). These exposures have been significantly associated with different cancer sites with some evidence for prostate cancer which will be discussed further. These exposures are also likely to exist in other natural resource based occupations such as agriculture, which makes it difficult to tease apart exposures by occupation. There may be limited exposure to pesticides in these wood related occupations, but it is important to note that forestry workers use herbicides for vegetation control accounting for exposure on the job (MacFarlane et al, 2013). Wood dust exposure is more common across forestry, logging, and wood working, and wood dust has been classified as a known carcinogen to humans by IARC (Group 1) (Bruschweiler et al, 2012). Wood dust exposure has also been linked to prostate cancer risk (RR 1.23, 95% CI 1.00-1.50) (Stellman et al, 1998). Furthermore, the incomplete combustion of wood products from heating of wood can lead to the formation of PAHs and exposure to PAHs is likely in these wood working occupations. Various PAHs have been classified as carcinogenic and probably or possibly carcinogenic to humans by IARC (Bruschweiler et al, 2012).

Diesel exhaust and whole body vibrations (WBV) are exposures primarily involved in wood processing, skidding/stacking logs, and machine operating of industrial vehicles (Jack et al, 2008; Nadalin et al, 2002). Diesel exhaust was also classified as a known human carcinogen by IARC, and exposure to it is likely with vehicle and machine related operations, both in use and stationary. Exposure to diesel exhaust is likely in natural resource based occupations, especially in forestry operations where diesel emitting vehicles may be used, but the evidence is limited (Magagnotti et al, 2013). Exposure to WBV occurs when mechanical energy is transmitted to the body from vibrating surfaces, which are usually through the feet or trunk (if seated). Previous studies have assessed WBV and prostate cancer with mixed findings and a recent meta-analysis observed a weak association overall (Nadaline et al, 2002; Sass-Kortsak et al, 2007; Jones et al, 2014; Young et al, 2009). The meta-analysis examined different occupations with WBV exposure, not only corresponding with forestry, logging, and wood working occupations. Based on job title, studies in the past have shown positive associations for prostate cancer in forestry, logging and wood related workers (Kawachi et al, 1989; Stellman et al, 1998; Sharma-Wagner et al, 2000; Alavanja et al, 2010), with the exception of one study that observed an inverse association (Pukkala et al, 2009). A recent case-control study observed an increased risk of prostate cancer among forestry and logging occupations (OR 1.9, 95% CI 1.2-3.0) and the logging industry (OR 1.7, 95% CI 1.0-2.8) (Sauve et al, 2016). They also observed a risk of high grade prostate cancer in forestry and logging occupations (OR 2.5, 95% CI 1.4-4.5) and the wood industries (OR 1.9, 1.0-3.6) (Sauve et al, 2016). Although it is difficult to tease out specific job-related exposures in forestry, logging, and wood working, there is a need for further evidence on the association between these occupations and prostate cancer risk.

2.5.3 Protective Services

Protective services occupations generally include firefighting, police occupations, and armed forces. These male dominated occupations are recognized as being high risk in nature with potential exposure to multiple occupational risk factors. Each major protective services group will be discussed further below.

2.5.3.1 Firefighting

Firefighting is the most frequently studied protective services occupation in relation to cancer risk. Firefighting is considered a highly hazardous occupation involved in both fire and rescue services. These workers are repetitively working with fires that lead to exposure to carcinogens through combustion byproducts and burning materials (LeMasters et al, 2006; Pukkala et al, 2014). Exposures from fires include pesticides, diesel exhaust, asbestos, benzene, metals, plastic products, and many other compounds (Demers et al, 1994; LeMasters et al, 2006; Bates et al, 2007; Tsai et al, 2015). Firefighters can be exposed to asbestos when older structures built with asbestos material are burning and they can be exposed to diesel exhaust from not only fires, but also from firefighting trucks (Pukkala et al, 2014). As first responders, firefighters experience emergency duties that are both physically and mentally demanding and can be accompanied by unexpected events. The emergency duties of firefighters can lead to prolonged stress levels in workers, which can lead to adverse health conditions (Kaikkonen et al, 2017). Firefighters are also affected by shift work as they are likely to work in rotating shifts which can cause disruption of their circadian rhythm (Pukkala et al, 2014).

Even though firefighters are recognized as wearing heavy duty protective equipment when fighting fires, they also spend time after the fire is extinguished in a phase called 'overhaul' to clear debris and clear any hidden fires (Bates et al, 2007). During overhaul, firefighters wear less protective equipment without the self-containing breathing apparatus that helps decrease respiratory exposure to toxins (Bates et al, 2007). Even while wearing protective equipment, firefighters can absorb toxins through dermal exposure in the neck region which is generally an unprotected area. Many epidemiologic studies have examined firefighting across multiple cancer types but no consensus has been made on the risk of prostate cancer (Bates et al, 2007).

Studies have identified significant increased risks for prostate cancer incidence and mortality in firefighters (Grimes et al, 1991; Demers et al, 1994; Ma et al, 1998; Bates et al, 2007; Pukkala et al, 2014; Tsai et al, 2015; Glass et al, 2016). Some studies have also seen decreased risks of prostate cancer in firefighters (Zeegers et al, 2004; Daniels et al, 2015). A meta-analysis on 32 studies in 2006 found a significant elevated risk for prostate cancer (SRE=1.28, 95% CI 1.15-1.43) and attributed mixed exposures involving prostate carcinogens to this finding (LeMasters et al, 2006). The International Agency for Research on Cancer (IARC) in 2010 evaluated firefighting across 42 studies that assessed multiple cancer types. IARC concluded that there was evidence for prostate cancer, among other types, and classified firefighting as possibly being associated with cancer (Class 2B) (Pukkala et al, 2014). Firefighters are observed to be healthier given the strenuous expectations of the job (Glass et al, 2016). Mortality is generally expected to be lower in firefighters than the general population due to the healthy worker effect. It is also suggested that increased prostate cancer incidence and decreased mortality in firefighters may be a result of increased PSA screening leading to early diagnosis (Daniels et al, 2015).

2.5.3.2 Police Work

Studies in the literature have generally focused on prostate cancer risk in men in firefighting with fewer studies on men in police work. Although men in police work may not experience numerous chemical exposures like men in firefighting and the armed forces, there are important occupational factors involved in police work. Diesel exhaust is one of the few potential chemical exposures in traffic stop officers as these workers may be exposed from other traffic vehicles. Similar to firefighting, police work also involves shift work which can lead to the disruption of the circadian rhythm. And these men are often working in challenging situations which contribute to increased psychological stress (Wirth et al, 2013). There are many stressors involved in police work, and to highlight a few, these officers make immediate decisions sometimes relating to life and death, work excessive hours in one period, and they are often on high alert (Wirth et al, 2013). Excessive stress and irregular shifts can lead to significant changes in the stress hormone, cortisol, which can lead to a number of alterations in the body (Wirth et al, 2011). These changes can cause increased inflammation, chronic fatigue, increased heart disease and possible risk for cancer. The increased stress and disruption to sleep/wake cycle can cause deregulation of immune responses and lead to tumor development (Wirth et al, 2011; Wirth et al, 2013). Men in police work are also exposed to air pollution and diesel exhaust as they are likely to spend more time in traffic related areas and in police vehicles (Wirth et al, 2013). Police officers also often use radar guns which can lead to potential exposure of polycyclic aromatic hydrocarbons (PAHs) and non-ionizing radiation (Finkelstein, 1998; Zeegers et al, 2004; Sauve et al, 2016).

Existing studies that have explored prostate cancer risk in police work observed mixed findings. A large cohort study found a statistically significant increased risk for prostate cancer among police officers (OR 3.91, 95% CI 1.14-13.42) (Zeegers et al, 2004), where other studies only observed non-significant elevated risks (Finkelstein, 1998; Band et al, 1999). A 2013 review on 14 studies reported inconsistent findings for prostate cancer risk among men in police work. The authors of the review outlined the importance of psychological stress and shift work in police work (Wirth et al, 2013). A recent study in 2016 observed consistent positive associations for police officer and detective occupations (OR 1.8, 95% CI 1.1-2.9) and for the overall protective services industry (Sauve et al, 2016). These findings indicate the importance of further investigating the association between police work and prostate cancer.

2.5.3.3 Armed Forces

Men employed in the armed forces or military can be exposed to numerous agents including toxic metals, asbestos, fuels, chemical/warfare agents, radiation, whole body vibration, stress, and shiftwork (US Department of Veteran Affairs, 2016; Silva et al, 2000). These men may be exposed at higher intensities with limited ventilation if they spend more time in confined areas or within vessels (Silva et al, 2000). Men in the armed forces are also similarly involved in intense stressful environments like firefighters, and experience shift work such as rotating shifts or night shifts (Kaikkonen et al, 2017). As seen in other protective services occupations, men in the armed forces are generally healthier than the general population and may have better access to cancer screening (Zhu et al, 2009; Statistics Canada, 2011). Even with the improved health resources for military workers, studies continue to recognize differences in prostate cancer risk across these workers.

A study on Vietnam veterans identified a non-significantly elevated risk for prostate cancer (OR 2.12, 95% CI 0.88-5.06). They also saw a significant risk for men with fathers who had prostate cancer (OR 1.90, 95% CI 1.20-3.00) or brothers who had prostate cancer (OR 2.05, 95% CI 1.20-3.50) (Leavy et al, 2006). The authors attribute findings to family history of prostate cancer, possible increased screening in the 1990s, and known occupational exposures. These men were recognized as having been exposed to large amounts of herbicides, known as Agent Orange during the herbicide warfare program (Leavy et al, 2006). Agent Orange was widely used by the US military during the Vietnam War, which contributed to both environmental and human exposure to this chemical hazard (Leavy et al, 2006). Other international studies have also shown significant increased risks and excesses in deaths from prostate cancer. A cohort study from 1953-2008 followed 28,345 Norwegian navy servicemen and observed an increased risk for prostate cancer (SIR 1.12, 95% CI 1.04-1.20). Significant excess deaths were reported in the Brazilian navy in men employed between 1991 and 1995 (Silva et al, 2000).

Studies in the United States have reported on prostate cancer risk and screening in military workers. In the United States, it is mandated that PSA testing be included in periodic physical examinations in men over the age of 40 years (Joseph & Hickey, 2004). In one study, military service members aged 50 years and over across three health clinics in the United States were assessed. The study found that PSA testing was more common in men over the age of 67 years and of those who were screened, 68% had a PSA test whereas only 13% had both PSA and DRE testing (Joseph & Hickey, 2004). Overall, there was low representation of different ethnic groups in this sample and low use of appropriate prostate cancer screening methods (Joseph & Hickey, 2004). Another study addressed the controversy surrounding the PSA test and how periodic screening in men over 40 years of age needs to be considered with different risk levels in men (Moul, 2005). Both studies specify that there should be better screening policies for military personnel that include recommendations based on age, ethnicity, and other potential risk factors (Joseph & Hickey, 2004; Moul, 2005).

Zhu et al (2009) found that rates for prostate cancer were twice as high in military workers when compared to the general population. The authors considered screening as an important issue contributing to increased incidence but they also acknowledge that workers may be exposed to depleted uranium which can increase risk for prostate cancer (Zhu et al, 2009). Wells et al (2010) examined a relatively younger US military group (>50 years of age) and observed relatively low prostate cancer incidence rates comparable to the general population. The study aimed to compare young military workers to the general population based on factors that military workers were healthier, had uniform and unlimited access to health resources, and were likely to get screened earlier. They did however, observe a statistically significant risk for black non-Hispanic men (HR 2.72, 95% CI 2.12-3.49) even though all servicemen had equal access to healthcare (Wells et al, 2010). The study outlines the importance of racial differences and potential occupational exposures involved.

Men in the Canadian Forces are also subject to periodic health assessments, every 5 years if under the age of 40 years, and every 2 years if 40 years of age and older (Born et al, 2010; National Defence and the Canadian Armed Forces, 2016). There is no indication that these men are required to undergo any prostate cancer screening. It is also unclear if men are complying with the recommended health assessments, as it has been reported that at least one in every five men over the age of 40 years did not have periodic health assessments completed in the past 2 years (Born et al, 2010). Very few studies have examined prostate cancer among the Canadian Forces. The most recent report on the Canadian Forces was initiated by the Government of Canada to examine cancer and all-cause mortality in this population (Statistics Canada, 2011). The study concluded that men in this cohort had a significantly lower risk of mortality from all cancers than the general population (Statistics Canada, 2011). Yet, this study did not differentiate between cancer types, so there were no specific findings for prostate cancer. Also, this study only evaluated mortality and given the high survival rate for prostate cancer, it is expected that there would be low mortality from prostate cancer.

2.5.4 Transportation & Whole Body Vibrations

Past studies have shown evidence that occupations related to transportation and driving are associated with prostate cancer (Seidler et al, 1998; Sass-Korstak et al, 2007; Nadalin et al, 2012) with possible exposures of PAH, diesel exhaust, metals and whole body vibrations (WBV) (Seider et al, 1998; Sass-Kortsak et al, 2007). Occupations related to transportation and driving include various jobs of trades, transport, equipment operators, construction related transportation, and vehicle driving. WBV has become of interest related to these jobs and has recently been studied in multiple job categories. WBV occur when mechanical energy is passed from vibrating surfaces to the body and this is usually through a standing position through the feet or in sitting position through the trunk (Nadalin et al, 2012). A systematic review and meta-analysis on whole body vibrations and prostate cancer across 8 studies found a pooled relative risk estimate of 1.14 (95% CI 0.99-1.30), concluding that further evidence is still needed (Young et al, 2009). More recently, Nadalin et al (2012) observed that occupations with exposure to WBV showed a non-significantly elevated risk for prostate cancer (OR 1.44, 95% CI 0.99-2.09). Another study by Jones et al (2014) observed that WBV exposed men in trades, transport, and equipment operator occupations had a reduced risk of prostate cancer (OR 0.91, 95% CI 0.86-0.97) and found no consistent relationship between WBV and prostate cancer. Due to the nature of these jobs, it is difficult to link specific exposures to these specific occupations because of misclassification and limited assessment of exposure (Sass-Kortsak et al, 2007; Nadalin et al, 2012). However, further investigation into transportation occupations and prostate cancer is warranted.

2.5.5 Rubber Manufacturing

Rubber manufacturing workers are involved in the production of rubber goods and can be exposed to aromatic amines, fumes, and inhalable aerosols as a result of rubber making processes. A recent study examining a cohort of Polish tire manufacturing plant workers found prostate cancer associated with aromatic amine exposure (RR 5.86, 95% CI 1.04-33.09), but with no exposure-response associations (Frank de Vocht et al, 2009). Another cohort looking at Swedish rubber tire workers observed a decreased risk for prostate cancer (SIR 0.74, 95% CI 0.59-0.92) based on work tasks and exposures (Wingren & Axelson, 2007). These studies are reflective of the inconsistent results across previous studies for prostate cancer risk among rubber workers (Stewart et al, 1999; Zeegers et al, 2004). Stewart et al (1999) conducted a meta-analysis of nine cohort studies and concluded that employment in a rubber and tire manufacturing plant was not associated with prostate cancer risk. A more recent study by Zeegers et al (2004) observed a non-statistically significant increased risk for prostate cancer. In 1982, IARC concluded that there was limited evidence for an association between prostate cancer and rubber manufacturing work. IARC re-assessed this association based on recent studies, and concluded that were was weak/limited evidence for an excess risk (IARC, 2012). Although the evidence for prostate cancer was limited, IARC observed sufficient evidence for carcinogenicity of exposures from the rubber manufacturing industry for cancer risk overall. This led to the classification of exposures from the rubber manufacturing industry as Group 1 – carcinogenic to humans (IARC, 2012). Based on these findings, there is a need to investigate prostate cancer risk in rubber manufacturing workers to provide further evidence.

2.5.6 Polychlorinated Biphenyls/Other Chemicals

Occupational exposure to polychlorinated biphenyls (PCBs) is possible in a number of different industries, primarily in the electrical industry (transformer and capacitor manufacturing plants) and in paper and printing industries (ATSDR, 2014). Workplace exposure to PCBs can occur through inhalation and dermal routes of passage (ATSDR, 2014). Even if PCBs are not being manufactured, these compounds can be persistent for decades after in the environment. PCBs are recognized as endocrine disruptors and have been linked to hormonal cancers, but less commonly with prostate cancer. Mortality patterns of deaths from 1982-1987 of US electrical workers showed a significant excess of deaths from prostate cancer (PMR=107) (Robinson et al, 1999). Another study of US electric utility workers examined if exposure to electromagnetic fields (EMFs) or PCBs were linked to prostate cancer mortality. A significant association was observed for EMFs exposure, however non-significant for PCB exposure. At high levels of exposure, both were not associated with prostate cancer mortality (Charles et al, 2003). A study that examined a cohort of over 24,000 capacitor-manufacturing plant workers observed significant associations with cumulative PCB exposure and prostate cancer mortality (Ruder et al, 2014). An increased risk of prostate cancer was recognized in the highest quartile of cumulative exposure compared to the lowest quartile (Ruder et al, 2014).

Studies over the years have shown mixed findings for PCB exposure and prostate cancer mortality, and further evidence is needed. Other chemical exposures such as hydrazine, trichloroethylene (TCE), polycyclic aromatic hydrocarbons (PAHs), benzene and mineral oils were assessed in a case-control study on nuclear energy and rocket engine-testing facility workers between 1950 and 1992 (Krishnadasan et al, 2007). Low and moderate TCE exposure was not significantly associated with prostate cancer (OR 1.3, 95% CI 0.8-2.1) but high TCE exposure was significantly associated with prostate cancer (OR 2.1, 95% CI 1.2-3.9). Increasing TCE exposure levels and prostate cancer demonstrated a positive trend (p_{trend}=0.02) (Krishnadasan et al, 2007). Some significant associations were seen for the other chemicals, but these associations attenuated with adjustments and when lagged for 20 years (Krishnadasan et al, 2007). IARC classified PCBs as a Group 1 carcinogen, however there is very minimal evidence for prostate cancer. Further investigation is needed on the risk of prostate cancer from exposure to PCBs.

2.5.7 Cadmium

Cadmium has been suspected as a prostate carcinogen commonly in occupations involving metal smelting and refining and alloy and battery manufacturing. As a widely used metal, its toxicity has been disclosed since the 1950s. Cadmium exposure may affect cellular function by inducing cell death, increasing mutagenesis and inhibiting DNA repair. The effects from exposure may also cause oxidative stress leading to DNA damage (Bertin & Averbeck, 2006). The prostate was historically one of the first cancer sites thought to be associated with cadmium exposure (Verougstraete et al, 2003). Although the evidence is still inconsistent and recent reviews are showing only some association, cadmium in workplace and environmental settings is still considered detrimental to human health. Exposure in these occupations can be from dust and fume inhalation or ingestion. Earlier studies found an association between cadmium exposure in workers and prostate cancer mortality (Elghany et al, 1990; IARC, 2012), whereas later studies repeatedly showed inconsistent findings (Sorahan et al, 1995; Verougstraete et al, 2003; Sorahan et al, 2004; Chen et al, 2016).

A recent meta-analysis on 12 cohort studies and 9 case-control studies was conducted to understand the overall association in both general and occupation populations. The meta-analysis did not identify convincing evidence as neither population demonstrated significant associations between cadmium exposure and risk of prostate cancer (Chen et al, 2016). Another meta-analysis comprised of 8 case-control studies and 14 cohort studies also examined cadmium exposure in general and occupation populations. The authors of this meta-analysis suggested that high exposure to cadmium in occupational populations is likely associated with prostate cancer (SMR 1.66, 95% CI 1.10-2.50), whereas exposure in the general population (non-occupational groups) showed no association to prostate cancer risk (OR 1.21, 95% CI 0.91-1.64) (Ju-Kun et al, 2016). In 2012, IARC classified cadmium and cadmium compounds as a Group 1 carcinogen based on both non-occupational and occupational exposures, however the risk for prostate cancer was only suggestive based on limited evidence (IARC, 2012).

2.5.7.1 Other Metals

Other metals that have been linked to prostate cancer in occupational settings include aluminum, lead, and arsenic. Aluminum is typically produced through electrolysis of alumina (Gibbs & Labreche, 2014). Electrolysis takes place in designated potrooms which involve airborne contaminants. The potrooms can expose workers to heat, carbon, carbon monoxide, carbon dioxide, cryolite dust, alumina, and other agents (Gibbs & Labreche, 2014). A recent systematic review on aluminum exposure identified one Australian study that reported significant increased prostate cancer mortality after 20 years of employment in an aluminum smelter, although not for incidence (Gibbs & Labreche, 2014). No other studies in the review identified significant associations. A challenge in the review was the difficulty comparing studies across nations as there are different screening practices across nations. Also, the high likelihood of survival from prostate cancer makes mortality a less accurate estimate for prostate cancer (Gibbs & Labreche, 2014). Increased incidence of prostate cancer was observed for aluminum smelter workers in a recent study in Spain, however this finding was not statistically significant (Maltseva et al, 2016). An earlier study found an excess in death from prostate cancer in smelter workers, which was highest in production workers and in those who worked at least 20 years. However, they did not find an excess in prostate cancer incidence (Sim et al, 2009).

The majority of lead exposure in adults stems from occupational exposure. Lead is often used as an industrial metal, typically used on its own or combined with other metals (Lam et al, 2007). Exposure to high levels of lead or exposure to lead for a long period of time can result in serious health problems (Lam et al, 2007). IARC evaluated lead in 1987 and classified lead as a possible human carcinogen based on sufficient evidence for carcinogenicity in animals but inadequate evidence for carcinogenicity in humans (Lam et al, 2007). The limited evidence for carcinogenicity does not include risk of prostate cancer. Very few studies have been able to show an association between occupational lead exposure and prostate cancer with most showing no association (Wong and Raabe, 2000; Siddiqui et al, 2002; Lam et al, 2007; Gwini et al, 2012). Based on the few studies available, it is unlikely that occupational lead exposure is associated with prostate cancer.

Inorganic arsenic and its compounds have been associated with multiple cancers and can be highly toxic to the human body. Studies evaluated by IARC showed limited evidence for prostate cancer risk but these were primarily non-occupational (IARC, 2012). The epidemiological evidence included in the IARC evaluation was from populations that had significant arsenic levels in drinking water, resulting in mainly non-occupational findings. Some were mortality studies that demonstrated a dose-response relationship between long term exposure in drinking water and risk of prostate cancer, while other studies observed no association (IARC, 2012). As the evidence for arsenic exposure and prostate cancer risk is limited, the evidence is even more minimal for occupational exposure to arsenic.

2.5.8 Radiation

Studies in the literature have explored the relationship between prostate cancer risk and various forms of radiation exposure. Solar ultraviolet (UV) radiation exposure has been of interest as it is speculated that outdoor workers may have a decreased risk for prostate cancer when compared to indoor workers based on the increased sun exposure in outdoor workers (John et al, 2005). This association may be a result of the protective nature of vitamin D for prostate cancer. Vitamin D has been considered a protective agent since the 1990s when prostate cancer studies focused on increasing incidence in the northern latitudes of the world, although there have been sparse epidemiological evidence for prostate cancer (John et al, 2005).

A recent study by Peters et al (2016) found no association between sun exposure and prostate cancer among outdoor workers. They did however find a statistically significant association for outdoor workers with highest cumulative occupational exposure to solar UV. Another study examined the Swedish population to look at cancer risks based on previous sun exposure and a significant elevated risk for prostate cancer was observed (OR 1.23, 95% CI 1.19-1.28) (Lindelof et al, 2012). Even though this population study was not based on occupation, the authors still adjusted for type of occupation (indoor or outdoor work) in their analysis (Lindelof et al, 2012). The findings contradict the theory that vitamin D from sun exposure is protective for cancers. Earlier studies that also looked at residential and occupational sun exposure and prostate cancer risk were also inconsistent (Freedman et al, 2002; John et al, 2005). One study found that prostate cancer was inversely associated with residential sunlight exposure, with only a significant positive association for outdoor farming workers. Other outdoor workers in this study had no associated risk for prostate cancer (Freedman et al, 2002). Another study identified that reduced risks for prostate cancer were associated with high sun exposure, high occupational outdoor activity, and high activity vitamin D receptors in the presence of high sun exposure (John et al, 2005).

There is some evidence that links thorium-232 and decay products and x-radiation/gamma radiation to prostate cancer risk (IARC, 2001; IARC 2000). Pukkala et al (2003) examined a cohort of over 10,000 male airline pilots from across multiple Nordic nations to look at cosmic radiation exposure and cancer incidence. An increase in prostate cancer was observed with an increasing number of flight hours in long distance aircrafts (SIR 1.56, 95% CI 0.67-3.07; p trend 0.07). An increase was also seen with increasing number of long-haul hours (p trend 0.01) in men 60 years of age and older and a significant increasing trend was seen with cumulative ionizing radiation dose in men under the age of 60 years (p trend 0.02) (Pukkala et al, 2003). The authors speculate the possibility of disrupted circadian rhythms affecting hormone related cancers such as prostate cancer (Pukkala et al, 2003). Circadian rhythm (sleep wake cycle) disturbances are common with airline occupations with workers flying across different time zones frequently and this can lead to suppression of melatonin secretion (Pukkala et al, 2003). Melatonin is thought to be protective against tumor development especially in hormone related cancers however the possible mechanisms involved are not clear. Buja et al (2005) examined cancer incidence among male flight attendants and civil and military pilots as a meta-analysis and observed an increased risk for prostate cancer in civil pilots (meta-SIR 1.47, 95% CI 1.06-2.05). An earlier meta-analysis also found that male pilots had an increased risk for prostate cancer (RR 1.65, 95% CI 1.19-2.29) (Ballard et al, 2000). Both studies suggest factors of ionizing radiation and other chemical exposures, age, and disrupted sleep patterns as being involved in these occupations (Ballard et al, 2000; Buja et al, 2005).

A cohort study of air Canada pilots in 1996 also observed a significantly increased risk for prostate cancer incidence (SIR 1.87, 90% 1.38-2.49) while observing a non-significantly elevated risk for prostate cancer mortality (Band et al, 1996). Previous studies also examined prostate cancer risk in the United Kingdom Atomic Energy Authority (UKAEA) employees who may be exposed to multiple occupational agents including radionuclides. The initial study in 1985 observed significantly increased mortality from prostate cancer but further investigation was needed on specific exposures (Beral et al, 1985). A second study in 1993 observed a significantly increased risk in men who worked in environments involving tritium, chromium-51, iron-59, cobalt-60 or zinc-65 (Rooney et al, 1993). No prostate cancer risk was associated with other metal exposures, organic or inorganic chemicals (Rooney et al, 1993). A third published study in 1994 included the UKAEA cohort along with two other industry workforces and found no association for external radiation exposure and prostate cancer which contradicts previous study findings (Carpenter et al, 1994). There is still significant inconsistency concerning different types of radiation exposure and prostate cancer risk.

2.5.9 Shift Work

As described in Section *1.4.1 Exposure-Response Mechanisms*, the circadian rhythm plays an important role in maintaining the body's rhythms. Shift work leads to sleep disruption which ultimately disrupts the body's circadian rhythm leading to potential adverse health problems (Dickerman et al, 2016). The body's circadian rhythm is important in regulating the time, duration and structure of the sleep cycle. Shift work can alter the sleep cycle when shift workers try to adjust to schedules by sleeping during the day time hours and by staying awake during night hours. This change contradicts the daytime wakefulness and nighttime sleep cycle of the circadian system (Sigurdardottir et al, 2012). Occupational studies involve airline workers to assess shift work as these workers are likely to endure long haul flights across multiple time zones which increases the likelihood of circadian rhythm disruption (Sigurdardottir et al, 2012). Additionally, night shift work is considered to be a useful proxy for circadian disruption which is generally derived from job titles, followed by sleep schedules and light at night exposure (Sigurdardottir et al, 2012). Shift work can lead to increased sleep disturbances, obesity, hypertension, and some cancers. Based on the existing evidence, IARC has classified shift work as probably carcinogenic to humans based on the evidence from experimental animal models and limited evidence from human studies (Sigurdardottir et al, 2012). Several previous studies have focused on shift work and breast cancer, linked to changes in hormone secretion as a possible factor leading to breast cancer (Kubo et al, 2006). This is also possible with prostate cancer, although the disruption of the circadian rhythm has been sparsely linked to prostate cancer in previous studies.

Kubo et al (2006) examined a large Japanese cohort and found rotating shift workers with a significantly elevated prostate cancer risk (RR 3.0, 95% CI 1.2-7.7) when compared to day workers. They also observed a nonsignificant elevated risk in night shift workers, with adjustments made for multiple factors. Another study published in 2007 observed only a non-significant elevated risk for prostate cancer in shift workers (SIR 1.04, 95% CI 0.99-1.10) (Schwartzbaum et al, 2007). The common types of shift work occupations in these men were paper/paperboard, paper/pulp, furnace, firefighting, police work, civilian protective work and railway engineer drivers (Schwartzbaum et al, 2007). Another study by Kubo et al (2011) on a Japanese manufacturing corporation observed a significant increased risk in shift workers (OR 1.79, 95% CI 0.57-5.68) when compared to daytime workers. Parent et al (2012) also reported an increased risk of prostate cancer in men who ever worked at night (OR 2.09, 95% CI 1.40-3.14) compared to men who never worked at night, although there was no increased risk with increasing duration of night work. Similarly, Papantoniou et al (2015a) observed a non-significantly elevated risk in night shift workers (OR 1.14, 95% CI 0.94-1.37) when compared to non-night shift workers but this study saw an increased risk with duration of exposure.

The most recent meta-analysis on shift work and prostate cancer reported a significant association (RR 1.24, 95% CI 1.05-1.46) with evidence of a dose response relationship with increasing night shift work of 5 years of duration (Rao et al, 2015). There is also evidence of a statistically significant association between shiftwork (men who worked regular night shifts or rotating shifts) and elevated PSA levels. Specifically, current shiftwork was associated with PSA levels 4.0 ng/ml and greater (OR 2.48, 95% CI 1.08-5.70) which continued to be significant with additional adjustments (Flynn-Evans et al, 2013). Furthermore, Papantoniou et al (2015b) assessed night shift work and sex steroid production and observed that night workers had higher levels of androgens (geometric mean ratio (GMR) 1.44, 95% CI 1.03-2.00) and total progestogens (GMR 1.65, 95% CI 1.17-2.32) when compared to daytime workers. The study also observed delayed peak androgen production in night shift workers compared to daytime workers (Papantoniou et al, 2015b). These hormone specific associations demonstrate that disruption of the circadian rhythm is likely to lead to internal hormonal changes possibly related to the development of prostate cancer.

Other studies have also shown no association between shift work, sleep duration, and prostate cancer (Gapstur et al, 2014; Yong et al, 2014; Hammer et al, 2015; Markt et al, 2015). Dickerman et al (2016) examined the relationship between self-reported chronotype, shift work and prostate cancer in a cohort of Finnish twins. The study found that chronotype significantly affected the relationship between shift work and prostate cancer. But overall, no associations were recognized between shift work, sleep duration and prostate cancer (Dickerman et al, 2016). Epidemiological studies exploring shift work and prostate cancer run into the challenge of defining shift work, latency period of prostate cancer, and accounting for possible confounding factors (Costa, 2010). Shift work continues to be an important factor in occupation and it is important to continue understanding how shift work affects the risk of prostate cancer.

This thesis will examine prostate cancer incidence in different occupation groups to strengthen the existing evidence and to provide new evidence on occupational risk factors. This thesis aims to provide evidence in a Canadian context by utilizing multiple Canadian population datasets. While examining occupation in Canadian populations, this thesis will account for important non-occupational factors that may influence the relationship between occupation and prostate cancer risk.

2.6 Occupation and Prostate Cancer: Possible Mechanisms

There are few existing theories that describe biological plausibility when linking occupational exposures and prostate cancer and currently there is no compelling evidence to show established mechanisms. As the prostate is a part of the reproductive system and relies on the function of hormones in the body, it is likely that occupational exposures have hormonal influences that affect prostate cancer risk. The strongest epidemiologic and experimental evidence for biological plausibility lies with endocrine disrupting compounds, with some epidemiologic evidence supporting associations to shift work and sedentary behaviour.

2.6.1 Endocrine Disruptors

Endocrine disrupting (ED) compounds can influence prostate cancer progression in both human and animal studies. *In vivo* studies involving animal models has shown evidence between endocrine disruptors and prostate carcinogenesis (Prins, 2008; De Coster & van Larebeke, 2012). As the prostate is controlled by testosterone, it is theorized that androgenic stimulation or increased estrogen levels may promote growth of cancerous cells in the prostate (Parent et al, 2009; Golden et al, 1998). Early studies on long term testosterone exposure in rats observed the development of prostate cancer in a limited number of the rats. However, when testosterone was administered with estradiol, prostate adenocarcinomas developed in a majority of the rats (>90%) within one year of administration (Tewari, 2013). Although there is evidence of hormonal carcinogenesis in rodent studies, it is important to note that the rat prostate anatomy and embryology significantly differs from the human prostate (Tewari, 2013).

In the human body, EDs can impact hormone levels which can progress to tumor initiation or DNA damage (Parent et al, 2009; Van Maele-Fabry & Willems, 2003). EDs can work through nuclear receptors, estrogen-related receptors, or interact with targets in the cytosol leading to the activation of different pathways or nitric oxide modulation (De Coster & van Larebeke, 2012). They can also interfere with multiple processes in the human body that affect endogenous hormones, genomic and non-genomic pathways, estrogen receptors, and DNA methylation (De Coster & van Larebeke, 2012). These include the ratio of estrogen and androgen in the prostate and plasma, the expression of steroid enzymes, the binding to membrane receptors, and genomic and non-genomic mechanisms of action (Tewari, 2013). Endocrine disruptors may disturb estrogen signaling by interfering with any of the mentioned factors leading to the alteration of estrogen levels in the body (De Coster & van Larebeke, 2012, Tewari, 2013). The prostate is likely to be estrogen sensitive and may respond to estrogen stimulators in critical windows of development over a lifetime (Prins, 2008). These hormonal influences apply to occupational agents that are in contact with the human body.

Notable endocrine disruptors such as organochlorine pesticides, polychlorinated biphenyl (PCB) and bisphenol A (BPA), toxic metals (cadmium and arsenic), and diesel exhaust have shown changes in cell proliferation, differentiation patterns, prostate size and other changes that may impact cancer risk (De Coster & van Larebeke, 2012). Most of these disruptors have estrogen like activity and can be referred to as xenoestrogens, accumulating in the environment and affecting estrogen-related diseases such as prostate cancer. Specific agriculture pesticides such as chlorpyrifos, fonofos, and phorate can inhibit enzymes that metabolize steroid hormones in the liver (Prins, 2008). It is possible that specific pesticides can interfere with steroid hormone metabolism in the prostate as well. Similarly, PCB and BPA exposures can influence estrogenic or anti-androgenic activities, affecting target organs like the prostate (Prins, 2008). PCBs are fat soluble chemicals that can bio-accumulate in the human body and can inhibit estrogen sulfotransferase activity leading to increased availability of estrogen in the body (Prins, 2008). Human epidemiology studies have shown associations between high exposure to PCBs and prostate cancer incidence and mortality, whereas animal studies have shown a suggestive association (Prins, 2008). BPA is a polymer used in polycarbonate plastics and resins with low binding capacity to estrogen receptors. Evidence from both animal and human cell line studies have shown that BPA can stimulate cancer progression and prostate cancer cell proliferation (Prins, 2008). BPA exposure during critical windows of life may lead to susceptibility of prostate cancer later in life (Richter et al, 2007). Prenatal exposure to BPA in rats have been shown to affect the prostate size and response to androgens. Also, BPA injections to neonatal rats led to prostate intraepithelial neoplasia lesions, also known as pre-tumorous cancer lesions in the rats later in their adult life (Richter et al, 2007).

The prostate gland is susceptible to hormonal carcinogenesis and this is important because of the increase in estradiol levels in men as they age and in return this may increase their risk for prostate cancer (Prins, 2008). Metals, such as cadmium and arsenic, can bio-accumulate in the body and interact with estrogen receptors leading to estrogen mimicking and endocrine disruption as shown in *in vitro* studies (Prins, 2008). Prostatic tumors were induced in rats by oral ingestion of cadmium. Epidemiological studies have shown associations between cadmium/arsenic exposure and prostate cancer, however there are studies that have also refuted these associations, with a need for future investigation (Prins, 2008). There is also some evidence from animal studies that observed diesel exhaust exposure inducing enzymatic changes in the prostate glands, while promoting the growth of prostate cancer cells through antiestrogenic effects (Lee et al, 1980; Seidler et al, 1998).

2.6.2 Disruption of the Circadian Rhythm

The working population has significantly evolved over time and has moved away from the traditional working day to include shift and night work and other forms of working hours. With changes in the regular working hours, there has been significant research published on shift work and how it affects the biological processes of the human body leading to diseases such as cancer (Costa, 2010). The circadian rhythm of the human body, also known as the 24 hour clock, regulates the body’s biological functions while maintaining the sleep/wake cycle and hormone levels (Costa, 2010; Boivin & Boudreau, 2014). By altering the sleep/wake cycle to adjust for shift work (night shift vs. day shift), the human body is forced to modify its biological clock and this can cause significant stress on biological functions (Costal, 2010; Boivin & Boudreau, 2014). Shift work affects all aspects that are routinely regulated and can cause significant changes in cortisol and melatonin levels, while also being impacted by gene-environment interaction (Boivin & Boudreau, 2014). The mechanisms that link shift work to cancer outcomes are quite complex and involve multiple factors. Specifically, melatonin levels may be affected which regulates the immune system and inhibits the growth of cancer cells by antimitosis, antioxidation and antiangiogenesis (Rao et al, 2015).

The existing evidence has focused primarily on breast cancer, as melatonin suppression can lead to endocrine responses in the breast and could possibly have the same effect in the prostate (Costa, 2010). Continuous shift work leads to a decrease in melatonin production which can promote continuous secretion of testosterone which further influences the growth and differentiation of prostate cancer and increase prostate specific antigen levels (Rao et al, 2015). Employment in night shift work can lead to less time spent outdoors during daylight hours, limiting sun exposure. Less sun exposure can lead to less circulating vitamin D in the body, and vitamin D is an important part of cellular processes, including prohibiting cancer cell growth (Fritschi et al, 2011). There has been limited evidence in animal studies that show that vitamin D could decrease the occurrence of cancer and even less for evidence related to prostate cancer risk (Fritschi et al, 2011; Rao et al, 2015).

2.6.3 Sedentary Behaviour and Obesity

Epidemiological evidence has shown that physical activity can reduce cancer risk by regulating hormone levels, insulin levels, and the immune system (Lynch et al, 2014). Sedentary behaviour, on the other hand, can have the opposite impact on cancer risk. Sedentary behaviour involves low energy expenditure and limited whole-body movement. This is generally recognized as sitting behaviour in the work environment (Lynch, 2010). Over time, sedentary behaviour can lead to accumulated adiposity which can lead to inflammation, insulin resistance, and increased hormone levels, all of which can promote carcinogenic activity (Lynch, 2010). Increased adiposity can lead to weight gain and obesity which are primary agents in facilitating the pathways to prostate cancer progression (Freedland & Aronson, 2004; Lynch et al, 2014). Weight gain and obesity have been associated with multiple health conditions, with evidence for cancer risk, and specifically, prostate cancer. Increased adiposity can lead to chronic inflammation and metabolic dysfunction which may be operative in the development of prostate cancer (Lynch et al, 2014). This can lead to insulin resistance which causes the imbalance of glucose homeostasis. It can also intensify the association between sex hormones and cancer risk, as seen in women affected by hormonal cancers (Freedland & Aronson, 2004). The visceral adipose tissue is important for adipocytokine production which influences estrogen biosynthesis (Lynch, 2010). This is especially important for prostate cancer as changes in estrogen levels can influence risk for prostate cancer. Although there is limited evidence for sedentary behaviour, obesity, and prostate cancer risk, further research is needed to understand the biological mechanisms involved.

2.7 Occupational Epidemiology Research Methods

2.7.1 Occupational Study Designs

There are different study designs that are typically used in occupational studies. The choice of study design can depend on the purpose of the study, feasibility, and availability of data and resources (Checkoway et al, 2007). As randomized controlled trials are often not suitable for occupational studies, there are multiple observational study designs which are better suited for assessing the relationship between risk factors and cancer outcomes (Song & Chung, 2011). Traditionally, case series reports or studies were utilized to investigate an excess of disease cases or clusters of disease cases in worker populations. Case series studies would examine the worker populations to investigate if these workers shared similar exposures in similar work environments (Checkoway et al, 2007). More reliable and valid epidemiologic approaches such as case-control and cohort designs were developed, which will be discussed further.

2.7.1.1 Case-Control Design

The case-control design is commonly used in occupational studies and is based on defined occupational groups or population based groups. In a case-control study, all incident cases that occurred in the source population over a period of time are studied and compared to a control group from the same source population over the same time period (Song & Chung, 2011). Collection of case and control information is based on specified source population over a defined time period. Cases are typically obtained from sources including hospitals records, cancer registries, death certificates, or birth certificates. In cancer case-control studies, it is common for cases to be drawn from registries which allow for identification of cases based on date of birth, gender, residence, and other factors (Checkoway et al, 2007). In a case-control design, cases are defined first, followed by the source population and risk period in order to define the controls. Controls can be from population sources or other occupation groups similar to the case groups as long as the controls do not have the disease of interest (Checkoway et al, 2007). Controls are typically sampled from the same source population as the cases, or are selected during the follow-up period or over the period of the study. Controls can be individually or frequency matched to cases. Individual matching involves matching case by case, for example, if a case is 30 years of age then a control is selected with the same age. Frequency matching involves matching based on a group of cases, for example, if 20 cases are aged 25-30 years, then 20 controls in the same age category will be selected. This can lead to similar distribution of confounding factors, such as age, across the case and control groups. When assessing specific job-related risk factors, an appropriate source population is needed which should include workers in multiple occupations and industries (Checkoway et al, 2007). This allows for exposures in the control group to be representative of the source population making it comparable to the case group and leading to better study validity.

Case-control studies are cost effective, time efficient, and ideal for studying outbreaks or rare diseases, and for preliminary study of potential risk factors. Case-control studies are useful for studying cancer outcomes such as prostate cancer because it can yield a large number of cases with prostate cancer as cases are selected based on outcome status. Case-control studies also allow for the study of multiple factors, which is advantageous to address potential confounders or risk factors for the disease outcome in detail (Checkoway et al, 2007). Exposure data from cases and controls are generally collected retrospectively and are usually self-reported via survey, interview, or retrieved from records. Self-reported information or information collected by an interviewer can be accompanied by information or recall bias (Song & Chung, 2011). These biases can affect the accuracy or completeness of the information, so careful consideration of these biases in case-control studies is important. Other disadvantages are that is can be difficult to validate the information provided by cases and controls, and selection of controls may be difficult if trying to match based on specific factors (Song & Chung, 2011).

2.7.1.2 Cohort Design

A cohort design is a comprehensive design for occupational studies that is favoured for assessing patterns of risk factors and disease outcomes. With this study design, a population is followed over time to determine the incidence of specific health outcomes and are designed for the temporal sequence from exposure to outcome (Checkoway et al, 2007). This design is useful for cancer diseases that have a long latency period to capture cancer cases over time. This design can provide evidence for cancer outcomes and is useful when exploring multiple outcomes. Cohort designs are often used as prospective or retrospective cohort studies. A prospective cohort study collects data from present to a future time and can provide complete and specific exposure data (Checkoway et al, 2007). This type of cohort design is costly, requires follow-up maintenance, and is likely to be susceptible to loss to follow-up. A retrospective cohort study looks into the past and examines outcomes based on exposures from the past years (Song & Chung, 2010). This type of cohort study may have less control over variables, is more susceptible to recall bias, and is often missing data on potential confounders. Although there are challenges with both type of cohort designs, these designs can provide strong scientific evidence for occupational research (Song & Chung, 2010).

A cohort can be defined in different ways, and the most common method is by defining all workers employed in a specific workplace or occupation as the cohort. Further complex designs can include additional workplaces and occupation groups, an entire professional organization or union of workers, or a large population cohort expanding across multiple regions (Checkoway et al, 2007). Limiting the cohort to workers from only single workplaces or fewer locations can make it less difficult to characterize exposures or work histories. When expanding the cohort to include multiple worker populations or population groups can lead to increased heterogeneity among exposures and work histories (Checkoway et al, 2007). However, this can be advantageous when investigating rare outcomes such as cancer because it provides a larger sample size increasing the likelihood of capturing more cases.

Once the cohort is defined, sources of information appropriate for the cohort can be linked together to capture details on work history, death, vital status, and morbidity. Cohort designs are complex and require resources to ensure that complete and appropriate follow-up is achieved without compromising the accuracy and validity of the information (Checkoway et al, 2007). Sources of cohort information include work history records, medical claims, disease registries, and employment rosters or union lists (Song & Chung, 2010). When defining a cohort group, few restriction criteria may be in place depending on the source population. For example in cohort groups involving workplaces, it may be necessary to remove those who did not work similar employment terms such as contract workers or short term workers. For cohort groups involving populations, individuals may be removed if they do not have a valid work history record or do not reside or live in the same location as others in the population. These restrictions are based on the study purpose and other defined elements (Checkoway et al, 2007).

Cohorts are followed up until a time end point and require information on vital status, morbidity, and cause of death to account for death, migration, and loss to follow-up. This is necessary for cohort studies in order to evaluate individuals who leave the cohort, individuals who achieve the disease outcome, or individuals who die from the disease outcome or other causes (Song & Chung, 2010). Ultimately, this will minimize bias, by accounting for loss to follow-up throughout the study. Once the cohort is established, the individuals who attain the disease outcome of interest are then compared to those who did not attain the disease outcome of interest. These two groups are further compared based on work history, exposure assessment, and other potential confounding factors. Cohort studies are valuable in that they can assess multiple outcomes based on specific exposures, while also providing detailed information on those who do and do not attain disease status (Song & Chung, 2010).

2.7.2 Collecting Occupation Information

Occupation information is obtained through similar methods in both case-control and cohort study designs. There are a variety of approaches to assessing occupational information and the design depends on the type of research question, resources available and time and cost constraints (Checkoway et al, 2007). Job title information is commonly reported by participants either in questionnaires or through interviews. Questionnaire and interview methods are useful when trying to capture a large sample size and when there are no other methods of collecting exposure data (Nieuwenhuijen, 2005). Questionnaire data generally includes job titles held over the lifetime, duration and frequency of jobs, and the potential exposures involved in the jobs held. By obtaining lifetime job history information from individuals, researchers are provided with concise job profiles for each individual (‘t Mannetje & Kromhout, 2003).

There are common challenges with obtaining occupational information from participants. Collecting concise and full job histories can be challenging if participants do not completely report job history or if they cannot recall their job history accurately. Recall bias is expected with data collection, which will be discussed in detail in the following thesis sections (Song & Chung, 2011). Reported job titles are then coded by qualified occupational hygienists using standardized national or international classifications for occupation and industry. Use of standardized classifications allow for comparability across studies, both nationally and internationally (‘t Mannetje & Kromhout, 2003). Potential exposures related to job titles are also used to understand occupational information. Exposure assessment can be done through questionnaires, biological samples, and sampling of occupational environments (‘t Mannetje & Kromhout, 2003). The reported exposures are then evaluated using databases that provide estimates on the number of workers occupationally exposed to agents in different nations. However, this is only relevant for known carcinogens and corresponding disease outcomes. For example, there are no established associations for occupational exposures and prostate cancer, which makes it challenging to use existing databases in the case of prostate cancer (‘t Mannetje & Kromhout, 2003).

2.7.3 Issues Affecting Occupation and Prostate Cancer Studies

2.7.3.1 Selection, Recall, and Reporting Biases

When selecting participants from a population, commonly known as the source population, there can be selection bias if the study population does not represent the source population (Delgado-Rodriguez & Llorca, 2004). Appropriate case and control recruitment from the source population for case-control designs is important to reduce selection bias (Pearce et al, 2007). To minimize selection bias, participants need to be recruited in the case and control groups independent of factors related to their exposure status. Selection bias is less likely with a cohort design as it uses the entire source population for recruitment and follow-up, but it is possible if there is incomplete participation or follow-up by participants (Pearce et al, 2007). To control for selection bias in the design of the study and through follow-up, it is important to consider maximizing participation or response rates and minimizing loss to follow-up. This can be achieved by adjusting for factors related to loss to follow-up through different methods of stratification, standard regression, or inverse probability-of-censoring weighted estimation (Howe et al, 2016).

Recall bias is a classic bias that is common in self-reported data. Recall bias commonly occurs in case-control studies if participants are aware of the disease of interest and of the risk factors that influence the disease of interest. It is less likely in cohort studies since participants in cohorts generally do not have the disease of interest when providing information about risk factors. This can influence the answers provided by participants (Delgado-Rodriguez & Llorca, 2004). Recall bias is less likely to be an issue with prostate cancer because there are very few known risk factors for prostate cancer. But it can affect occupational information if participants cannot accurately report the exact timing and duration of specific occupations they held over time. Recall bias can be minimized in a number of different ways such as: utilizing a nested case-control study design, choosing an appropriate control group, using appropriate data collection protocols, using well-structured questionnaires, giving participants enough time to respond to questions, blinding the study participants to the study hypothesis or specific factors of interest, and by using other sources of reported data to confirm collected data (Hassan, 2005).

Reporting bias occurs when the reported information from participants is provided in the direction of interest to researchers. For example, when asked about behavioural factors (e.g. smoking or alcohol consumption), participants may perceive these factors as undesirable and under-report their habits (Delgado-Rodriguez & Llorca, 2004). Reporting bias leads to participants under-reporting or selectively reporting. Reporting bias can be minimized by blinding the study participants to the study hypotheses or specific factors of interest that may be linked to the outcome of interest (Hassan, 2005). Also, by making sure questionnaires or questions are regarded equally and by asking repetitive questions in different ways to ensure accuracy in participant responses.

2.7.3.2 Random Error (Chance)

In any epidemiological study, random error is likely to occur and can contribute to chance findings. In any epidemiological study, the study population is only a sample of the general population, and each study population varies from one another (Checkoway et al, 2007). The random variation from study to study results in random error which can cause an overestimation or underestimation of estimates. To reduce random error, studies can increase the sample size to retrieve more observations from a large population or studies can take repeated estimates (Pearce et al, 2007). Reducing random error leads to increased precision of estimates and narrow confidence intervals (Checkoway et al, 2007).

2.7.3.3 Misclassification

Misclassification can be non-differential or differential and is very difficult to overcome in occupational studies. Non-differential misclassification is when both groups of exposed and non-exposed people have the same probability of being misclassified by disease status or if the diseased and non-diseased people have the same probability of being misclassified by exposure. Non-differential misclassification can result in a false negative leading to an underestimation of the association between exposure and disease outcome (Pearce et al, 2007; Delgado-Rodriguez & Llorca, 2004). Differential misclassification, on the other hand, is when misclassification of exposure differs across both groups of diseased and non-diseased people or when misclassification of disease status differs across both exposed and non-exposed people (Pearce et al, 2007; Delgado-Rodriguez & Llorca, 2004). It is important to address the potential impact of misclassification in a study. Using statistical methods to compute reliable sensitivity and specificity estimates is useful in controlling misclassification, however it is difficult to avoid misclassification in occupational study designs. When assessing job history files, it is important to appropriately code these jobs into accurate exposure categories to reduce potential misclassification. By further assessing these jobs by duration of employment, examining job-specific exposures, and performing sensitivity analyses, misclassification can be further prevented.

2.7.3.4 Healthy Worker Phenomenon

The healthy worker effect is often observed in occupational diseases where worker populations tend to have lower morbidity and mortality than the general population. The healthy worker effect reflects that individuals must be relatively healthy to be employed in the workforce (Li & Sung, 1999; Shah, 2009). In this regard, excesses found in disease morbidity and mortality may be due to exposures in the workplace. Healthy workers are also likely to stay in the workforce longer which can lead to a healthier occupational cohort (Li & Sung, 1999). There are common biases associated with the healthy worker effect. Individuals with symptomatic illnesses are less likely to be employed and some industries may restrict employment based on certain physical or health requirements or they may evaluate the health of individuals before hiring to assess if the individuals are fit for employment (Li & Sung, 1999). Industries involving physically demanding work, like protective services involving firefighting and military work, tend to have healthier workers than industries with less physical demand. With improved health care and better accessibility to health resources, some major industries also provide employees with greater access to health services (Li & Sung, 1999). Generally, if the reference group being compared to the occupation group is the general population, then the healthy worker effect is inevitable. However, comparison of an occupation group to the general population is necessary to understand the differences in cancer risk across both groups. It has been suggested that instead of using the general population as the reference group, one should use other reference groups like other occupation groups (Li & Sung, 1999; Shah, 2009). But this is not a practical method for studies included in this thesis. It is difficult to determine what would be the ideal reference group, especially given that prostate cancer is increasingly common in aging men across different occupation groups. There are no identified standard reference occupation groups for prostate cancer in previous studies. Occupation groups are categorized based on type of work and by comparing occupation groups with different work hazards, there may be increased misclassification or overlap of exposures. Utilizing the general population as a comparison group will provide a large reference group with the least likely overlap of work exposures (Li & Sung, 1999).

2.7.3.5 Confounding

Confounding is an important issue in most epidemiological studies addressing exposure and outcome relationships. A confounder can bias the exposure-disease association if it is a factor that influences or confounds the exposure or disease outcome (Pearce et al, 2007; Delgado-Rodriguez & Llorca, 2004). A confounder can be associated with the disease outcome in the absence of the exposure and it can be associated with the exposure (Pearce et al, 2007). For example, age is a known risk factor for prostate cancer and even though it does not directly cause prostate cancer, it is still a potential confounder. Studies tend to match participants based on potential confounders at baseline to prevent residual confounding. This is usually done for baseline characteristics that affect all participants in the study such as age and gender. Other ways to account for confounders are based on prior knowledge and by understanding the effect that each confounder has on the estimate (Pearce et al, 2007). If there are known confounders for a specific exposure or outcome based on prior knowledge, then these confounders can be adjusted for within the analysis. For potential confounders that are not based on prior knowledge, these can be included in the analysis to observe the effect on the estimate (Pearce et al, 2007). If there are confounders of interest that are not within the provided data, then possible surrogates for the confounder can be used to try to address the impact the confounder of interest has on the outcome (Pearce et al, 2007). In occupational studies, job titles are often used as surrogates for unavailable exposure data. These surrogates can provide useful data on exposures with careful interpretation. For prostate cancer, confounders that need to be accounted for, are known and potential risk factors. This includes age, family history of prostate cancer, ethnicity, and other factors such as marital status, socioeconomic status, and screening behaviours. As there are only few known risk factors for prostate cancer, other potential risk factors are often adjusted for to understand the influence they have on estimates for prostate cancer.

2.7.3.6 Predictors of Screening Behaviours

Understanding predictors of screening behaviour is important as screening was an influential component of prostate cancer patterns over the years. The screening behaviours of men in industrialized nations has been greatly influenced by the introduction of PSA testing. In Canada, prostate cancer incidence rose steadily until 1991 when incidence increased to a peak until 1993. Following this there was a decline from 1993 to 1996, followed by a steady increase until incidence peaked again in 2001 (Dickinson et al, 2016). After 2001, incidence slightly declined and remained steady. These incidence patterns are similar to PSA testing patterns over the same time period. Prostate cancer incidence steadily increased until the introduction of PSA testing which contributed to the peak in incidence from 1991 to 1993 and in 2001 (Dickinson et al, 2016). In Ontario alone, 50,000 PSA tests were performed in 1990 followed by 180,000 tests in 1993 and 700, 000 tests in 2001 (Dickinson et al, 2016). This trend is similar to other Canadian provinces as well. By 2001, almost half of the Canadian men aged 50 years and older had at least one PSA test in their lifetime (Dickinson et al, 2016). These patterns are shown in Figure 1 (Dickinson et al, 2016). With the recent PSA testing controversy, there have been no conclusive recommendations put forward for individuals or for population-based approaches which leaves differential screening to be widespread across populations. Prostate cancer screening has been associated with multiple factors that may influence decisions surrounding the uptake of PSA testing. Factors of interest that have been studied are age, family history of prostate cancer, marital status, ethnicity, and occupation. These factors are recognized as influencing screening in individuals and influencing other coinciding factors as well.

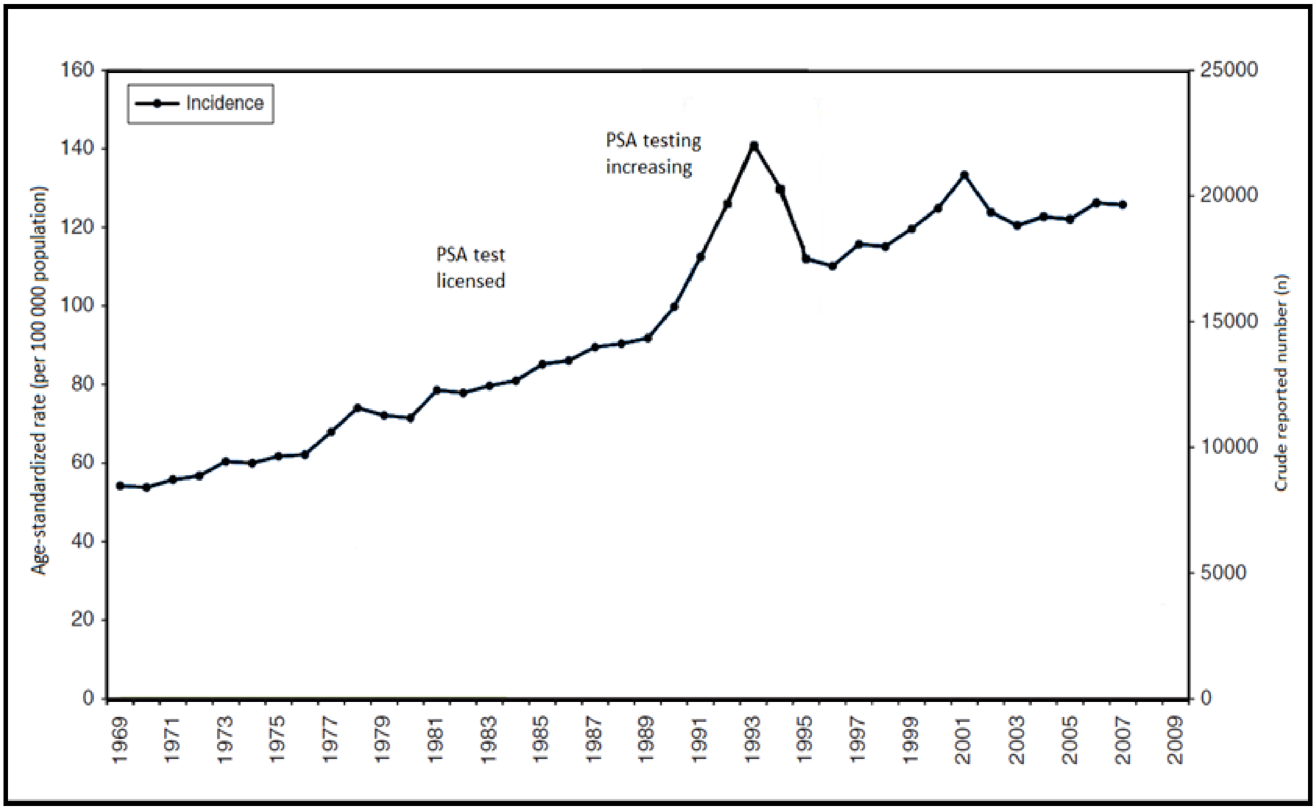

Figure 3. Age standardized prostate cancer incidence, 1969-2009, Canada.
Prostate cancer incidence rates changed over time in Canada, coinciding with the development and release of the prostate specific antigen (PSA) test. The patterns of incidence increased during the time periods of when PSA testing increased, which is represented by the peaks in the early 1990s and 2000s in this graph. This image was adapted from the paper published by Dickinson et al, 2016.

Age is an important predictor that influences screening for prostate cancer as screening rates steadily increase with age. Screening is commonly advised in older men, especially after the age of 50 years (Canadian Cancer Society, 2016). As prostate cancer progression tends to be slow and over a long period of time, screening is usually only recommended in the later part of life when most prostate cancer cases are diagnosed. Aging men have other health concerns which can involve other issues with the prostate gland, leading to increased use of prostate cancer screening methods. Also, with increasing life expectancy it is expected that the number of men diagnosed will also increase. The number of younger men being screened for prostate cancer has also increased with the improvements in screening and treatment methods (Stangelberger et al, 2008).

Men with a family history of prostate cancer are also more likely to be advised by their health care provider to have a PSA test in their lifetime. Based on the knowledge of having a higher risk of prostate cancer due to family history and based on recommendations from their health care provider, these men are likely to get screened (Wallner et al, 2008). Also, married men who have a family history of prostate cancer are more likely to get screened. Studies have shown that marital status impacts prostate cancer screening. Married men are more likely to have a PSA test or seek screening than unmarried men (Wallner et al, 2008; Tyson et al, 2013; Hosain et al, 2012; Fowke et al, 2005). It is suggested that the influence of the partner strongly affects the male partner's decision to seek out prostate cancer screening (Wallner et al, 2008).

Ethnicity is also associated with differences in prostate cancer screening. It is suggested that individuals identifying with ethnic minority groups have decreased participation in cancer screening and as a result are likely to have advanced stages of cancer (Licqurish et al, 2016). Minority groups, specifically in the United States, are less likely to have access and availability to screening resources when compared to other ethnic groups, leading to uninformed decision making around cancer screening (Khan et al, 2015). Studies in the United States have shown that African American and Hispanic men are less likely to seek PSA screening than Caucasian men (Hosain et al, 2012). African American men are recognized as having higher rates of prostate cancer and are more likely to be diagnosed at a younger age than Caucasian men (Hosain et al, 2012). African American men may also have less accessibility to screening resources and are less knowledgeable about PSA screening tests (Fowke et al, 2005; Fradet et al, 2009). Evidence shows that African American men may not be completely aware of the signs and symptoms of prostate cancer and many do not perceive themselves at a higher risk than other ethnic groups (Licqurish et al, 2016). Other ethnic groups that are generally at a lower risk for prostate cancer, such as Asian/Pacific Islander and Hispanic men, are less likely receive PSA testing from their physician until later in age because of their reduced risk (Cheng et al, 2009). Additional factors that may be influential in the decision making around prostate cancer screening are social stigma, fear and, limited health literacy (Licqurish et al, 2016).

A higher socioeconomic status (SES), generally defined as having higher education and income, can also influence screening behaviours. Men with higher SES are likely to have make more informed decisions around PSA testing with better accessibility and utilization of health resources (Cheng et al, 2009; Hosain et al, 2012). A higher SES is associated with lower mortality from prostate cancer which may reflect better health status, affordable and accessible medical care, early detection and treatment and limited high risk health behaviours (Cheng et al, 2009). Men of higher SES more often have better proximity to resources, transportation and scheduling of diagnostic procedures which leads to early detection and treatment and better prostate cancer outcomes (Rundle et al, 2014). Whereas men with lower SES are less likely to pursue PSA screening. These men may be affected by poverty or socioeconomically disadvantaged residential areas, limited availability and accessibility to health resources, limited health infrastructure and lack of knowledge on PSA screening (Tshiswaka et al, 2016).

Occupation is another factor that can influence screening behaviours of men. Employment has been associated with increased prostate cancer screening when compared to those who are unemployed (Jeihooni et al, 2015). But it is expected that there is considerable variation in screening behaviours based on the type occupations held. A large USA 24-state case-control study assessed information on occupation and industry and death certificates on over 60,000 men from 1984 to 1993. Findings showed excess risks of prostate cancer among white collar jobs, like administrators, managers, teachers, engineers and sales (Krstev et al, 1998). Decreased risks of prostate cancer were also observed for other blue collar jobs relating to natural resource based occupations (ex. farmers, fishermen). The associations in the white collar jobs may be related to higher socioeconomic status even though jobs with generally lower socioeconomic status also showed increased risks (Krstev et al, 1998). A Nordic study across five nations (Denmark, Finland, Iceland, Norway and Sweden) examined 15 million people and multiple cancer sites by occupation category. The highest prostate cancer incidence rates were among dentists, administrators and religious workers, whereas the lowest incidence rates were among forestry and fishing workers (Pukkala et al, 2009). The authors suggest that male workers who are less economically active (ex. blue collar jobs) are less likely to go for PSA testing (Pukkala et al, 2009).

White collar jobs involve work related to professional, managerial, or administrative work. These jobs are generally associated with a higher SES which leads to informed decision making and better access to healthcare and screening (Rundle et al, 2013). Men in white collar jobs are recognized as having more contact with health professionals, flexibility, and fewer barriers to access care. If prostate cancer incidence is observed to be higher in white collar jobs than in other jobs, then this could be due to these men having better knowledge and accessibility to screening (Krstev et al, 1998; Pukkala et al, 2009). Blue collar jobs involve skilled and unskilled manual labour with generally lower education and income levels. These workers have more barriers than white collar workers with access to care and screening (Krstev et al, 1998; Pukkala et al, 2009). Men in blue collar jobs may have more difficulty accessing care and have limited flexibility when seeking medical care (Krstev et al, 1998). If blue collar jobs are observed to have a low prostate cancer incidence than other jobs, this could mean that these men are not getting screened as frequently as men in white collar jobs. Although jobs are defined as white collar or blue collar, there are also blended jobs with roles that may overlap or not entirely fit each grouping. Further understanding into these types of jobs and their risk of prostate cancer is needed. When examining occupation, it is useful to have occupational history available in order to account for different jobs held by individuals. At the same time, it is also important to have information on education and income to understand if these factors are consistent with reported occupations. Factors related to screening behaviours will be accounted for in this thesis, to understand their role in the relationship of occupation and prostate cancer risk.

2.7.4 Relevance to Dissertation

Based on the comprehensive literature review, it is clear that previous studies have examined numerous occupational factors and prostate cancer, however most of these studies have resulted in no definitive conclusions or have indicated that further research is needed. By evaluating large population studies we can identify if there are consistent patterns of risk by occupation and industry in Canada. By including both occupational and non-occupational factors, we can also understand the relationship that these factors have to one another and prostate cancer. Given the distribution of prostate cancer across Canada, it is likely that the etiology of prostate cancer involves environmental/occupational influences.

While studying occupational factors, important established risk factors of age, family history of prostate cancer, and ethnicity need to be acknowledged with consideration of potential risk factors that are related to lifestyle and screening behaviours. Prostate cancer is a complex disease involving many factors and with efforts to understand the occupational etiology, promising evidence for future research can be provided.

A single epidemiological study may not be able to investigate multiple occupational research questions, but by conducting multiple separate occupational studies based on tailored research questions, a spectrum of occupational factors can be assessed (Checkoway et al, 2007). At the start of this thesis, fewer studies in Canada were able to capture a range of occupations and industries, account for non-occupational factors, and were limited in population sample size. A majority of the evidence on prostate cancer risk by occupation and industry were published by non-Canadian studies. Through the duration of this thesis, more Canadian studies, including Chapters 4-7 in this thesis, add to the literature providing crucial evidence (Jones et al, 2015; Sharma et al, 2016; Sauve et al, 2016; Sritharan et al, 2016; 2017a; 2017b; 2018). In an often understudied area, these studies provide updated evidence of occupation and prostate cancer relationships.

Chapter 3. Research Aims and Hypotheses

There are no established, accepted preventable factors for prostate cancer and there is a lack of evidence that occupational factors are associated with prostate cancer incidence. By examining occupation and industry groups, there will be a better understanding of how these groups are related to prostate cancer and what type of exposures may be involved, which can help to generate new hypotheses and better direct future research. By utilizing population groups in Canada that have not been thoroughly examined, supporting evidence for current findings with larger sample sizes, occupational variables, and non-occupational variables can be provided. By evaluating if workplace employment is associated to prostate cancer, existing patterns across Canada and potential interventions can be identified. In this thesis, we investigate if there is a relationship between occupation and industry groups and prostate cancer risk. To achieve this, we examine three Canadian population-based studies and conduct a meta-analysis on prostate cancer risk in protective services occupations, a group that was identified in these three Canadian studies and in previous published literature.

3.1 Research Aims & Hypotheses

The primary purpose of this thesis is to investigate the relationship between occupation, industry, and prostate cancer risk in Canadian workers. We proposed to examine Canadian population studies to further understand whether occupational factors play a role in the etiology of prostate cancer, while recognizing how non-occupational factors are involved. The findings of this thesis are presented as four manuscripts that are individual and connected studies (Chapters 4-7). The specific aims and hypotheses of each of the four chapters are described in the following paragraphs.

3.1.1 Specific Aim and Hypotheses for Study 1

Title*: "*Natural Resource Based Industries and Prostate Cancer Risk in Northeastern Ontario: A Case-Control Study"

The first study (Chapter 4) involved the Northeastern Ontario Prostate Cancer case-control study. The case-control was originally created to assess risk factors for prostate cancer in Northeastern Ontario where cancer rates are higher than in other regions of Ontario. This study was used to examine the relationship between specific natural resource based occupations and industries in Northeastern Ontario and prostate cancer risk in men 50 years of age and older (*Aim 1).* Reported job titles were assessed by occupation and industry and reported occupational exposures were assessed to understand the relationship these exposures have to job titles and prostate cancer. This unique dataset is one of the few that provides detailed occupational history and prostate cancer information on men in Northeastern Ontario and involved 760 prostate cancer cases and 1632 controls.

Hypotheses - We hypothesized that there would be associations between natural resource based work and prostate cancer, specifically, that significant associations would be observed with mining and farming occupations. We hypothesized that associations in mining and agriculture would remain consistent with duration of employment (<10 years and >10 years). It was also hypothesized that there would be some association between occupational exposures and prostate cancer, specifically with pesticide exposure. In order to explore these hypotheses, the Northeastern Ontario Prostate Cancer population case-control study was explored to evaluate lifetime work histories of prostate cancer cases and population controls. By cleaning, re-coding, and organizing all occupation and industry job titles, the most detailed job descriptions were used to classify jobs based on tasks and potential related exposures. Available job-specific exposure data related to natural resource based jobs were also evaluated, alongside duration of employment, duration of exposures, and trend analyzes with these data.

3.1.2 Specific Aim & Hypotheses for Study 2

Title: *"***Occupation, industry and prostate cancer risk in Canadian men: a case-control study across eight provinces"**

The second study (Chapter 5) involved the National Enhanced Cancer Surveillance System (NECSS) which was originally created with the purpose of assessing environment-cancer relationships in Canada and to make use of valuable information collected (Johnson et al, 1998). Based on the findings of our first Northeastern Ontario study, we recognized the importance of increasing our sample size, capturing a wider range of occupations and industries, and achieving results across more regions of Canada. In this second study, we sought to examine the relationship between multiple categorized occupation and industry groups and prostate cancer involving 1737 cases and 1803 population controls across eight provinces in Canada (*Aim 2)*. This study is unique in that it is one of the few Canadian studies available with detailed information on occupational factors, non-occupational factors, and prostate cancer in men aged 50 years and older (Villeneuve et al, 1999). Through appropriate data cleaning and re-coding, information on detailed job histories, duration of employment, and self-reported exposure data was utilized.

Hypotheses - We hypothesized that we would observe associations between natural resource based jobs and prostate cancer, with consistent findings in agriculture and mining work. It was also hypothesized that new associations between occupations, industries, and prostate cancer would be observed. Given the limited occupational knowledge on prostate cancer, it was hypothesized that new associations that had not been clearly defined in previous literature would be identified. It was crucial to understand the relationship between occupation, industry, and prostate cancer at a large scale especially as this had not been done before across Canada.

3.1.3 Specific Aim & Hypotheses for Study 3

Title: *"*Prostate cancer surveillance by occupation and industry: Canadian Census Health and Environment Cohort (CanCHEC, 1991-2011)"

The third study (Chapter 6) involved the Canadian Census Health and Environment Cohort (CanCHEC). This cohort is one of the largest population cohort studies available in Canada and includes 1.1 million men from across all provinces and territories (Peters et al, 2013). The cohort was created through a linkage of the 1991 Canadian Census Mortality and Cancer Follow up Cohort, Canadian Mortality Database (1991-2011), Canadian Cancer Database (1969-2010), and annual Tax Summary Files (1981-2011). It is an up to date cohort that allows assessment of occupations held in 1991 and prostate cancer risk in Canadian men aged 25-74 years (Peters et al, 2013), providing a much larger sample size, power, and wide range of age groups. CanCHEC also had administrative data that would allow us to examine not only occupation-prostate cancer relationships but also the possible trends of incidence useful for understanding screening patterns (*Aim 3)*.

Hypotheses - We hypothesized that there would be a significantly higher incidence of prostate cancer across white collar jobs when compared to other jobs. We hypothesized that consistent associations would be observed in agriculture, farming and other natural resource based work and prostate cancer risk. It was also hypothesized that trends of prostate cancer incidence would be reflective of trends of prostate specific antigen testing and screening in Canada. Specifically, we hypothesized that incidence rates in CanCHEC would be similar to incidence rates across Canada and reflect prostate cancer secular screening patterns.

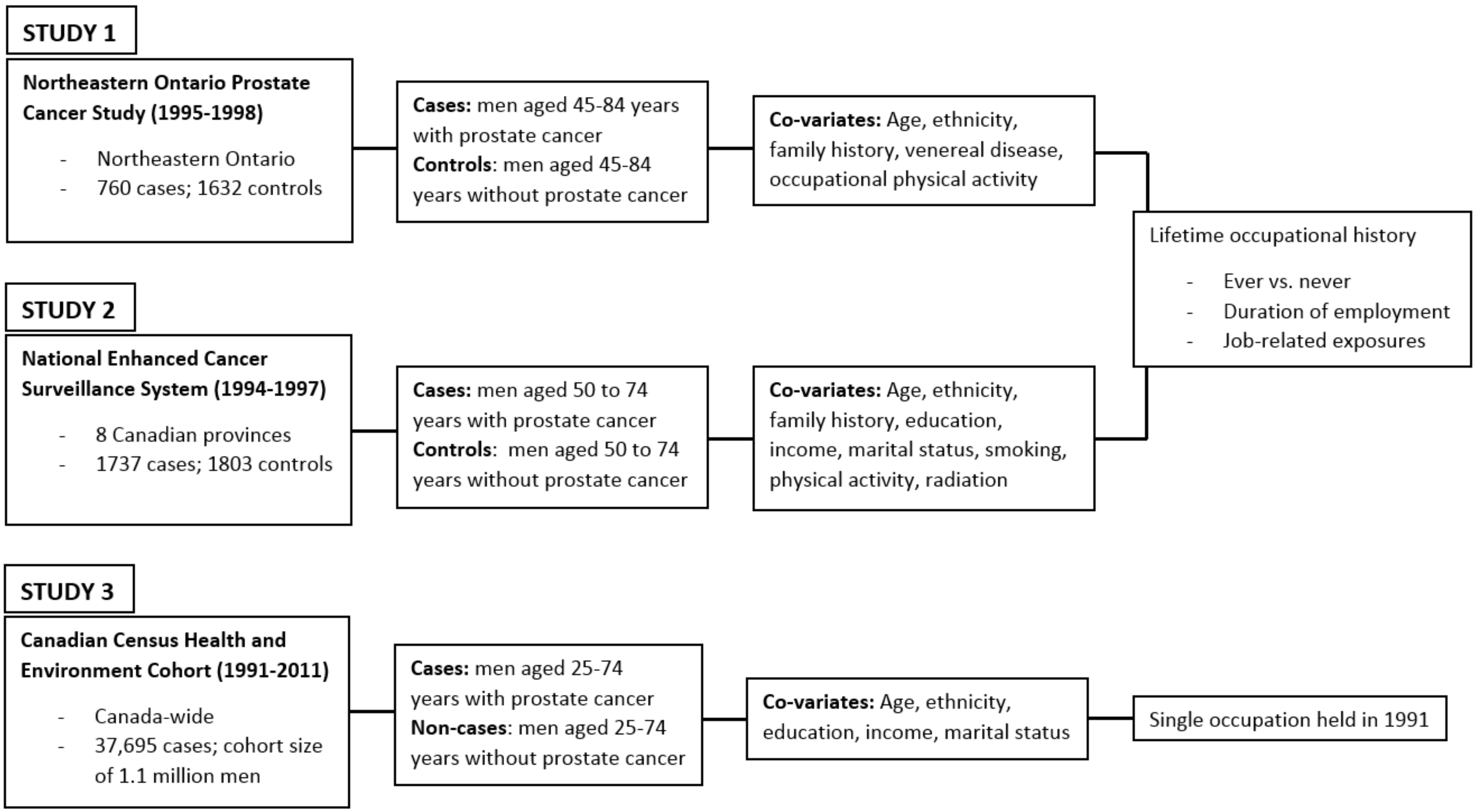

Figure 4. Description of the three population-based studies included in this thesis.
This detailed image shows the three core population datasets used in this thesis with similarities and differences by study design, years of data collection, cases versus non-cases, potential confounding variables available for analysis, and occupational information.

3.1.4 Specific Aims & Hypotheses for Study 4

Title: "**Prostate cancer in firefighting and police work: a systematic review and meta-analysis of epidemiologic studies"**

The fourth study (Chapter 7) is a meta-analysis study that combines the three above studies and other published studies in the literature. In the three previous studies (Chapters 4-6), we identified similar associations between men employed in protective services occupations and industries (e.g. firefighting, police, military) and prostate cancer risk, consistent with recent literature. In order to understand study findings and the existing literature, we recognized that there was only one existing meta-analysis that was published over a decade before (LeMasters et al, 2006). For this fourth chapter, a meta-analysis was conducted to update, quantify, and interpret published studies with prostate cancer estimates in protective services workers (*Aim 4)*. This would be the first available meta-analysis to evaluate both firefighting and police work and prostate cancer risk.

Hypotheses - We hypothesized that the meta-risk estimates would be statistically significant for protective services workers and prostate cancer incidence, specifically for firefighting and police work. With increased incidence estimates, it was also hypothesized that significant decreased mortality estimates would be observed which would strengthen that notion that screening bias does affect findings. By using standard epidemiological methodology to conduct a meta-analysis, findings can provide substantial evidence for future research in protective services.

Chapter 4. Natural Resource Based Industries and Prostate Cancer Risk in Northeastern Ontario: A Case-Control Study

This chapter has been published:

Sritharan J, Demers PA, Harris SA, Cole DC, Kreiger N, Sass-Korstak A & Lightfoot N. (2016). Natural resource-based industries and prostate cancer risk in Northeastern Ontario: a case-control study. Occupational and Environmental Medicine, 73: 506-511.

4.1 Abstract

Objective Prostate cancer continues to be the most commonly diagnosed cancer in men, and there is limited knowledge on preventable risk factors. A number of occupational exposures in natural resource based industries are suspected to be related to prostate cancer risk. This study investigates associations between employment in these industries and prostate cancer.

Methods Data were from a population-based, case-control study previously conducted in Northeastern Ontario. Incident cases (N=760) aged 45-85 years who were diagnosed between 1995 and 1998 were identified from the Ontario Cancer Registry. Controls (N=1632) were recruited using telephone listings and were frequency-matched to cases by age. Lifetime occupational history was collected for all participants. Logistic regression was used to estimate odds ratios (OR) and their associated 95% confidence internals (CI).

Results Elevated risks were observed for employment in forestry and logging industries (OR=1.87, 95% CI=1.32-2.73 and occupations (OR=1.71, 95% CI=1.24-2.35), and these risks increased with duration of employment for ≥10 years. Elevated risks were also found for employment in wood products industries (OR=1.45, 95% CI=1.07-1.97) and paper and allied products industries (OR=1.43, 95% CI=1.03-2.00) and when duration of employment was ≥10 years. There were also elevated risks in agriculture and mining related work, however these findings were not consistent across industry and occupation categories.

Conclusions Prostate cancer risk may be associated with work in several natural resource industries, primarily in the forest industries. To further evaluate observed associations, studies should focus on natural resource based exposures in larger populations with improved exposure assessment.

4.2 Introduction

Prostate cancer is the most commonly diagnosed cancer in North American and European men (Sass-Kortsak et al, 2007; Demichelis & Stanford et al, 2014). The risk factors for prostate cancer are poorly understood with the exception of age, family history, and ethnicity (Hsing & Chokkalingam, 2006; Plata & Concepcion, 2014; Bashir, 2015). Exogenous factors may play a role in the etiology of prostate cancer, but there are still no well-established risk factors (Sass-Kortsak et al, 2007; Parent & Siemiatycki, 2001). Occupational exposures (e.g., pesticides, metals, diesel exhaust, polycyclic aromatic hydrocarbons, and mineral oils) have been evaluated in relation to prostate cancer in previous studies with mixed findings (Parent & Siemiatycki, 2001; Parent et al, 2009; Nelles et al 2011; Boers et al, 2005; Doolan et al, 2014).

It is speculated that these occupational exposures may be related to prostate cancer risk but further research is necessary to strengthen the evidence. Many of these occupational exposures are commonly found in industries which involve the harvesting and extracting of raw materials from natural resources (Statistics Canada, 2006). Many of these exposures have also been classified as known or probably carcinogenic to humans by the International Agency for Research on Cancer. Although there is limited physiologic evidence, these occupational exposures may be involved in impacting hormone levels leading to DNA damage and tumor initiation in the prostate (Sass-Kortsak et al, 2007; Parent et al, 2009; Van Maele-Fabry & Willems, 2003). As the prostate is controlled by testosterone it is theorized that hormonal imbalances or androgenic stimulation may cause carcinogenesis as androgenic stimulation is important for promoting the growth of both normal and cancerous prostate cells. There is also evidence from human and animal studies that show high estrogen levels may lead to increased prostate cancer risk (Parent et al, 2009; National Cancer Institute, N/A; Golden et al, 1998). Androgenic stimulation and higher estrogen levels may be influenced by exposure to occupational, environmental, dietary and lifestyle factors (Parent et al, 2009; Van Maele-Fabry & Willems, 2003; National Cancer Institute, N/A; Golden et al, 1998).

The current study utilizes data from a previously reported case-control study in Northeastern Ontario. Previous publications from this study primarily focused on potential risk factors unrelated to occupation, however one publication by Sass-Kortsak et al. addressed occupational factors related to prostate cancer (Sass-Kortsak et al, 2007; Van Maele-Fabry & Willems, 2003; International Agency for Research on Cancer, 2013; Lightfoot et al, 2000). The paper reported on multiple potential exposures based on expert assessed cumulative lifetime exposure and identified a strong association for whole body vibrations and prostate cancer. Sass-Kortsak et al (2007) also found a significant association for employment in “trades, transport, equipment operators, and related occupations” and prostate cancer, however this was based on very broad occupation groups and longest held job. Sass-Kortsak et al (2007) did not explore detailed occupations and industries or duration of employment which is necessary for comparison to other studies in the literature. There is a need to build upon existing knowledge by evaluating risk using detailed information on occupation, industry, and exposures.

In Canada, primary industries include agriculture, forestry and logging, fishing and trapping, mining, and oil and gas extraction with a majority of workers being men (Statistics Canada, 2006). The Northeastern region in the province of Ontario in Canada has a higher number of natural resource based workers than other parts of the country, primarily in the mining and forestry industries (Statistics Canada, 2006). Major mining industries in Northeastern Ontario include uranium, gold, nickel, copper, and other metal mines. Risk of prostate cancer has not been studied exclusively in natural resource based industry workers, and since exposure levels to known and suspected carcinogens may be higher in these workers as compared to other occupational groups, it is important to conduct additional work. The objective of this study was to investigate potential associations between work in natural resource industries and occupations and the risk of prostate cancer in Northeastern Ontario. This study specifically focused on natural resource based exposures using detailed employment titles, duration of employment, and exposure to occupational agents that have not been examined in previous analyses of the data.

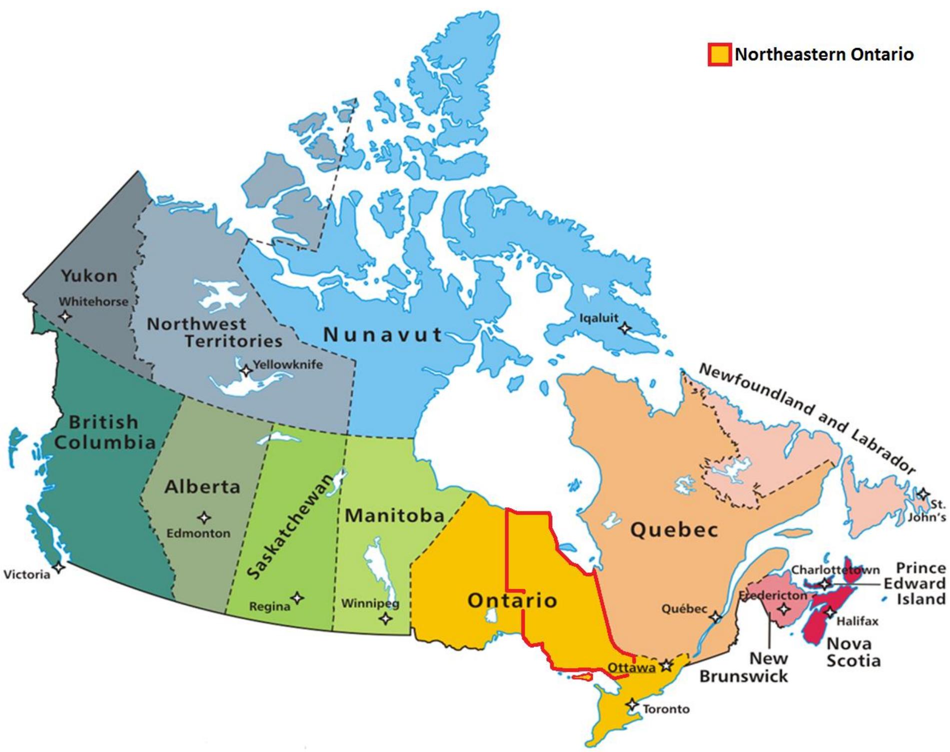

Figure 5. Map of Canada depicting the Northeastern Ontario region.
This map was created to show the target region of Northeastern Ontario involved in Study 1: The Northeastern Ontario Prostate Cancer Study.

4.3 Methods

4.3.1 Study Population

The case-control study took place in Northeastern Ontario which represents a majority of the Northern Ontario population (~500,000) and included the regions of Sudbury, Algoma, Cochrane, Timiskaming, Parry Sound, Muskoka, Manitoulin, and Sudbury District. The economy in Northern Ontario historically relied on natural resource based industries and these industries still remain as important contributors to economic growth in the region (Industry Canada, 2011). The Sudbury region is recognized for its extensive development of copper and nickel mining, smelting, and refining processes and as a result Canada was a world leader in nickel production in the 1900s. Other metal discoveries included gold and silver deposits that spanned across Northeastern Ontario and included the regions of Cobalt, Porcupine Lake, Timmins, and Kirkland Lake. In the 1950s, Elliot Lake in the Algoma District became a booming area for uranium mining (Industry Canada, 2011). The forestry and wood industries were primarily sawmill and pulp and paper mills and in 2004 at least one third of Northern Ontario was dependent on the forestry industry (Bollman et al, 2006). Farming and agriculture has continued in multiple regions across Northern Ontario, including Timiskaming, Cochrane, Sudbury, Parry Sound, Algoma, and Manitoulin and production is expected to increase by 20 to 50% in the coming years (Caldwell, 2011).

As this was a secondary analysis of a previously conducted study, the detailed description of the study sample can be found in previously published papers (Sass-Kortsak et al, 2007; Lightfoot et al, 2000; Lightfoot et al, 2004; Darlington et al, 2007). Briefly, incident prostate cancer cases were men between the ages of 45 to 85 years, who resided in Northeastern Ontario, and were identified in the Ontario Cancer Registry with primary histologically confirmed prostate cancer diagnosed between January 1995 and December 1998. Controls were randomly selected from the Northeastern Ontario population using residential telephone listings and were frequency matched 2:1 to cases based on 5 year age groups. Participation rates in the study were 73.6% for cases and 47.5% for controls (Lightfoot et al, 2004).

4.3.2 Exposure Classification

Consenting participants were mailed a questionnaire followed by telephone contact by trained interviewers. The questionnaire included sections on demographics, general health, smoking, diet, physical activity, family, and occupational history. Interviewers utilized the questionnaire to assess detailed lifetime job histories based on jobs held for 1 or more years. Each job history included information on job titles, employer name and type, job duties, work description, and work environment (Sass-Kortsak et al, 2007; Lightfoot et al, 2000; Lightfoot et al, 2004). An occupational hygienist coded job descriptions (four digit) using the 1991 Standard Occupation Classification (SOC91) and 1980 Standard Industry Classification (SIC80) systems (Statistics Canada, 1980; Statistics Canada, 1993). Industries and occupations were then broadly grouped into 58 new occupation categories and 38 new industry categories based on their SOC91 and SIC80 codes (Statistics Canada, 1980; Statistics Canada, 1993) and similarities in job tasks and potential exposures. For this current analysis only industries and occupations related to natural resources were included, resulting in 10 industry and 9 occupation categories (Table 1, Supplementary File). Ever employment was defined as any job held for at least one year with corresponding SOC91 and SIC80 codes. Duration of employment was examined by categorizing employment as less than 10 years and 10 years or greater to assess short term and long term exposures. Potential exposure response trends in duration of employment and prostate cancer risk were also examined using tertile categories, based on the distribution of controls in each industry and occupation. Self-reported data were also used to assess ever versus never exposure in cases and controls based on participant responses to occupational agents listed in the questionnaire.

4.3.3 Statistical Analysis

Unconditional logistic regression models were used to assess if duration of employment in different natural resource industries and occupations, and if relevant occupational exposures, were associated with prostate cancer. All cases or controls not employed in the specific category being evaluated served as the non-exposed referent category. Only categories with at least 5 cases or 5 controls were analyzed. SAS version 9.2 was used for statistical modelling (SAS Institute Inc, 2015). Odds ratios with 95% confidence intervals above 1 were considered statistically significant. Adjustments were made for five year age groups and family history of prostate cancer. Ethnicity was not included as a covariate as the majority of participants were Caucasian (Sass-Kortsak et al, 2007; Lightfoot et al, 2000; Lightfoot et al, 2004). Education and income were considered as potential confounders however these factors did not present any significant changes in the odds ratios. History of venereal disease and cumulative lifetime occupational physical activity were found to be significant in previous publications, but adjusting for these variables resulted in no significant changes in our estimates (Sass-Kortsak et al, 2007; Lightfoot et al, 2004). Exposure response trends were evaluated using logistic regression by treating the ordinal variables as continuous in the model to calculate the p-values for trend. Additionally, industries and occupations in this study that were previously associated with prostate cancer in the literature (i.e., farming and agriculture) were also reported and discussed.

4.4 Results

Cases and controls were of similar age (mean 68.2 years, SD=7.5) (Table 1). Of the potential covariates examined, only family history of prostate cancer was significantly associated with prostate cancer risk (OR 2.85, 95% CI 2.13-3.83). All subsequent analyses by industry group (Table 2) and occupation group (Table 3) were adjusted for both age and family history.

Table 1. Selected characteristics of cases and controls in the Northeastern Ontario Prostate Cancer Study

	Cases (N=749) (%)	Controls (N=1608) (%)	OR* (95%)
Age Groups (years)			
45 to <50	8 (1.1)	18 (1.1)	
50 to <55	25 (3.3)	68 (4.2)	
55 to <60	48 (6.4)	135 (8.4)	
60 to <65	133 (17.7)	271 (16.8)	
65 to <70	220 (29.0)	439 (27.3)	
70 to <75	177 (23.63)	381 (23.69)	
75 to <80	106 (14.1)	198 (12.3)	
80 to <85	31 (4.1)	95 (5.9)	
Missing	1 (0.1)	3 (0.2)	
Family History of Prostate Cancer			
Yes	108 (14.4)	90 (5.6)	2.83 (2.10-3.80)
No	641 (85.6)	1519 (94.4)	Ref
Ethnicity			
English Canadian	402 (53.7)	901 (56.0)	0.98 (0.79-1.22)
French Canadian	173 (23.1)	332 (20.7)	1.15 (0.89-1.50)
Aboriginal (Native)	7 (0.9)	6 (0.4)	2.69 (0.89-8.18)
Other	165 (22.0)	361 (22.5)	Ref
Missing	2 (0.3)	8 (0.5)	0.56 (0.12-2.67)
Education			
No school	2 (0.3)	3 (0.2)	1.29 (0.21-7.87)
Some elementary	99 (13.2)	188 (11.7)	Ref
Elementary	158 (21.1)	341 (21.2)	0.87 (0.64-1.18)
Some high school	226 (30.2)	415 (25.8)	1.04 (0.77-1.39)
Finished high school	138 (18.4)	319 (19.8)	0.83 (0.60-1.14)
Some college/university	32 (4.3)	84 (5.2)	0.73 (0.45-1.17)
Finished college/university	67 (9.0)	189 (11.8)	0.68 (0.47-0.99)
Post graduate	17 (2.3)	43 (2.7)	0.78 (0.42-1.44)
Professional	5 (0.7)	17 (1.1)	0.56 (0.20-1.57)
Missing	5 (0.7)	10 (0.6)	1.03 (0.34-3.2)
Total Family Income			
<$20,000	94 (12.6)	183 (11.4)	Ref
$20,000-$39,000	269 (35.9)	517 (32.1)	0.97 (0.72-1.30)
$40,000-59,000	178 (23.8)	455 (28.3)	0.72 (0.52-0.98)
$60,000-$79,000	87 (11.6)	171 (10.6)	0.97 (0.66-1.41)
$80,000-$99,999	28 (3.7)	55 (3.4)	0.97 (0.57-1.65)
>$100,000	21 (2.8)	59 (3.7)	0.69 (0.39-1.21)
Missing	72 (9.6)	168 (10.5)	0.80 (0.55-1.16)

*adjusted for age

A non-significantly elevated risk was observed for employment in the agricultural industry (agriculture and farm work, and services incidental to agriculture) (OR 1.15, 95% CI 0.96-1.38). Fishing and trapping industry work demonstrated an elevated risk (OR 3.32, 95% CI 1.14-9.67), which was highest for those employed for <10 years (OR 4.49, 95% CI 1.05-19.17). For employment in the forestry and logging industry, there was an elevated risk (OR 1.87, 95% CI 1.32-2.73), which was highest for employment ≥10 years (OR 2.55, 95% CI 1.59-4.11) and a significant trend was observed with duration of employment (p_{trend}<0.0001). An elevated risk was observed for employment in the wood products industry (OR 1.45, 95% CI 1.07-1.97), which somewhat increased with ≥10 years duration of employment (OR 1.73, 95% CI 1.08-1.90). A significant increasing trend was also observed for employment in the wood products industry (p_{trend}=0.011). There was an elevated risk for employment in the paper and allied products industry (OR 1.43, 95% CI 1.03-2.00), especially with ≥10 years of employment (OR 1.98, 95% CI 1.29-3.02) and a significant trend was observed (p_{trend}=0.007). For the mining industry, there was an elevated risk for employment in other services incidental to mining (OR 2.09, 95% CI 1.18-3.72) and a non-significantly elevated risk with ≥10 years of employment duration (OR 2.50, 95% CI 0.90-7.00). A significant trend for duration of employment was also observed for these mining related workers (p_{trend}=0.004). A non-significantly elevated risk was observed for employment in the quarrying industry (OR 3.33, 95% CI 0.76-14.54) however, due to the small sample size, a trend analysis could not be performed. There were no strong associations observed for employment in metal mining, non-metal mining, and petroleum and coal mining industries.

Table 2. Odds ratios and 95% CIs for associations between prostate cancer and employment in natural resource based *industries*

			Duration			
			>0 to <10 Years		≥10 Years	
Industry Groups	**Cases/ Controls**	**OR* (95% CI)**	**Cases/ Controls**	**OR* (95% CI)**	**Cases/ Controls**	**OR* (95% CI)**
Agriculture and Farm Work, Services Incidental to Agriculture	276/531	1.15 (0.96-1.38)	92/159	1.29 (0.97-1.71)	184/372	1.10 (0.89-1.35)
Forestry and Logging	60/68	1.90 (1.32-2.73)	33/45	1.51 (0.94-2.40)	27/23	2.70 (1.52-4.79)
Fishing and Trapping	8/6	3.32 (1.14-9.67)	5/3	4.49 (1.05-19.17)	3/3	2.25 (0.45-11.22)
Metal Mining	202/460	0.96 (0.79-1.17)	71/137	1.15 (0.85-1.57)	131/323	0.88 (0.85-1.57)
Non Metal Mining	12/28	0.90 (0.45-1.80)	8/21	0.77 (0.33-1.76)	4/7	1.34 (0.39-4.66)
Quarrying	5/3	3.33 (0.76-14.54)	3/3	2.08 (0.40-10.68)	2/0	--
Petroleum and Coal	3/11	0.62 (0.17-2.24)	3/8	0.80 (0.21-3.07)	0/3	--
Other Services Incidental to Mining	24/25	2.09 (1.18-3.72)	16/18	1.94 (0.97-3.86)	8/7	2.50 (0.90-7.00)
Wood Products	79/120	1.45 (1.07-1.97)	46/77	1.30 (0.88-1.90)	33/43	1.73 (1.08-1.90)
Paper and Allied Products	62/99	1.43 (1.03-2.00)	20/49	0.90 (0.53-1.53)	42/50	1.98 (1.29-3.02)

*adjusted for age and family history of prostate cancer

At an occupation level, there was an elevated risk for general farm workers and labourers (OR 1.23, 95% CI 1.02-1.49) which was higher for those employed <10 years (OR 1.42, 95% CI 1.06-1.91). No significant trends were identified for duration of employment in agriculture and farm work. A non-significantly elevated risk was found for occupations related to fishing, trapping, and hunting (OR 3.03, 95% CI 0.91-10.06). No trend analysis was performed on this group due to its small sample size. Elevated risks were also observed for forestry and logging occupations (OR 1.71 95% CI 1.24-2.35), which was highest for duration of employment of ≥10 years (OR 2.55, 95% CI 1.58-4.11). A significant trend with duration of employment was observed for forestry and logging (p_{trend}<0.0001). For wood processing and making occupations, the risk was not elevated (OR 1.16, 95% CI 0.86-1.57). An elevated risk was observed for men employed in wood processing and making occupations within the wood industry (OR 1.64, 95% CI 1.06-2.54), although an excess was also observed among non-wood-related occupations in the same industry (OR 1.45, 95% CI 1.07-1.97). There were no strong associations observed for employment in pulp and papermaking occupations and mining related occupations.

Table 3. Odds ratios and 95% CIs for associations between prostate cancer and employment in natural resource based *occupations*

			Duration			
			>0 to <10 Years		≥10 Years	
Occupation Groups	**Cases/ Controls**	**OR* (95% CI)**	**Cases/ Controls**	**OR* (95% CI)**	**Cases/ Controls**	**OR* (95% CI)**
Farmers, Farm and Agriculture Managers	48/128	0.74 (0.52-1.05)	12/39	0.59 (0.30-1.14)	36/89	0.81 (0.54-1.22)
General Farm Workers and Labourers	243/443	1.23 (1.02-1.49)	84/134	1.42 (1.06-1.91)	159/309	1.15 (0.92-1.44)
Agriculturists and Related Specialists	3/8	0.79 (0.21-3.03)	2/0	--	1/8	0.25 (0.03-2.08)
Forestry and Logging	75/97	1.71 (1.24-2.35)	37/63	1.26 (0.83-1.93)	38/34	2.55 (1.59-4.11)
Fishing, Trapping, and Hunting	6/5	3.02 (0.91-10.03)	4/3	3.65 (0.80-16.67)	2/2	2.18 (0.31-15.55)
Mining, Quarrying, Oil, and Gas	149/297	1.12 (0.89-1.39)	64/115	1.21 (0.88-1.68)	85/182	1.05 (0.80-1.39)
Wood Processing and Making	76/139	1.16 (0.86-1.57)	27/60	0.94 (0.58-1.50)	49/79	1.33 (0.92-1.93)
Pulp and Papermaking	28/47	1.32 (0.82-2.14)	18/34	1.17 (0.65-2.09)	10/13	1.75 (0.76-4.05)
Primary Production and Manufacturing Managers	21/44	1.05 (0.61-1.78)	5/14	0.77 (0.27-1.16)	16/30	1.18 (0.63-2.20)

*adjusted for age and family history of prostate cancer

For self-reported occupational exposures, a number of exposures presented non-significantly elevated odds ratios (Table 4).

Table 4. Associations between prostate cancer and self-reported occupational exposures

Exposure	Number of Cases (n=749)	Number of Controls (n=1608)	OR* (95%)
Dust	634	1333	1.14 (0.89-1.45)
Metal	334	741	0.94 (0.78-1.12)
Diesel Exhaust	414	838	1.17 (0.98-1.40)
Pesticides	124	218	1.25 (0.98-1.60)
PCB	82	161	1.09 (0.85-1.50)
Combustion	274	559	1.09 (0.91-1.31)
Asphalt	88	181	1.06 (0.80-1.40)
Welding	324	699	1.00 (0.84-1.19)
Fertilizer	115	228	1.09 (0.86-1.40)
Lubricating Oils	422	858	1.17 (0.98-1.40)
Radiation	80	197	0.86 (0.65-1.13)
Asbestos	186	386	1.03 (0.84-1.26)
Noise	637	1320	1.23 (0.96-1.56)
Sun	459	886	1.27 (1.06-1.52)

*adjusted for age and family history of prostate cancer

4.5 Discussion

This study reports on multiple strong associations and trends between employment in natural resource industries and occupations and prostate cancer risk. These results provide additional evidence on the potential occupational risk factors for prostate cancer in an area where natural resource-based employment is concentrated.

In our study, a small overall increase among agricultural workers was observed. The excess appeared to be restricted to farm workers and labourers with the highest risk among those employed for less than 10 years. Previous studies have been conducted to investigate the relationship between prostate cancer and agriculture related occupations with inconsistent findings (Jones et al, 2015; Ragin et al, 2013; Barry et al, 2012; Fragar et al, 2011; Band et al, 2011). Prostate cancer in relation to agriculture and farming occupations has been more commonly studied than other occupations with most studies focused on pesticide exposures. A meta-analysis that looked at the association between farming and prostate cancer found a nearly four-fold increased risk overall (OR 3.83, 95% CI 1.96-7.48) but found an inverse association between pesticide exposure and prostate cancer (Ragin et al, 2013). A recently published study of prostate cancer in a rural population in Saskatchewan, Canada identified that combined workplace exposure to insecticides and fungicides was significantly associated with prostate cancer (OR 2.23, 95% CI 1.15-4.33) (Sharma et al, 2015). Specific organophosphate insecticides such as fonofos, malathion, terbufos, and aldrin have been associated with aggressive prostate cancer (Koutros et al, 2013). Other studies have found pesticide exposure from farming occupations to be a possible risk factor for prostate cancer (Parent et al, 2009; Van Maele-Fabry et al, 2006). Specifically, pesticide applicators with exposure to chlorinated pesticides and methyl bromide were linked to increased prostate cancer risk ($p=0.005$) (Alavanja et al, 2003). There is evidence that insecticides, herbicides and metal (e.g. cadmium) exposures are linked to prostate cancer risk (Sharma et al, 2015; Sahmoun et al, 2005).

In 2013, a report was published on the use of 2, 4, 5-Trichlorophenoxyacetic acid (2, 4, 5-T) herbicide in Ontario and the possible health effects (Ritter et al, 2013). From the early 1940s to late 1970s, chemical agents such as 2, 4, 5-T were utilized to aid in the re-establishment of the conifer forest in Northern Ontario. This herbicide is classified as a possible carcinogen (group 2B) by IARC (likely due to its contamination with 2, 3, 7, 8-TCDD, a carcinogenic dioxin) and is linked to prostate cancer with limited evidence (Ritter et al, 2013). Given that the time period of occupational use of this herbicide overlaps with the work records of the study cases, it is likely that Northern Ontario agricultural workers were exposed to 2, 4, 5 T and the associated dioxin contaminants. The interpretation of these important findings across different studies continues to be inconsistent. But the existence of an excess risk in agriculture and farming related occupations demonstrates the need for further research.

Employment in fishing and trapping was also found to be associated with prostate cancer risk in this study, however the number of exposed workers was quite small and the confidence intervals were wide. The strongest associations were observed for work <10 years. Men employed in fishing and trapping are considered to have a high fatality rate and are more prone to injuries given the stressors of the work environment (Health & Safety Authority, 2015). These workers may be exposed to diesel exhaust when spending long hours on fishing vessels or exposed to PAHs and PCBs through polluted waters. They are also likely to have a poor diet with higher fish consumption than the general population, leading to possible exposure to organochlorine compounds and metal toxins (Svensson et al, 1995).

Employment in forestry and logging in this case-control study was found to be associated with prostate cancer, especially among those employed for greater than 10 years. Based on an analysis of tertile categories, employment in forestry and logging at both an occupation and industry level demonstrated a significant trend with duration of employment. Employment in this occupation included work as forestry and logging professionals, operators, and labourers. Forestry and logging operations involve use of heavy machinery and equipment that may lead to exposure of diesel exhaust, wood dust and whole body vibrations (Sass-Kortsak et al, 2007; Magagnotti et al, 2013). There are few studies that examine forestry and logging related exposures, and currently there are no studies that examine prostate cancer. It is also unclear how the interaction of these exposures contributes to the risk of prostate cancer.

Employment in the wood products industry was also associated with prostate cancer and the risk increased with ≥10 years duration. An excess was observed among men in both wood-related and non-wood-related occupations within the wood products industry. This may indicate that the risk in the wood products industries are due to exposures unique to that industry, rather than woodworking itself. The wood industries include sawmills and planing mills, as well as other wood product industries where there may be exposure to the volatile components of fresh wood as well as pesticides, such as fungicides and wood preservatives. Employment in the paper and allied products industry was also associated with prostate cancer, especially with ≥10 years duration and a significant trend was observed with duration of employment. At an occupational level, the specific group of pulp and papermaking occupations had no increased risk. Primarily, exposure in the wood products and paper industries include wood dust and wood pulping and papermaking chemicals such as sulphates and chlorine compounds (Statistics Canada, 2010; Vallieres et al 2015; Villeneuve et al, 2010). These chemical exposures in forestry, wood products, and paper industries may act as endocrine disruptors in the human body (Villeneuve et al, 2010). These disruptors could influence hormone levels and play a role in prostate cancer etiology (Parent et al, 2009).

At an industry level, metal mining, non-metal mining, quarrying, and petroleum and oil industries were not found to be associated with prostate cancer. However, employment in other services incidental to mining was found to be associated with prostate cancer and increased with duration. This group included contract drilling and any other services related to mining. It is unclear as to what other specific services were included in this group but there may be a heterogeneous combination of mining jobs. At an occupation level, mining related work was not found to be associated with prostate cancer. Employment in mining can result in many different exposures depending on the type of mining (surface vs. underground) and the substance being mined. Other studies have identified multiple exposures in mining including but not limited to metals, dust, diesel exhaust, whole body vibrations, radiation, shift work, and other chemicals (Peters et al, 2013; Huvinen & Pukkala, 2013).

As a part of the original study, participants were asked in the study questionnaire to report if they were ever exposed to listed occupational agents. Based on these self-reported data, an elevated risk was observed for sun exposure and non-significantly elevated risks were observed for exposure to diesel exhaust, pesticides, combustion products, lubricating oils, and noise. (Table 4). Although the ever/never exposure classifications represents unadjusted associations and are self-reported, these findings may provide further evidence on specific agents related to natural resource based work.

This study has a number of limitations based on data collection and approach. The response rate of cases and controls were lower than desired and recall bias may be a factor with questionnaires provided to both cases and controls (Lightfoot et al, 2000; Lightfoot et al, 2004). Not unexpectedly, the response rate of controls was much lower than for cases such that selection bias could occur while also making the results less generalizable to the population. Some industry and occupation categories also presented small sample sizes. This study relied on job titles and even though similar exposure jobs were grouped together there is still room for heterogeneity as significant findings in sub-sector groups may be diluted and not detected in these broader level categories. There was also no information collected on the stage or aggressiveness of the tumors in cases which may have been useful to examine occupational exposure differences by aggressiveness of prostate cancer. This study also has a number of strengths. The availability of lifetime job histories provided useful detailed job information for this specific region with a high prevalence of natural resource industry work. This study also collected data on three known risk factors for prostate cancer, age, family history, and ethnicity, which have not always been available in other prostate cancer studies.

This study offers additional evidence that employment in natural resource based industries and occupations may be associated with a higher risk of prostate cancer. Specifically, long-term employment in forestry, logging, wood, and the paper industry was observed to be associated with increased risks of prostate cancer. Additional elevated risks were observed for other natural resource based industries and occupations. Although there were no clear occupational agents identified, workers in these industries are exposed to multiple known and suspected carcinogens that are important to assess in further analyses. Use of detailed exposure data in larger study populations is needed to further evaluate the potential role of occupational exposures in the development of prostate cancer.

Chapter 5. Occupation and risk of prostate cancer in Canadian men: a case-control study across eight Canadian provinces

This chapter has been published:

Sritharan J, Demers PA, Harris SA, Cole DC, Peters CE, the Canadian Cancer Registries Epidemiology Research Group & Villeneuve PJ. (2017a). Occupation and risk of prostate cancer in Canadian men: a case-control study across eight Canadian provinces. Cancer Epidemiology, 48: 96-103.

5.1 Abstract

Background: The etiology of prostate cancer continues to be poorly understood, including the role of occupation. Past Canadian studies have not been able to thoroughly examine prostate cancer by occupation with detailed information on individual level factors.

Methods: Occupation, industry and prostate cancer were examined using data from the National Enhanced Cancer Surveillance System, a large population-based case-control study conducted across eight Canadian provinces from 1994 to 1997. This analysis included 1737 incident cases and 1803 controls aged 50 to 79 years. Lifetime occupational histories were used to group individuals by occupation and industry employment. Odds ratios and 95% confidence intervals were calculated and adjustments were made for known and possible risk factors.

Results: By occupation, elevated risks were observed in farming and farm management (OR=1.37, 95% CI 1.02-1.84), armed forces (OR=1.33, 95% CI 1.06-1.65) and legal work (OR=2.58, 95% CI 1.05-6.35). Elevated risks were also observed in office work (OR=1.20, 95% CI 1.00-1.43) and plumbing (OR=1.77, 95% CI 1.07-2.93) and with ≥10 years duration of employment. Decreased risks were observed in senior management (OR=0.65, 95% CI 0.46-0.91), construction management (OR=0.69, 95% CI 0.50-0.94) and travel work (OR=0.37, 95% CI 0.16-0.88). Industry results were similar to occupation results, except for an elevated risk in forestry/logging (OR=1.54, 95% CI 1.06-2.25) and a decreased risk in primary metal products (OR=0.70, 95% CI 0.51-0.96).

Conclusion: This study presents associations between occupation, industry and prostate cancer, while accounting for individual level factors. Further research is needed on potential job-specific exposures and screening behaviours.

5.2 Introduction

Worldwide, prostate cancer is the second most commonly diagnosed cancer in men, with higher rates in industrialized countries (International Agency for Research on Cancer (IARC), 2016), and it is the third leading cause of death from cancer (Canadian Cancer Society, 2015). The only well-established risk factors for prostate cancer are age, family history of prostate cancer and ethnicity (IARC, 2016; Canadian Cancer Society, 2015). Occupational factors may also play a role in prostate cancer development, however in Canada these are understudied due to small sample sizes and limited information on occupation and non-occupational factors (Howe & Lindsay, 1983; Aronson et al, 1999; Sass Kortsak et al, 2007; Sritharan et al, 2016; Buxton et al, 1999; Aronson et al, 1996).

The International Agency for Research on Cancer (IARC) has reported on possible associations between occupation and industry groups, specific exposures and prostate cancer. These include firefighters, rubber production workers, shift workers, cadmium compounds, arsenic compounds, X and γ radiation, and malathion (IARC, 2010; IARC, 2012a; IARC, 2012b; IARC, 2012c; IARC, 2015). IARC has shown some evidence that linked firefighter and rubber manufacturing occupations to prostate cancer risk (IARC, 2010; IARC 2012a). Other international studies have shown mixed findings for occupation and industry groups and prostate cancer based on cohorts with limited information on employment or non-occupational factors (Pukkala et al, 2009; Krstev et al, 1998; Sharma-Wagner et al, 2000). Some studies have observed associations between shift work and prostate cancer but the mechanism relating circadian rhythm disruption to prostate cancer is unclear (IARC, 2010). The association between prostate cancer risk and cadmium compounds, arsenic compounds, and X and γ radiation has also been inconsistent across studies (IARC, 2012b; IARC, 2012c). Occupational exposure to malathion insecticides has been positively associated with prostate cancer, but only with aggressive forms (IARC, 2015). It is likely that different mechanisms are involved in job-related exposures, and some exposures can mimic endocrine disruptors or affect estrogen levels in the body, leading to tumor initiation in the prostate gland (Parent et al, 2009; Van Maele-Fabry & Willems, 2003; National Cancer Institute, 2014; Golden et al, 1998). There is also evidence that a sedentary work environment and lifestyle can lead to lower levels of physical activity and increased weight or obesity, increasing the risk for prostate cancer (IARC, 2014; World Cancer Research Fund International, 2014).

Few population-based studies have been able to thoroughly capture a range of occupation and industry groups and account for known and possible prostate cancer risk factors (Howe & Lindsay, 1983; Aronson et al, 1999; Sass Kortsak et al, 2007; Sritharan et al, 2016; Buxton et al, 1999; Aronson et al, 1996; Pukkala et al, 2009; Krstev et al, 1998; Sharma-Wagner et al, 2000; Sauve et al, 2016). Our study sought to examine prostate cancer by occupation, industry and by duration of employment, while including individual level factors. Our study used the National Enhanced Cancer Surveillance System (NECSS) population-based case-control study which was established to provide a better understanding of the environmental risk factors for cancer (Villeneuve et al, 1999; Hystad et al, 2014; Johnson et al, 1998). The NECSS is one of the few large Canadian population-based studies that has multiple covariates and substantial power to detect relationships between occupation, industry and prostate cancer. *The objective of our study was to examine the relationship between job title and prostate cancer using the NECSS.*

5.3 Methods

5.3.1 Study design and population

The NECSS was conducted in eight Canadian provinces from 1994-1997 and examined 19 cancer sites and multiple environmental factors. Details on the NECSS case-control study design have been published elsewhere (Villeneuve et al, 1999; Hystad et al, 2014; Johnson et al, 1998). Briefly, prostate cancer cases were defined using the International Classification of Diseases for Oncology (ICDO-2) and were histologically confirmed (Villeneuve et al, 1999; Hystad et al, 2014; Johnson et al, 1998). Controls were sampled by random digit dialing in Newfoundland and Alberta, from provincial health insurance plan databases in British Columbia, Manitoba, Saskatchewan, Nova Scotia, and Prince Edward Island, and from a stratified random sample using Ministry of Finance data in Ontario (Villeneuve et al, 1999; Hystad et al, 2014; Johnson et al, 1998). Controls were frequency matched to all cancer cases by sex, province and by 5 year age groups. Self-administered questionnaires were used to collect data with a response rate of 69% for cases and 69% for controls (Villeneuve et al, 1999). The analysis reported here were restricted to male participants aged ≥50 years as prostate cancer in younger populations is rare (Villeneuve et al, 1999).

5.3.2 Analysis of employment history

The NECSS questionnaire asked participants about their lifetime employment history for jobs that were held for at least 12 months. This included job title, industry, location, main tasks, and duration. An occupational hygienist and exposure assessment expert (CP) coded the jobs based on the National Occupational Classification System for Statistics (NOC-S 2006) and the North American Industry Classification System (NAICS 2002). Using the four digit NOC-S 2006 and NAICS 2002 codes, the occupations and industries were then categorized into 63 occupation groups and 44 industry groups based on job titles and tasks. Analysis by occupation provides specific job titles that can act as exposure proxies. Analysis by industry may also acts as an exposure proxy and can support associations found at an occupation level. Occupation and industry groups were examined as ever/never (i.e. did a participant ever have that job title, versus never). Duration of employment was assessed as <10 years ≥10 years of employment.

Unconditional logistic regression was used to compute odds ratios and 95% confidence intervals to determine associations between job title and prostate cancer risk. All models were adjusted for age and province of residence to reflect matching criteria and the varied selection of controls. Adjustments were also made for the known risk factors of family history of prostate cancer and ethnicity. Men of African American/Black ethnicity are at a higher risk and men of Asian ethnicity are at a lower risk for prostate cancer when compared to European/Caucasian men (IARC, 2016; Canadian Cancer Society, 2015). Adjustments for socioeconomic status (education and income) and marital status were also made in an attempt to account for potential screening biases. Men with a higher socioeconomic status have better access to health care and are more likely to get screened compared to men with a lower socioeconomic status (Richardson et al, 2007). Similarly, men who are married may be more likely to seek out screening than those who are not married (Wallner et al, 2008). Odds ratios were initially adjusted for both education and income but when income was added there was <10% or no change in findings so income was removed from the final model. Additional adjustments were also made for body mass index, smoking in pack-years, moderate and strenuous physical activity, and total radiation exposure based on associations identified in previous published studies from the NECSS (Villeneuve et al, 1999; Hystad et al, 2014; Johnson et al, 1998; Pan et al, 2004; Peters et al, 2016). All analyses were minimally adjusted for age, province of residence, ethnicity, and family history of prostate cancer and then fully adjusted with the addition of education, body mass index, smoking in pack-years, marital status, moderate and strenuous physical activity and total radiation exposure. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc.).

5.4 Results

A total of 1737 prostate cancer cases and 1803 controls were included. Selected non-occupational characteristics of prostate cancer cases and controls are shown in Table 5. Family history of prostate cancer was significantly associated with prostate cancer (OR 2.67, 95% CI 1.52-4.71). Participants with Asian ancestry had a decreased risk of prostate cancer (OR 0.17, 95% CI 0.12-0.26) when compared to those with European ancestry. Levels of income were associated with prostate cancer, however these associations attenuated when fully adjusted. As smoking pack-years increased prostate cancer odds decreased when compared to never smoking participants.

Table 5. Characteristics of prostate cancer cases and controls from the NECSS

	Number of cases (n=1737)	Percent (%)	Number of controls (n=1803)	Percent (%)	OR[a] (95% CI)	OR[b] (95% CI)
Age						
50-54	64	3.7	153	8.5		
55-59	169	9.7	210	11.6		
60-64	348	20.0	352	19.5		
65-69	546	31.4	517	28.7		
70-74	564	32.5	536	29.7		
75-79	46	2.6	35	1.9		
Province of Residence						
Newfoundland	68	3.9	82	4.5	1.05 (0.75-1.49)	1.07 (0.78-1.51)
Prince Edward Island	67	3.9	54	3.0	**1.55 (1.06-2.27)**	**1.59 (1.09-2.33)**
Nova Scotia	109	6.3	263	14.6	**0.51 (0.40-0.66)**	**0.52 (0.41-0.68)**
Ontario	527	30.3	645	35.8	Ref	Ref
Manitoba	98	5.6	108	6.0	1.11 (0.83-1.50)	1.14 (0.84-1.54)
Saskatchewan	76	4.4	98	5.4	0.94 (0.68-1.29)	0.96 (0.69-1.33)
Alberta	267	15.4	234	13.0	**1.43 (1.15-1.76)**	**1.50 (1.21-1.86)**
British Columbia	525	30.2	319	17.7	**2.03 (1.69-2.44)**	**2.46 (2.03-2.98)**
Family History of Prostate Cancer						
No	1696	97.6	1784	98.9	Ref	Ref
Yes	41	2.4	19	1.1	**2.86 (1.63-5.02)**	**2.67 (1.52-4.71)**
Ethnicity						
European/Caucasian	1621	93.3	1603	89.9	Ref	Ref
Black	10	0.6	11	0.6	0.94 (0.39-2.27)	0.58 (0.23-1.49)
Asian	29	1.7	119	6.6	**0.17 (0.11-0.26)**	**0.17 (0.12-0.26)**
Aboriginal/Inuit/Metis	10	0.6	6	0.3	1.68 (0.59-4.76)	1.67 (0.59-4.79)
Other/missing/unknown	67	3.9	64	3.6	1.07 (0.75-1.53)	1.11 (0.77-1.62)
Number of Years of Education						
<10	509	29.3	548	30.4	Ref	Ref
10 or more	1206	69.4	1226	68.0	1.04 (0.89-1.21)	1.04 (0.88-1.23)
Missing	22	1.3	29	1.6	0.73 (0.41-1.31)	0.83 (0.44-1.58)
Household Income						
<$19,999	212	12.2	267	14.8	Ref	Ref
$20,000 to $29,999	293	16.9	292	16.2	**1.29 (1.01-1.66)**	1.21 (0.94-1.57)
$30,000 to $49,999	459	26.4	452	25.1	**1.33 (1.06-1.68)**	1.24 (0.97-1.58)
$50,000 to $99,999	320	18.4	327	18.1	**1.40 (1.09-1.79)**	1.28 (0.98-1.66)
>$100,000	65	3.7	76	4.2	1.26 (0.85-1.87)	1.13 (0.75-1.71)
Prefer not to answer	388	22.3	389	21.6	**1.33 (1.05-1.68)**	1.22 (0.96-1.57)
Marital Status						
Married, common-law	1520	87.5	1557	86.4	Ref	Ref
Single, divorced, other	128	7.4	172	9.5	**0.77 (0.60-0.99)**	0.77 (0.60-1.00)
Widowed	87	5.0	72	4.0	1.21 (0.87-1.68)	1.34 (0.96-1.89)
Missing/unknown	2	0.1	2	0.1	1.19 (0.17-8.50)	2.44 (0.21-28.19)
Smoking by Pack-Years						
0	400	23.4	382	21.6	Ref	Ref
>0-<10	317	18.5	302	17.1	0.99 (0.79-1.23)	0.89 (0.71-1.11)
10-<25	467	27.3	464	26.3	0.93 (0.77-1.14)	0.83 (0.68-1.01)
25-<40	288	16.8	320	18.1	0.83 (0.66-1.03)	**0.74 (0.59-0.93)**
>40	241	14.1	299	16.9	**0.74 (0.59-0.93)**	**0.66 (0.52-0.83)**
Missing/unknown	24	1.4	36	2.0	0.65 (0.38-1.12)	0.60 (0.34-1.05)

[a]adjusted for age and province

[b]adjusted for age, province, family history of prostate cancer, ethnicity, education, body mass index, smoking by pack years, marital status, moderate physical activity, strenuous physical activity, total radiation exposure

**odds ratios by province were requested by a reviewer during the publication process, but are not meaningful because control selection varied by province*

For occupation groups (Table 6), an elevated risk was observed for those in legal work (judges, lawyers, and related) (OR 2.58, 95% CI 1.05-6.35). There was an elevated risk for farmers and farm/agriculture managers (OR 1.38, 95% CI 1.02-1.84) and a non-significantly elevated risk with ≥10 years duration (OR 1.37, 95% CI 0.95-1.96). An increased risk was observed for office workers (OR 1.20, 95% CI 1.00-1.43) and with ≥10 years duration (OR 1.31, 95% CI 1.02-1.68) with a significant trend for duration (p_{trend}=0.027). An elevated risk was observed for industrial mechanics with >0 to <10 years duration of employment (OR 1.45, 95% CI 1.01-2.09), but not with longer employment. An elevated risk was observed with plumbing, gas maintenance, and pipefitting (OR 1.77, 95% CI 1.07-2.93) and with ≥10 years duration (OR 2.08, 95% CI 1.10-3.91) with a significant trend for duration (p_{trend}=0.037). An elevated risk was observed for armed forces (OR 1.33, 95% CI 1.06-1.65) and with >0 to <10 years duration (OR 1.45, 95% CI 1.11-1.89) with a significant trend for duration (p_{trend}=0.001). A non-significant elevated risk was observed for firefighting (OR 1.67, 95% CI 0.94-2.95). A decreased risk was observed for travel clerks and related attendants (OR 0.37, 95% CI 0.16-0.88) and government/senior managers (OR 0.65, 95% CI 0.46-0.91). Decreased risks were also observed with ≥10 years duration for sports and recreation workers (OR 0.33, 95% CI 0.12-0.88) and brick and cement workers (OR 0.39, 95% CI 0.19-0.83). There was a decreased risk among construction managers and supervisors (OR 0.69, 95% CI 0.50-0.94) and with ≥10 years duration (OR 0.62, 95% CI 0.41-0.94) with a significant trend for duration (p_{trend}=0.025). Sensitivity analyses were also performed by removing occupations held during the time of diagnosis or 10 years prior to diagnosis to reduce screening potential bias. This resulted in <10% change or no change across findings.

Table 6. Odds ratios and 95% confidence intervals for prostate cancer by occupation group in the NECSS

	Ever Employment			≥10 Years Duration of Employment		
Occupation Groups	**Cases/Controls**	**OR[a] (95% CI)**	**OR[b] (95% CI)**	**Cases/Controls**	**OR[a] (95% CI)**	**OR[b] (95% CI)**
Administration and Related						
Senior Managers and Government Officials	70/95	**0.68 (0.49-0.94)**	**0.65 (0.46-0.91)**	43/50	0.83 (0.54-1.27)	0.81 (0.52-1.26)
Office Occupations (excluding Managers)	355/328	**1.19 (1.00-1.41)**	**1.20 (1.00-1.43)***	170/146	**1.28 (1.00-1.63)**	**1.31 (1.02-1.68)***
Office Managers	53/39	1.34 (0.87-2.06)	1.33 (0.86-2.07)	24/21	1.21 (0.65-2.24)	1.21 (0.65-2.25)
Financial Managers, Accountants, other Bank and Clerk Work	136/125	1.17 (0.89-1.52)	1.13 (0.86-1.49)	83/74	1.23 (0.89-1.73)	1.21 (0.85-1.71)
Lawyers, Judges, and Related	16/9	**2.59 (1.07-6.29)**	**2.58 (1.05-6.35)**	11/6	2.67 (0.91-7.86)	2.60 (0.88-7.68)
Teachers, Library, Museum, Archival Sciences, Social Sciences	116/106	1.13 (0.85-1.51)	1.09 (0.81-1.47)	75/59	1.30 (0.90-1.88)	1.28 (0.88-1.87)
Natural Resources						
Farmers, Farm and Agriculture Managers	137/98	**1.38 (1.04-1.82)**	**1.37 (1.02-1.84)**	86/62	1.37 (0.97-1.94)	1.37 (0.95-1.96)
Agriculturists and Related Scientists	35/33	1.06 (0.65-1.75)	1.01 (0.43-2.36)	17/14	1.10 (0.54-2.27)	1.75 (0.49-6.27)
General Farm Workers and Labourers	274/278	0.95 (0.78-1.15)	0.96 (0.79-1.18)	130/144	0.88 (0.68-1.15)	0.90 (0.69-1.18)
Forestry and Logging	97/93	0.98 (0.72-1.34)	1.00 (0.73-1.39)	38/40	1.03 (0.64-1.66)	0.98 (0.59-1.62)
Fishing, Trapping, Hunting	35/44	0.74 (0.46-1.19)	0.89 (0.54-1.47)	14/27	0.57 (0.29-1.13)	0.70 (0.34-1.43)
Mining, Quarrying, Oil and Gas	69/75	0.88 (0.62-1.24)	0.88 (0.62-1.27)	23/31	0.75 (0.43-1.33)	0.79 (0.44-1.42)
Primary Production and Manufacturing Managers	57/62	0.96 (0.66-1.41)	0.87 (0.58-1.28)	27/26	1.06 (0.60-1.87)	0.96 (0.54-1.72)
Wood Processing and Making	129/139	0.87 (0.67-1.12)	0.86 (0.66-1.12)	78/76	1.00 (0.72-1.40)	0.95 (0.67-1.34)
Pulp and Papermaking	72/57	1.09 (0.75-1.58)	1.13 (0.76-1.67)	29/24	1.05 (0.59-1.87)	1.13 (0.62-2.07)
Machinery and Processing						
Food and Beverage Preparation, Serving, and Related	143/160	0.99 (0.77-1.27)	1.00 (0.77-1.29)	56/69	0.94 (0.64-1.36)	0.98 (0.67-1.45)
Food Processing, Preserving, and Packing	34/40	0.97 (0.60-1.57)	1.05 (0.64-1.70)	14/24	0.61 (0.31-1.21)	0.68 (0.34-1.35)
Mineral and Metal Processing	109/105	1.09 (0.82-1.45)	1.15 (0.86-1.54)	50/47	1.12 (0.74-1.70)	1.16 (0.76-1.78)
Machinists	49/62	0.76 (0.51-1.12)	0.75 (0.50-1.12)	25/35	0.69 (0.41-1.18)	0.69 (0.40-1.19)
Machine Operators and Assemblers	47/47	1.06 (0.69-1.63)	1.08 (0.70-1.66)	20/20	1.08 (0.57-2.05)	1.10 (0.57-2.11)
Material Handling and Related	94/81	1.09 (0.80-1.49)	1.18 (0.85-1.63)	44/31	1.36 (0.84-2.20)	1.47 (0.90-2.41)
Industrial Mechanics	180/162	1.14 (0.90-1.44)	1.13 (0.89-1.44)	98/99	0.96 (0.71-1.29)	0.94 (0.69-1.28)
Motor Vehicle Repairers	101/95	1.07 (0.80-1.45)	1.06 (0.78-1.43)	65/57	1.16 (0.80-1.70)	1.13 (0.77-1.66)
Rubber and Plastic Products	11/15	0.89 (0.40-1.99)	0.90 (0.40-2.01)	6/7	1.19 (0.39-3.62)	1.17 (0.38-3.58)
Construction and Trades						
Brick and Cement	29/36	0.70 (0.42-1.17)	0.71 (0.42-1.20)	11/23	**0.38 (0.18-0.79)**	**0.39 (0.19-0.83)**
Plumbers, Gas Maintenance, and Pipefitters	48/27	**1.71 (1.05-2.79)**	**1.77 (1.07-2.93)***	31/16	**2.05 (1.10-3.82)**	**2.08 (1.10-3.91)***
Painters, Paperhangers, Decorators, and Related Occupations	31/33	0.99 (0.59-1.67)	1.14 (0.67-1.93)	10/16	0.71 (0.31-1.62)	0.89 (0.38-2.08)
Electrical and Related Equipment	122/111	1.14 (0.86-1.50)	1.12 (0.84-1.50)	64/71	0.93 (0.65-1.33)	0.91 (0.63-1.31)
Electronic Assemblers	26/23	1.28 (0.71-2.28)	1.10 (0.60-2.01)	5/11	0.53 (0.18-1.53)	0.39 (0.12-1.27)
Construction Labourers	100/119	0.85 (0.64-1.13)	0.88 (0.66-1.18)	25/33	0.84 (0.49-1.43)	0.84 (0.48-1.45)
Construction Managers and Supervisors	82/111	**0.68 (0.50-0.93)**	**0.69 (0.50-0.94)***	40/64	**0.62 (0.41-0.94)**	**0.62 (0.41-0.94)***
Other Construction Work	49/51	0.86 (0.57-1.30)	0.89 (0.59-1.35)	27/14	1.65 (0.84-3.20)	1.67 (0.85-3.29)
Transportation and Equipment Operators						
Equipment Operators	144/134	1.10 (0.85-1.41)	1.13 (0.87-1.47)	68/57	1.23 (0.85-1.79)	1.27 (0.87-1.87)
Transportation Drivers	225/215	1.04 (0.85-1.28)	1.10 (0.89-1.37)	111/120	0.92 (0.70-1.21)	0.95 (0.71-1.27)

Transportation Technicians	95/91	1.02 (0.75-1.40)	1.02 (0.74-1.41)	36/38	0.97 (0.60-1.57)	0.90 (0.55-1.48)
Technologists and Technicians	99/105	0.93 (0.69-1.24)	0.90 (0.66-1.22)	49/40	1.28 (0.82-2.00)	1.24 (0.78-1.97)
Technicians and Other Trades						
Printing and Related	11/8	1.38 (0.54-3.50)	1.46 (0.55-3.84)	2/5	0.48 (0.09-2.51)	0.32 (0.04-2.81)
Natural Sciences and Related	46/29	1.56 (0.96-2.54)	1.54 (0.94-2.53)	23/18	1.34 (0.70-2.56)	1.38 (0.72-2.67)
Architects and Landscape Technologists and Technicians	39/38	1.04 (0.65-1.67)	1.05 (0.65-1.70)	16/18	0.87 (0.43-1.77)	0.90 (0.44-1.85)
Engineers	61/56	1.17 (0.79-1.73)	1.02 (0.71-1.48)	31/28	1.14 (0.67-1.96)	0.98 (0.60-1.60)
Laboratory Technologists and Technicians	21/28	0.75 (0.41-1.35)	0.68 (0.37-1.26)	8/8	0.85 (0.32-2.31)	0.76 (0.27-2.15)
Chemical Processing and Operators	37/27	1.53 (0.92-2.57)	1.45 (0.85-2.46)	17/16	1.26 (0.62-2.55)	1.26 (0.61-2.58)
Health and Personal Care						
Dentists and Related	6/10	0.49 (0.17-1.41)	0.56 (0.18-1.68)	5/9	0.46 (0.15-1.43)	0.55 (0.17-1.84)
Physicians and Surgeons	13/14	1.08 (0.47-2.45)	1.12 (0.49-2.57)	10/13	0.84 (0.34-2.06)	0.89 (0.36-2.22)
Veterinarians	1/3	0.23 (0.02-2.33)	0.30 (0.03-3.09)	1/3	0.23 (0.02-2.33)	0.30 (0.03-3.09)
Nurses and Aides	11/12	1.19 (0.51-2.80)	1.30 (0.54-3.12)	8/4	2.91 (0.83-10.28)	3.45 (0.87-13.62)
Dry Cleaning, Laundering and Services	3/6	0.56 (0.13-2.47)	0.53 (0.11-2.50)	3/2	1.25 (0.19-8.46)	1.09 (0.16-7.48)
General Cleaning	90/101	0.97 (0.72-1.32)	0.99 (0.72-1.36)	43/50	0.94 (0.61-1.44)	0.95 (0.61-1.48)
Barbers, Hairdressers and Related	5/11	0.43 (0.14-1.29)	0.46 (0.15-1.39)	4/10	0.39 (0.12-1.31)	0.41 (0.12-1.39)
Other Health, Medicine, and Related Fields	27/42	0.73 (0.44-1.23)	0.65 (0.38-1.11)	17/26	0.67 (0.35-1.28)	0.63 (0.32-1.23)
Protective Services						
Firefighters	38/22	1.59 (0.92-2.74)	1.67 (0.94-2.95)	19/12	1.46 (0.69-3.09)	1.70 (0.76-3.77)
Police Officers and Agents	35/26	1.23 (0.72-2.09)	1.15 (0.66-1.99)	18/15	1.10 (0.54-2.25)	1.03 (0.49-2.17)
Armed Forces	265/196	**1.32 (1.07-1.63)**	**1.33 (1.06-1.65)***	81/70	1.21 (0.85-1.70)	1.11 (0.78-1.59)*
Other Protective Services	43/35	1.34 (0.83-2.14)	1.41 (0.87-2.31)	16/13	1.49 (0.82-2.71)	1.59 (0.85-2.98)
Retail, Art, Recreation, and Other Occupations						
Furniture and Fixtures	7/5	1.38 (0.42-4.50)	1.95 (0.54-7.04)	2/1	2.00 (0.17-23.47)	-
Textiles	23/34	0.74 (0.42-1.29)	0.72 (0.41-1.27)	8/17	0.52 (0.22-1.26)	0.50 (0.21-1.20)
Retail Trade	96/97	1.01 (0.74-1.37)	1.02 (0.75-1.40)	47/51	0.98 (0.65-1.49)	1.01 (0.66-1.54)
Sales and Services	233/236	1.01 (0.83-1.24)	1.02 (0.83-1.25)	137/119	1.18 (0.91-1.54)	1.16 (0.88-1.53)
Travel Clerks and Related Attendants	8/19	**0.37 (0.16-0.87)**	**0.37 (0.16-0.88)**	3/5	0.58 (0.13-2.52)	0.56 (0.13-2.46)
Art, Entertainment, and Religion	49/63	0.79 (0.53-1.17)	0.80 (0.53-1.20)	27/40	0.70 (0.42-1.17)	0.71 (0.42-1.21)
Sports and Recreation	32/33	0.81 (0.49-1.34)	0.86 (0.50-1.45)	6/14	**0.33 (0.12-0.88)**	0.41 (0.14-1.13)
Other Services	22/25	0.92 (0.51-1.69)	0.88 (0.48-1.61)	10/9	1.26 (0.50-3.22)	1.24 (0.49-3.16)

Ever employment was compared to men who were never employed in the given occupation group

≥10 years duration of employment was compared to men employed in all other occupation groups for the same duration

[a]*adjusted for age, province, family history of prostate cancer, and ethnicity*

[b]*adjusted for age, province, family history of prostate cancer, ethnicity, education, body mass index, smoke pack years, marital status, moderate physical activity, strenuous physical activity, total radiation exposure*

p_{trend} values <0.05

Industry results (Table 7) were similar to occupation results with few additional findings. An elevated risk was observed for forestry/logging workers (OR 1.54, 95% CI 1.06-2.25) with non-significantly elevated risks for >0 to <10 years duration (OR 1.57, 95% CI 0.97-2.54) and ≥10 years duration (OR 1.65, 95% CI 0.90-3.03) and a significant trend for duration (p=0.01). Elevated risks were also observed for >0 to <10 years duration of employment in plastic production (OR 3.54, 95% CI 1.23-9.67) and for ≥10 years duration of employment in architecture and landscaping (OR 1.84, 95% CI 1.00-3.38). A decreased risk was observed for employment in the tourism and recreation (OR 0.63, 95% CI 0.43-0.91) and for primary metal production (OR 0.70, 95% CI 0.51-0.96), the latter also with ≥10 years employment duration (OR 0.60, 95% CI 0.39-0.94).

Table 7. Odds ratios and 95% confidence intervals for prostate cancer by industry group in the NECSS

	Ever Employment			≥10 Years Duration of Employment		
Industry Groups	**Cases/Controls**	**OR[a] (95% CI)**	**OR[b] (95% CI)**	**Cases/Controls**	**OR[a] (95% CI)**	**OR[b] (95% CI)**
Administrative and Related						
Office	64/73	0.91 (0.64-1.30)	0.95 (0.66-1.37)	36/34	1.05 (0.64-1.72)	1.14 (0.68-1.90)
Government	176/183	1.07 (0.85-1.35)	1.04 (0.82-1.32)	87/92	1.11 (0.81-1.53)	1.10 (0.80-1.52)
Finance and Business	169/162	1.06 (0.84-1.35)	1.05 (0.82-1.34)	82/84	0.99 (0.71-1.37)	0.97 (0.69-1.36)
Legal Services	21/10	**2.77 (1.22-6.25)**	**2.65 (1.16-6.05)**	13/8	**2.70 (1.04-7.01)**	2.11 (0.80-5.53)
Education	179/192	0.99 (0.79-1.24)	0.97 (0.77-1.23)	127/115	1.10 (0.83-1.44)	1.12 (0.84-1.49)
Natural Resources						
Crop Agriculture and Farming	358/334	1.06 (0.89-1.27)	1.08 (0.90-1.31)	200/188	1.06 (0.84-1.32)	1.10 (0.86-1.40)
Animal Agriculture and Farming	35/39	0.83 (0.52-1.34)	0.81 (0.50-1.32)	17/21	0.75 (0.38-1.46)	0.75 (0.38-1.48)
Forestry and Logging	86/57	1.32 (0.92-1.90)	**1.54 (1.06-2.25)***	34/23	1.38 (0.79-2.42)	1.65 (0.90-3.03)*
Petroleum and Oil	87/92	0.89 (0.64-1.22)	0.88 (0.64-1.23)	49/43	1.05 (0.68-1.63)	1.05 (0.66-1.65)
Mining	112/112	1.00 (0.75-1.32)	1.00 (0.75-1.34)	40/48	0.89 (0.57-1.37)	1.10 (0.76-1.59)
Fishing and Trapping	36/45	0.75 (0.47-1.21)	0.92 (0.56-1.52)	16/28	0.64 (0.33-1.23)	0.80 (0.40-1.57)
Wood Products	112/104	0.85 (0.63-1.14)	0.87 (0.65-1.18)	54/45	0.99 (0.65-1.52)	1.00 (0.65-1.56)
Paper and Allied Products	73/74	0.96 (0.68-1.36)	0.91 (0.64-1.31)	41/38	1.03 (0.64-1.65)	0.98 (0.60-1.61)
Transportation, Trades, and Products						
Transportation Services	325/321	0.97 (0.81-1.16)	0.98 (0.82-1.18)	182/178	0.99 (0.79-1.25)	0.99 (0.78-1.26)
Transportation Equipment	175/187	1.05 (0.84-1.31)	1.05 (0.83-1.33)	77/92	0.98 (0.71-1.36)	1.02 (0.73-1.43)
Trade Construction/ Contractors	173/182	0.90 (0.72-1.13)	0.90 (0.71-1.14)	81/86	0.93 (0.68-1.29)	0.96 (0.69-1.33)
Other Construction	234/216	1.09 (0.89-1.34)	1.10 (0.89-1.37)	100/105	1.02 (0.76-1.37)	0.95 (0.70-1.28)
Electrical and Electronics	104/108	0.98 (0.73-1.30)	0.94 (0.70-1.27)	46/48	0.94 (0.61-1.44)	0.96 (0.65-1.41)
Repair Products	112/102	1.11 (0.83-1.48)	1.11 (0.83-1.50)	50/47	1.09 (0.72-1.66)	1.05 (0.68-1.62)
Other Manufacturing	18/16	1.15 (0.57-2.34)	1.27 (0.61-2.65)	4/9	0.47 (0.14-1.58)	0.51 (0.15-1.78)
Food, Beverage, and Tobacco	113/137	0.92 (0.70-1.21)	0.94 (0.71-1.24)	41/60	0.75 (0.49-1.14)	0.81 (0.52-1.26)
Food Management, Processing	171/174	1.05 (0.83-1.32)	1.09 (0.87-1.38)	85/73	1.29 (0.93-1.80)	0.90 (0.66-1.23)
Metal and Non-Metal Products						
Primary Metals Products	80/105	**0.71 (0.52-0.97)**	**0.70 (0.51-0.96)**	38/57	**0.64 (0.41-0.98)**	**0.60 (0.39-0.94)**
Non-Metal Mineral Products	34/44	0.79 (0.49-1.26)	0.80 (0.50-1.30)	20/25	0.76 (0.41-1.39)	0.82 (0.44-1.53)
Fabricated Metal Products	96/90	1.08 (0.79-1.46)	1.10 (0.80-1.52)	43/42	1.00 (0.64-1.55)	0.98 (0.62-1.55)
Machinery & Equipment Products	70/75	1.01 (0.72-1.44)	1.01 (0.71-1.44)	27/33	0.83 (0.49-1.40)	0.82 (0.48-1.40)
Plastic Products	22/15	1.60 (0.81-3.16)	1.65 (0.83-3.30)	5/10	0.57 (0.19-1.72)	0.65 (0.21-1.98)
Rubber Products	12/17	0.83 (0.39-1.79)	0.73 (0.33-1.60)	8/8	1.37 (0.50-3.77)	1.12 (0.39-3.22)
Chemical Products	57/53	1.16 (0.78-1.72)	1.13 (0.76-1.69)	34/25	1.41 (0.82-2.40)	0.81 (0.45-1.47)
Technical, Information, and Protective Services						
Communications and Utilities	145/160	0.96 (0.75-1.23)	0.97 (0.76-1.25)	73/94	0.86 (0.62-1.19)	0.85 (0.61-1.18)
Printing	20/24	0.85 (0.46-1.59)	0.85 (0.45-1.59)	10/11	0.91 (0.38-2.20)	0.89 (0.35-2.26)
Architecture and Landscaping	76/67	1.07 (0.76-1.53)	0.98 (0.68-1.40)	37/19	**1.89 (1.05-3.41)**	**1.84 (1.00-3.38)**
Natural Sciences	24/30	0.80 (0.46-1.40)	0.77 (0.43-1.35)	12/10	1.16 (0.49-2.75)	1.17 (0.49-2.79)

Defense Services (Armed Forces)	434/326	**1.37 (1.15-1.63)**	**1.38 (1.15-1.66)***	150/124	**1.32 (1.02-1.72)**	**1.29 (0.97-1.70)***
Other Protective Services	83/63	1.36 (0.96-1.93)	1.30 (0.91-1.87)	40/31	1.27 (0.78-2.07)	1.23 (0.74-2.04)
Retail, Art, and Recreation						
Furniture and Fixtures	79/72	1.21 (0.87-1.70)	1.25 (0.88-1.77)	28/23	1.41 (0.79-2.51)	1.36 (0.75-2.47)
Textiles	29/43	0.76 (0.46-1.25)	0.74 (0.44-1.24)	10/11	0.53 (0.21-1.32)	0.45 (0.17-1.23)
Retail	138/151	0.89 (0.69-1.15)	0.90 (0.69-1.16)	62/64	1.00 (0.69-1.45)	0.86 (0.61-1.21)
Wholesale Products	191/167	1.12 (0.89-1.41)	1.13 (0.90-1.42)	96/74	1.24 (0.90-1.71)	1.24 (0.89-1.72)
Art and Culture	22/23	0.90 (0.49-1.65)	0.93 (0.50-1.74)	6/10	0.57 (0.20-1.62)	0.60 (0.20-1.74)
Tourism and Recreation	52/91	**0.59 (0.41-0.85)**	**0.63 (0.43-0.91)***	21/35	**0.55 (0.32-0.98)**	0.61 (0.34-1.11)*
Health and Other Services						
Health Professionals	65/91	0.77 (0.54-1.08)	0.78 (0.55-1.11)	41/54	0.84 (0.54-1.30)	0.83 (0.53-1.30)
Personal Health and Household	65/80	0.90 (0.63-1.27)	0.94 (0.66-1.35)	35/41	1.01 (0.63-1.64)	0.90 (0.55-1.47)
Other Services	50/38	1.33 (0.85-2.07)	1.26 (0.80-1.97)	25/21	1.22 (0.66-2.24)	1.21 (0.65-2.25)

Ever employment was compared to men who were never employed in the given industry group
≥10 years duration of employment was compared to men employed in all other industry groups for the same duration
[a]*adjusted for age, province, family history of prostate cancer, and ethnicity*
[b]*adjusted for age, province, family history of prostate cancer, ethnicity, education, body mass index, smoke pack years, marital status, moderate physical activity, strenuous physical activity, total radiation exposure*
p_{trend} values <0.05

5.5 Discussion

Our study identified few associations by occupation and industry. An elevated risk was observed for farmer and farm/agriculture manager occupations, though this was non-significantly elevated for ≥10 years of duration. Farming occupations are linked to pesticide exposure which can disrupt endocrine function and include estrogen-like compounds which promote tumor growth (Ragin et al, 2013). A recent meta-analysis that examined exposure to pesticides from farming found that prostate cancer cases were more likely to be farmers when compared to controls with benign prostate hyperplasia (OR 3.83, CI 95% 1.96-7.48) (Ragin et al, 2013). However, they observed an inverse association for pesticide exposure and prostate cancer (OR 0.68, 95% CI 0.49-0.96) (Ragin et al, 2013). Recent publications on pesticide applicators in the Agricultural Health Study (AHS) reported various results for specific pesticides and prostate cancer risk (Mahajan et al, 2006; Christensen et al, 2010; Jones et al, 2015; Koutros et al, 2013; Koutros et al, 2015). An earlier AHS study observed that fonofos exposure was not associated with prostate cancer risk overall, but found a significant dose-response trend for lifetime exposure days in men who had a family history of prostate cancer (p_{trend}=0.02) (Mahajan et al, 2006). This was similar to another AHS study that reported no association between coumaphos exposure and prostate cancer risk overall, but observed a positive association in men with a family history of prostate cancer (Christensen et al, 2010). Recent AHS studies observed significant associations between specific pesticides (diazinon, fonofos, malathion, terbufos and aldrin) and aggressive prostate cancer (Jones et al, 2015; Koutros et al, 2013). Another AHS study also reported a positive association between serum concentrations of oxychlordane and metastatic prostate cancer, with non-significantly elevated risks for chlordane/heptachlor metabolites (heptachlor expoxide, HCB and mirex) (Koutros et al, 2015).

A systematic review (1993-2015) examining pesticide exposure and prostate cancer found that 32 of the 49 studies reported positive associations between pesticides, agricultural occupations and prostate cancer (Silva et al, 2016). Previous studies have shown significant associations for specific pesticides used in farming and prostate cancer risk (Band et al, 2011; Morrison et al, 1993) whereas a recent Canadian case-control study found no association between agriculture work and prostate cancer (Sauve et al, 2016). A previous NECSS publication also found a decreased risk in long term outdoor workers with high levels of solar radiation exposure (Peters et al, 2016).

Elevated risks were also observed for men working in the armed forces. This profession may involve exposure to metals, asbestos, fuels, chemical/warfare agents, radiation and whole body vibration, stress and shiftwork (US Department of Veterans Affairs, 2016). The healthy worker effect is often addressed in military workers as they tend to be healthier than the general population (Statistics Canada, 2011) and have frequent access to health care resources and possibly screening (Government of Canada, 2016). A large Canadian forces cohort study examined cancer death overall and found a decreased risk for cancer deaths in military men when compared to the general population (Statistics Canada, 2011). A 2009 United States study found significantly increased risks for prostate cancer in military men (incidence rate ratio=2.12 (white men), 2.09 (black men) when compared to rates in the general population (Zhu et al, 2009). Findings were linked to cancer screening and other unknown factors (Zhu et al, 2009). A previous Australian study on Vietnam veterans identified a non-statistically-significant elevated risk for prostate cancer (OR 2.12, 95% CI 0.88-5.06) (Leavy et al, 2006). The study related findings to family history of prostate cancer, increased screening and use of herbicides (Agent Orange) (Leavy et al, 2006). Further research is needed to assess prostate cancer risks in the Canadian military with information on related exposures and screening practices.

Non-significantly elevated risks were observed for firefighting occupations and the protective services industry (includes firefighters and police officers). A meta-analysis on 32 studies found that firefighter occupations had a possible association with prostate cancer (summary risk estimate 1.28, 95% CI 1.15-1.43) (LeMasters et al, 2006). The authors concluded that the firefighters were exposed to mixed exposures involving prostate carcinogens. Based on this meta-analysis and other previous studies, IARC classified firefighting as a risk for prostate cancer (IARC, 2010). A large cohort analysis that included 45 years of follow-up in five Nordic countries identified a more than twofold excess odds of prostate cancer in firefighters <50 years of age, but not for firefighters >50 years of age (Pukkala et al, 2014). The study identified shift work and exposure to polycyclic aromatic hydrocarbons and diesel exhaust as possible factors (Tsai et al, 2015). Two large US cohort studies published different results, with one observing decreased mortality risks for prostate cancer (HR 0.71, 95% CI NC-0.90) with no exposure-response trend (Daniels et al, 2015; Wirth et al, 2013). The second study identified an elevated risk of prostate cancer among firefighters (OR 1.5, 95% CI 1.3-1.7) (Daniels et al, 2015; Wirth et al, 2013). Prostate cancer risk among police occupations has been assessed in fewer studies. A 2013 review on 14 studies reported inconsistent findings for prostate cancer risk among police officers. The authors addressed multiple factors in police work, with psychological stress and shift work being significant factors (Wirth et al, 2013). A large cohort study found a statistically significant increased risk for prostate cancer among policemen (OR 3.91, 95% CI 1.14-13.42) (Zeegers et al, 2004) and a recent Canadian case-control study observed an association for police officers and detectives (OR 1.8, 95% CI 1.1-2.9) (Sauve et al, 2016).

Other elevated risks were observed in legal occupations and industries, office occupations, industrial mechanic occupations, plumbing/pipefitting occupations, plastic products industry, architecture and landscaping industry, and the forestry/logging industry. Elevated risks in forestry/logging have been previously reported in recent Canadian studies (Sritharan et al, 2016; Sauve et al, 2016). Decreased risks were observed across occupations of senior management and government, brick and cement, construction management, and the primary metal products industry.

Specifically, travel clerks and related attendant occupations had a decreased risk for prostate cancer and when minimally adjusted, sports and recreation occupations had a decreased risk with duration. At an industry level, tourism and recreation workers also had a decreased risk. Physical activity may play a role in these findings as previous studies have shown that lifelong occupational physical activity was significantly associated with a decreased risk of prostate cancer (Parent et al, 2011). Physical activity demonstrates a similar decreased risk among other cancer types and helps to decrease obesity, hormone level modulation and growth factors, and activation of carcinogenic activity while increasing DNA repair and immune function (Parent et al, 2011).

Our study findings may also be explained by the screening behaviours of participants. Prostate cancer incidence started to rise in 1990 and peaked from 1991-1993 which had the highest annual percent change of incidence (12.81%) (Dickinson et al, 2016). It began to slowly decline from 1993-1996 and plateau off. These patterns are reflective of prostate specific antigen screening practices over the same time period (Dickinson et al, 2016). As our data collection was from 1994-1997, our findings are likely reflective of the complicated relationship between prostate cancer incidence and screening patterns. Studies have shown that screening behaviours are also linked to factors of socioeconomic status, marital status and family history of prostate cancer (Richardson et al, 2007; Wallner et al, 2008; Liu et al, 2001; Beaulac et al, 2006; Littlejohns et al, 2016; Bratt et al, 2010). Men who have higher education, higher income, and/or who are married have better access to health resources making them more likely to seek PSA screening and further diagnostic testing (Richardson et al, 2007; Wallner et al, 2008; Liu et al, 2001; Beaulac et al, 2006; Littlejohns et al, 2016; Bratt et al, 2010; Tangen et al, 2016). Men with a family history of prostate cancer have also shown to have increased diagnostic activity (Bratt et al, 2010; Tangen et al, 2016). Based on these associations, it is likely that detection bias plays a role in our findings (Littejohns et al, 2016; Bratt et al, 2010; Tangen et al, 2016). Our findings are also affected by participation bias which is similarly related to factors of age, socioeconomic status and occupation (Pearce et al, 2007). Some occupation groups may be more likely to participate than other occupation groups. Also, there was a low representation of non-Caucasian ethnic groups in our study which may be related to language barriers, stigma and inaccessibility. To account for differences in both screening and participation, adjustments were made for age, ethnicity, family history, socioeconomic status and marital status. Results should also be interpreted with multiple testing in mind as the use of multiple jobs can lead to some chance findings. We did however see consistency in findings across similar groups in occupation and industry.

Our study is one of the few large population-based studies that examined prostate cancer risk by job title and included non-occupational risk factors. Significant strengths of this study were the availability of multiple individual level covariates and lifetime occupational history. There were also limitations as there was no information on screening behaviours or on the aggressiveness of prostate cancer cases. Non-differential misclassification is also likely as participants were categorized into multiple occupation and industry groups. Occupation and industry may act as weak surrogates for exposures but with very little knowledge on exposures linked to prostate cancer, this is an important step to identify job-specific exposures.

Overall, this study presents few associations between occupation, industry and prostate cancer. Findings for agriculture workers are similar to those in previous studies, but new associations were also uncovered. This study demonstrates the need for individual level covariates to account for known and possible risk factors for prostate cancer. Further research should continue to explore job-specific exposures and should address the impact of varying screening behaviours. By understanding these factors, there can be improved knowledge on occupation and prostate cancer leading to evidence-based prevention.

Chapter 6. Prostate cancer surveillance by occupation and industry: the Canadian Census Health and Environment Cohort (CanCHEC)

This chapter has been published:

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6.1 Abstract

Objective: As there are no well-established modifiable risk factors for prostate cancer, further evidence is needed on possible factors like occupation. Our study uses one of the largest Canadian worker cohorts to examine occupation, industry, and prostate cancer and to assess patterns of prostate cancer rates.
Methods: The Canadian Census Health and Environment Cohort (CanCHEC) was established by linking the 1991 Canadian Census Cohort to the Canadian Cancer Database (1969-2010), Canadian Mortality Database (1991-2011), and Tax Summary Files (1981-2011). A total of 37,695 prostate cancer cases was identified in men aged 25-74 based on age at diagnosis. Cox proportional hazards models were used to estimate hazards ratios and 95% confidence intervals.
Results: In men aged 25-74 years, elevated risks were observed in the following occupations: senior management (HR=1.12, 95% CI 1.04-1.20); office and administration (HR=1.19, 95% CI 1.11-1.27); finance services (HR=1.09, 95% CI 1.04-1.14); education (HR=1.05, 95% CI 1.00-1.11); agriculture and farm management (HR=1.12, 95% CI 1.06-1.17); farm work (HR=1.11, 95% CI 1.01-1.21); construction managers (HR=1.07, 95% CI 1.01-1.14); firefighting (HR=1.17, 95% CI 1.01-1.36); police work (HR=1.22, 95% CI 1.09-1.36). Decreased risks were observed across other construction and transportation occupations. Results by industry were consistent with occupation results.
Conclusions: Associations were identified for white collar, agriculture, protective services, construction, and transportation occupations. These findings emphasize the need for further study of job-related exposures and the potential influence of non-occupational factors like screening practices.

6.2 Introduction

Prostate cancer is one of the most commonly diagnosed cancers worldwide and accounts for 15% of all cancers diagnosed in men (IARC, 2012; Prostate Cancer Canada, 2016). It is more common in men over the age of 50, but in recent years it has been diagnosed with increased frequency in younger men (Prostate Cancer Canada, 2016). Through efforts to understand the etiology of prostate cancer, the most well-established risk factors are age, family history of prostate cancer, and ethnicity (Bashir, 2016). Other factors of diet, obesity, smoking, sexual behavior, sexually transmitted diseases, genetic mutations, hormone levels, and occupation have shown mixed evidence (Bashir, 2016; Perdana et al, 2016; Gann et al, 2002). There are currently no established occupational risk factors for prostate cancer; however, the International Agency for Research on Cancer (IARC) has concluded there is limited evidence for arsenic and cadmium compounds, the insecticide malathion, radiation, and the rubber production industry (IARC, 2017). Other associations have also been observed for agriculture occupations, firefighting occupations, shift work, and whole body vibrations (Cerhan et al, 1998; Sharma-Wagner et al, 2000; LeMasters et al, 2006; Sass-Kortsak et al, 2007; Nadalin et al, 2012; Ragin et al, 2013; Jones et al, 2014; Rao et al, 2015).

Examining disease risks across occupational and industry groups can lead to better understanding of associated occupational exposures (t'Mannetje et al, 2002). Occupation and industry groups can be surrogates for exposure and indicative of where prevention research should focus. In recent years, large international cohort studies examined prostate cancer risk across a range of occupation and industry groups and observed inconsistent associations (Krstev et al, 1998; Pukkala et al, 2009; Zeegers et al, 2004). These cohort studies observed associations with white collar occupations suggesting these workers may have better access to screening (Krstev et al, 1998; Pukkala et al, 2009; Zeegers et al, 2004). Further understanding of occupation and screening behaviours is needed. It is well established that prostate cancer incidence has increased over time, and that this increase can be accounted for primarily because of prostate specific antigen (PSA) screening (Dickinson et al, 2016). However, it is still unclear how screening patterns affect changes in incidence within an occupational group. Given the current uncertainty regarding the benefits of early diagnosis of prostate cancer using PSA screening (Hayes et al, 2014), it is important to strengthen the evidence on preventative factors, like occupation. This will not only confirm existing associations and generate new hypotheses, but will also provide better understanding of how associations between occupation and prostate cancer are influenced by screening related factors.

The 1991 Canadian Census Health and Environment Cohort (CanCHEC) is one of the largest population based cohort studies in Canada spanning across all provinces and territories (Peters et al, 2013). This cohort provides unique linked data that contains valuable information on occupation and prostate cancer. This study provides national level data with a large sample size with detailed information on occupational and non-occupational factors measured at baseline (Wilkins et al, 2008). *The purpose of this study was to evaluate prostate cancer by occupation and industry employment in the 1991 CanCHEC.*

6.3 Methods

6.3.1 Study Population & Linkage

The CanCHEC (n=2,743,835) was established by Statistics Canada linking data from the long form 1991 Canadian Census to the Canadian Cancer Database (1969-2010), Canadian Mortality Database (1991-2011), and annual Tax Summary Files (1981-2011) (Figure 6). A detailed description of the linkage methodology is published elsewhere (Peters et al, 2013; Wilkins et al, 2008), and a brief flow chart of the linkage is shown in Figure 6. The mandatory 1991 Canadian long form census questionnaire was administered to 20% of Canadian households on June 4, 1991. Individuals included in the cohort were 25 years or older on census day, non-institutional residents, and had filed taxes in 1991 or 1992 (Peters et al, 2013; Wilkins et al, 2008). The Canadian Cancer Database provided cancer morbidity information and was prepared from data received by the Canadian Cancer Registry (1992-2010) and the National Cancer Incidence Reporting System (1969-1991). The Canadian Mortality database provided information on cause of death and date of death. Residential, marital status, and loss to follow-up information were identified using the Tax Summary Files. Loss to follow-up was determined if individuals emigrated out of Canada or if they did not file income taxes for over four consecutive years. Follow-up of all individuals began on census day, June 4, 1991 and continued until the end of follow-up on December 31, 2010 or until date of prostate cancer diagnosis, date of death, or loss to follow-up (Peters et al, 2013; Wilkins et al, 2008).

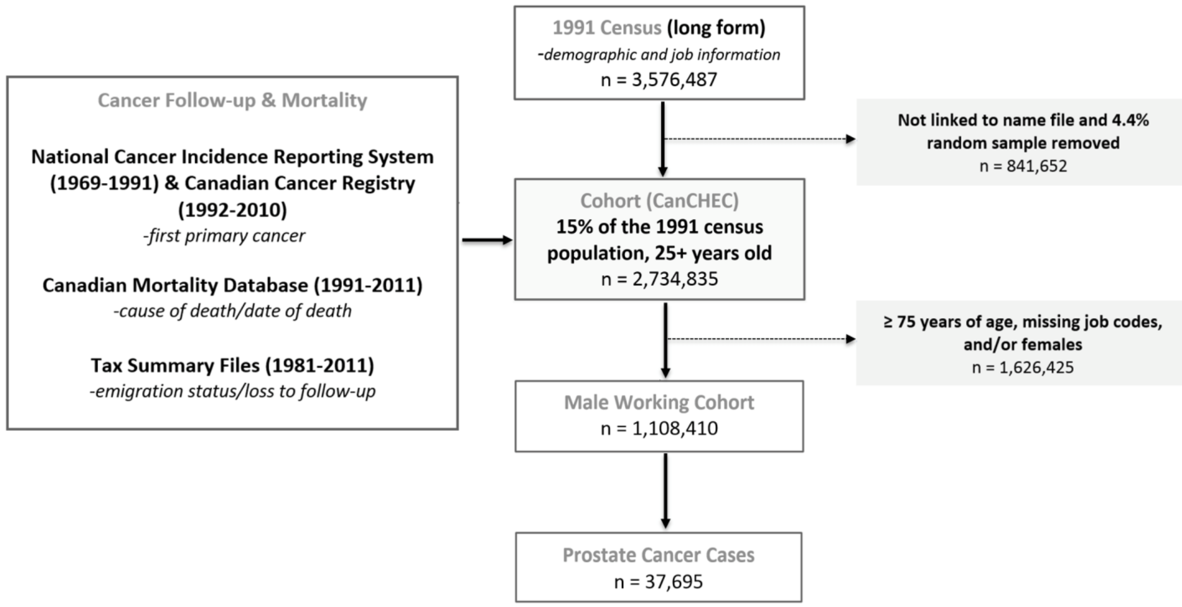

Figure 6. Flow chart illustrating the Canadian Census Health and Environment Cohort (CanCHEC) linkage. The 1991 Census was linked to the Canadian Cancer Database, Canadian Mortality Database, and the Tax Summary Files to create the CanCHEC. This established cohort represents 15% of the population that participated in the 1991 Census. From this cohort, the male working cohort was developed and 37, 695 prostate cancer cases were identified.

6.3.2 Work History

In the 1991 long form census, respondents were asked to report on the occupation they held in the week prior to the census. If no job was held in the week prior, respondents were asked for the job of longest duration since January 1, 1990. If more than one job was held in the week prior to the census, respondents answered based on the job in which the most hours were worked (Peters et al, 2013; Wilkins et al, 2008). Job information from each individual was then coded to occupation and industry classification codes using the 1991 Standard Occupation Classification (SOC91) and 1980 Standard Industrial Classification (SIC80). We then used the four digit codes from SOC91 and SIC80 to obtain the most descriptive job titles and we categorized workers based on similar job titles and tasks (related to potential exposures) to ensure they were in the appropriate occupation and industry groups for analysis. The working cohort included 2,051,315 individuals (Peters et al, 2013; Wilkins et al, 2008). For this study, the cohort was restricted to only men (n=1,108,410), aged 25 to 74 years (at baseline) who had a valid entry for occupation in the 1991 long form census (Peters et al, 2013; Wilkins et al, 2008). The valid entry for occupation was based on if they reported an occupation in the census questionnaire – the job they held in the week prior to the census, longest held since the year prior, or the job they worked the most hours in. Individuals who did not list an occupation were excluded from the working cohort.

6.3.3 Prostate Cancer Diagnosis

Prostate cancer was the primary interest of this study and each prostate cancer case was defined as an incident diagnosis between 1992 and 2010 based on information from the Canadian Cancer Database. This database provided information on cancer diagnoses going back to 1969 to capture cases prior to 1992 and to confirm that each case included in this study was a primary prostate cancer diagnosis. Year of death was obtained from the Canadian Mortality Database to remove any decreased individuals from the cohort and to make sure that the prostate cancer diagnosis preceded the death date. The mortality database provided cause of death information to identify prostate cancer related deaths. Cancer cases were classified according to the 9^{th} revision of the International Classification of Diseases (ICD-9) and 3^{rd} revision of the International Classification of Diseases for Oncology (ICD-O-3) (Peters et al, 2013; Wilkins et al, 2008).

6.3.4 Statistical Analysis

Hazard rate ratios (HRs) and corresponding 95% confidence intervals (CI) were calculated using Cox proportional hazard regression models to estimate prostate cancer risks associated with employment by occupation and industry. Men not employed in the specific occupation or industry being evaluated served as the non-exposed reference group. Prostate cancer is more common in men over the age of 50 years as risk of prostate cancer significantly increases with older age and these men are more likely to get screened for prostate cancer. Whereas younger diagnoses for prostate cancer (>50 years) are rare, likely to be aggressive forms, or from genetic susceptibility, and younger men are less likely to get screened (Prostate Cancer Canada, 2016). These factors make it difficult to capture a large number of prostate cancer cases in younger men (<50 years) in population studies and our study is unique in that it had the ability to capture both younger and older prostate cancer cases. We originally analyzed the data with two age groups (25-49 years and 50-74 years) but given that there were smaller case counts in the younger men and there were no significant differences in findings between the two age groups, we decided to use the combined age group of men 25-74 year for the final analysis. The primary focus of this analysis was prostate cancer incidence, with an additional analysis on mortality from prostate cancer (data not shown). All HR estimates were adjusted for baseline co-variates of age, province of residence, ethnicity, education, and marital status - all of which were obtained from the 1991 Census.

Income adjustment showed less than a 10% change in HR estimates, and therefore was removed from the model. Age-standardized prostate cancer rates were also examined for the working overall cohort and specific occupation groups, standardized to the 2001 CanCHEC population. In accordance with Statistics Canada disclosure rules, case counts of less than five were not included in reported tables and all frequencies were rounded to the nearest 100. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and took place in the secure facility of the Statistics Canada Research Data Centre in Toronto.

The linkage was approved by the Statistics Canada Executive Management Board and this study was approved by the Statistics Canada Research Data Centre and the University of Toronto Health Sciences Research Ethics Board.

6.4 Results

A total of 37,695 incident prostate cancer cases and 1700 deaths from prostate cancer were identified between 1992 and 2010 in the overall working cohort of men aged 25 to 74 years (n=1,108,410) (Figure 6). Table 8 presents the baseline characteristics of prostate cancer cases. An increased risk of prostate cancer was observed among black men when compared to Caucasian men (HR 1.77, 95% CI 1.66-1.89; fully adjusted). Men in other ethnic groups had reduced risks when compared to Caucasian men. Prostate cancer risks increased with increasing level of education. Decreased risks were observed among men who were never married or separated/divorced/widowed when compared to men who were legally married/common law.

Prostate cancer by selected occupations is shown in Table 9 and by selected industries in Supplementary Table 10. Figure 7 shows prostate cancer rates for specific occupation groups and for the overall working cohort.

Table 8. Baseline characteristics of the working cohort and of men with prostate cancer in the CanCHEC (Ages 25-74 years)

	All workers (%) (n=1,108,410)	Workers with PC (%) (n=37, 695)	Workers with PC HR[a] (95% CI)
Age Group			
25-34	359, 075 (32.4)	765 (2.0)	
35-44	341, 515 (30.8)	5, 885 (15.6)	
45-54	229, 460 (20.7)	13, 285 (35.2)	
55-64	143, 895 (13.0)	14, 045 (37.3)	
65-74	34, 465 (3.1)	3, 720 (9.9)	
Province of Residence			
Ontario	404, 130 (36.5)	15, 605 (41.4)	
Quebec	276, 120 (24.9)	6, 195 (16.4)	
Manitoba	47, 375 (4.3)	1, 585 (4.2)	
Saskatchewan	42, 050 (3.8)	1, 825 (4.8)	
Alberta	107, 405 (9.7)	4, 035 (10.7)	
British Columbia	130, 815 (11.8)	4, 965 (13.2)	
Yukon, NWT, Nunavut	11, 395 (1.0)	225 (0.6)	
Newfoundland	21, 815 (2.0)	680 (1.8)	
Prince Edward Island	4, 945 (0.4)	210 (0.6)	
Nova Scotia	34, 750 (3.1)	1, 245 (3.3)	
New Brunswick	27, 600 (2.5)	1, 130 (3.0)	
Ethnicity			
Caucasian	1, 018, 990	35, 345 (93.8)	Ref
Black	15, 120	910 (2.4)	**1.77 (1.66-1.89)**
South/East/Southeast Asian/Pacific Islander	58, 100	1, 120 (3.0)	**0.54 (0.51-0.57)**
Southwest Asian/Arabic	10, 850	235 (0.6)	**0.72 (0.63-0.82)**
Latin American	3, 925	55 (0.2)	**0.67 (0.52-0.88)**
Other, Multiple	1, 425	35 (0.1)	0.93 (0.68-1.28)
Highest Level of Education Completed			
No High School	Ref	13, 090 (34.7)	Ref
High School	444, 560 (40.1)	13, 430 (35.6)	**1.06 (1.03-1.08)**
Postsecondary Non-University/Trade School	154, 165 (13.9)	4, 375 (11.6)	**1.10 (1.06-1.14)**
University Degree	187, 495 (16.9)	6, 805 (18.1)	**1.22 (1.19-1.26)**
Marital Status			
Legally Married/Common Law	152, 205	33, 770 (89.6)	Ref
Never Married	92, 435	1, 550 (4.1)	**0.75 (0.71-0.79)**
Separated/Divorced/Widowed	63, 770	2, 380 (6.3)	**0.92 (0.88-0.96)**
Broad Occupational Groups			
(A) Management	158, 105	6, 620	**1.07 (1.04-1.10)**
(B) Business, Finance and Administrative	98, 265	3, 340	**1.04 (1.00-1.08)**
(C) Natural, Applied Sciences and Related	85, 390	2, 470	0.99 (0.95-1.03)
(D) Health	22, 575	805	0.99 (0.92-1.07)
(E) Social Science, Education, Government Service, Religion	64, 525	2, 715	1.00 (0.96-1.05)

(F) Art, Culture, Recreation, and Sport	19, 560	555	0.98 (0.90-1.07)
(G) Sales and Services	174, 795	5, 835	1.01 (0.98-1.04)
(H) Trades, Transport, Equipment Operators, and Related	300, 690	9, 020	0.92 (0.90-0.95)
(I) Occupations Unique to Primary Industry	78, 010	3, 445	**1.08 (1.04-1.12)**
(J) Occupations Unique to Processing, Manufacturing and Utilities	106, 495	2, 895	0.95 (0.91-0.98)
Person years of follow-up	19, 635, 045	463, 760	
Mean person years of follow-up	17.7	12.0	

PC – prostate cancer
[a]*adjusted for age, province, ethnicity, education, and marital status*
**case counts are rounded to base 5 using random rounding*

Significant elevated risks were observed across most administrative and management occupations for both men aged 25-74 years. Significant elevated risks were observed for senior managers (HR 1.12, 95% CI 1.04-1.20), office managers (1.19, 95% CI 1.11-1.27), finance service occupations (1.09, 95% CI 1.04-1.14), and education service occupations (1.05, 95% CI 1.00-1.11). Elevated risks were also observed for office (non-managerial) and legal service occupations, although these results were not significant. Industry findings were similar to occupation findings, with elevated risks across administrative jobs. No statistically significant associations were observed for prostate cancer mortality.

Significant elevated risks were observed in occupations of agriculture/farm managers and supervisors (HR 1.12, 95% CI 1.06-1.17), farm workers and labourers (HR 1.11, 95% CI 1.01-1.21) and primary production/transportation/manufacturing managers (HR 1.11, 95% CI 1.03-1.20). Non-significant elevated risks were observed for forestry, fishing and trapping and wood working occupations. Industry findings also showed a significant elevated risk for agriculture industries (1.11, 95% CI 1.06-1.16), with non-significantly elevated risks across other natural resource based work. With mortality, a statistically significant association was observed for agricultural managers (HR 1.42, 95% CI 1.21-1.68).

Significant elevated risks were observed across protective services occupations for firefighters (HR 1.17, 95% CI 1.01-1.36), and police officers (HR 1.22, 95% CI 1.09-1.36) and a non-significant elevated risk was observed for armed forces (HR 1.10, 95% CI 0.95-1.26) and other protective services (0.97, 95% CI 0.90-1.04). Protective services are categorized under government services at an industry level and cannot be grouped separately, however, the government industry groups were observed to be elevated. No statistically significant associations were observed for prostate cancer mortality.

A significant elevated risk was observed for construction managers (HR 1.07, 95% CI 1.01-1.14), with significant decreased risks for construction trades (HR 0.89, 95% CI 0.83-0.96), transportation equipment operators (HR 0.91, 95% 0.85-0.97), motor vehicle repairers (HR 0.87, 95% CI 0.80-0.95) and vehicle drivers (HR 0.92, 95% CI 0.87-0.97). Non-significantly elevated risks were observed for electrical assemblers, electricians and electrical trade, and transportation technologists and technicians. Industry results were similar to occupation results for construction and transportation workers, showing mixed findings overall. No statistically significant associations were observed for prostate cancer mortality. By industry, there were additional statistically significant findings for utility services and telecommunications industries (Supplementary Table 10).

Figure 7 presents the prostate cancer rates for specific occupation groups and for the overall CanCHEC working cohort. Government, management, education, and law occupations had higher prostate cancer rates than the overall working cohort, whereas construction and transportation occupations had lower prostate cancer rates than the overall working cohort. The rates for protective services occupations were similar to the overall working cohort rate.

Table 9. Hazard Ratios (HR) and Confidence Intervals (CI) by Occupation Group in the CanCHEC (Ages 25-74 years)

Occupation Groups	Number of PC cases (n=37, 695)	Number of non-cases (n=1,070,715)	HR[a] (95% CI)
Administrative and Related			
Senior and Government Managers	755	13505	**1.12(1.04-1.20)**
Office Managers	820	17285	1.00(0.96-1.05)
Other Office and Administration	2120	63705	**1.19(1.11-1.27)**
Finance Managers and Financial Services	1860	45935	**1.09(1.04-1.14)**
Legal Services and Related	300	6995	1.00(0.89-1.12)
Education Instructors and Related	2030	43795	**1.05(1.00-1.11)**
Natural Resources			
Agriculture/Farm Managers and Supervisors	1945	29445	**1.12(1.06-1.17)**
Agricultural Specialists and Technicians	120*	3435	1.04(0.87-1.24)
General Farm Workers and Labourers	475	11120	**1.11(1.01-1.21)**
Logging Operators and Labourers	50*	2100	0.92(0.70-1.20)
Forestry Technicians and Professionals	320*	11000	1.04(0.93-1.16)
Fishing Labourers, Trapping and Hunting	260	6995	1.00(0.88-1.13)
Mining Production and Labourers	195*	6975	0.89(0.77-1.02)
Primary Production, Transportation, Manufacturing Managers	645	13955	**1.11(1.03-1.20)**
Wood Working, Carpentry, and Processing, Sawmill	995	32480	0.95(0.89-1.01)
Pulp and Paper Mill Machine Operators	190*	8215	0.90(0.78-1.04)
Metal Processing, Machinery and Construction			
Metal and Mineral Processing	750	23515	0.96(0.89-1.03)
Machinists and Tool Operators	405	12065	1.01(0.92-1.11)
Machine Assemblers and Manufacturers	340	10410	1.05(0.94-1.17)
Rubber and Plastic Products	100*	4750	0.88(0.72-1.06)
Plumbers, Pipefitters, and Gas fitters	340*	10095	0.98(0.88-1.09)
Painters	185	6060	0.95(0.82-1.10)
Construction Managers and Supervisors	1125	24015	**1.07(1.01-1.14)**
Construction Trades	720	26830	0.89(0.83-0.96)
Transportation and Related			
Transportation Equipment Operators	925	27180	0.91(0.85-0.97)
Transportation Technicians and Maintenance Workers	285	8900	1.01(0.89-1.13)
Motor Vehicle Repairers	545	23135	0.87(0.80-0.95)
Vehicle Drivers	1605	51270	0.92(0.87-0.97)
Protective Services			
Firefighters	165*	4365	**1.17(1.01-1.36)**
Armed Forces	200	8965	1.10(0.95-1.26)
Police Officers	325	9730	**1.22(1.09-1.36)**
Other Protection Services	565*	12435	0.97(0.90-1.04)
Health and Personal Care			
Dentists and Related	120	2585	1.08(0.91-1.30)
General and Specialist Physicians	305*	6295	0.92(0.82-1.03)
Registered Nurses, Supervisors and Aides	120	5130	0.98(0.82-1.17)
Other Health Professionals and Related	595	16275	1.02(0.94-1.11)

PC – prostate cancer

[a]Hazard ratios (HR) adjusted for age, province, ethnicity, education, and marital status; Reference group: men employed in all other occupations except the occupation of interest

**Missing +/- 5 to 10 cases because of low case counts in younger age categories; All case counts are rounded to base 5 using random rounding and counts <5 are not shown as per Statistics Canada reporting guidelines*

Table 10. Hazard Ratios (HR) and Confidence Intervals (CI) by Industry Group in the CanCHEC (Ages 25-74 years)

Industry Groups	Number of PC cases (n=37, 695)	Number of non-cases (n=1,070,715)	HR[a] (95% CI)
Government and Administrative			
Federal Government Services	1435	37870	1.11(1.05-1.17)
Provincial and Territorial Government Services	1020	26005	1.04(0.97-1.10)
Local and Other Government Services	1250	37520	0.96(0.91-1.02)
Business Services	2300	60370	1.02(0.98-1.06)
Finance Services	1055	27110	1.13(1.06-1.20)
Educational Services	2645	58590	1.02(0.98-1.06)
Natural Resources			
Agriculture Industries	2545	44430	1.11(1.06-1.16)
Services Incidental to Agriculture	70*	1890	1.05(0.83-1.32)
Forestry Services	95*	3640	0.99(0.82-1.21)
Logging Services	310*	10285	0.94(0.84-1.05)
Fishing and Trapping	250	6730	1.02(0.90-1.15)
Wood Products	465	16315	0.96(0.87-1.05)
Paper and Allied Products	580	16625	1.04(0.96-1.13)
Mining (Metal, Non-Metal, Coal Mines)	465	15945	0.88(0.80-0.96)
Metal and Non-Metal Products			
Primary Metal Products	590	16430	0.98(0.90-1.06)
Fabricated Metal Products	625	18515	1.03(0.95-1.11)
Non-Metal Mineral Products	275*	7360	1.04(0.93-1.18)
Plastic Products	200*	6285	1.12(0.98-1.29)
Rubber Products	75*	2870	0.88(0.70-1.10)
Chemical Products	285	8885	0.98(0.88-1.11)
Transportation and Trades			
Transportation Equipment and Repair	1130	33845	0.98(0.93-1.04)
Service Industries Incidental to Transportation	325	58315	1.01(0.97-1.06)
Other Transportation	2070	10080	0.86(0.77-0.96)
Automotive Vehicles, Parts and Accessories	1080	38305	0.96(0.90-1.02)
Construction			
General Contracting and Development	1000	31690	0.96(0.91-1.03)
Trade Contracting and Site Work	1645	55315	0.93(0.88-0.98)
Heavy Industrial Construction	420	12655	0.93(0.85-1.02)
Service Industries Incidental to Construction	340	9320	1.03(0.93-1.15)
Technical and Informational Industries			
Telecommunications	930	27770	1.11(1.04-1.18)
Other Utility Industries (Electric, Gas, Water)	695	18955	1.10(1.02-1.19)
Printing, Publishing, and Allied Industries	430	13775	0.96(0.87-1.05)
Health Service Industries			
Health and Social Services	1260	36690	0.96(0.91-1.01)

PC – prostate cancer

[a]Hazard ratios (HR) adjusted for age, province, ethnicity, education, and marital status; Reference group: men employed in all other industries except the industry of interest

**Missing +/- 5 to 10 cases because of low case counts in younger age categories; All case counts are rounded to base 5 using random rounding and counts <5 are not shown as per Statistics Canada reporting guidelines*

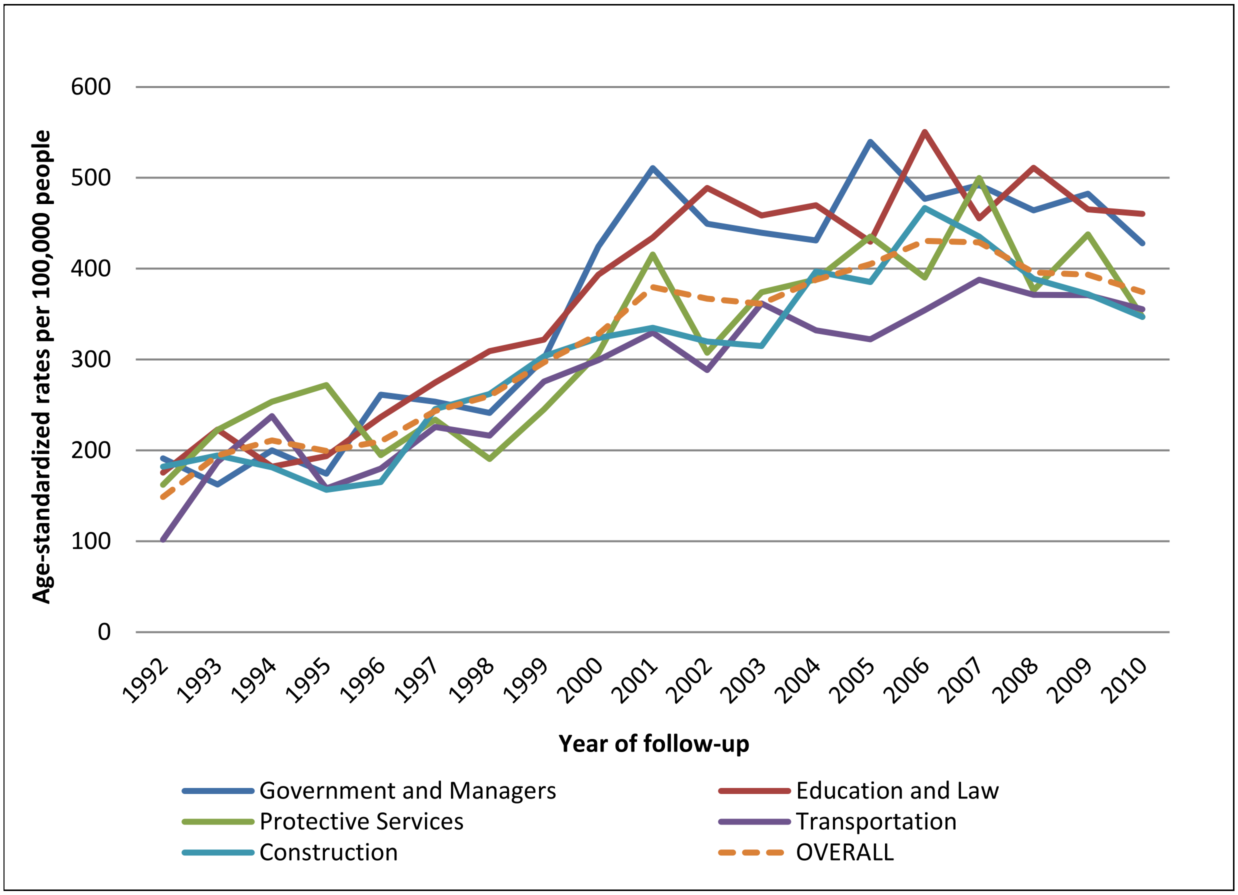

Figure 7. Age standardized prostate cancer rates by year for specific occupation groups and for the overall working cohort. The solid lines represent major occupation groups of government and managers, education and law, protective services, transportation, and construction. The dash line represents the overall working cohort. All prostate cancer rates were standardized to the 2001 CanCHEC population to account for differences in age structure each year and to allow for comparability of rates each year.

6.5 Discussion

In this large cohort study, significant associations with prostate cancer risk were observed for ethnicity, education, and marital status. Based on primarily United States studies, risk of prostate cancer is known to be highest among Black/African American men than any other race, followed by Caucasian men (IARC, 2012; CDC, 2016). Men of other ethnic groups are recognized as having reduced risks of prostate cancer (IARC, 2012; CDC, 2016). Differences by ethnicity may be influenced by dietary differences, genetic predisposition, socioeconomic factors, access to quality care, and disparities in screening and diagnosis (Fradet et al, 2009; Wu, 2012). The elevated risks observed in men with higher education can be interpreted with socioeconomic status. Men with higher socioeconomic status (SES) may have better access to health care and screening resources leading to early diagnosis, whereas men with lower SES may face more barriers to accessing screening and medical facilities (Zeegers et al, 2004; Rundle et al, 2013). In Canada, it is unclear to what extent health care accessibility is affected by differences in SES, as universal health care coverage has been shown to reduce inequalities in different SES groups (Veugelers et al, 2003). Also, married men are more likely to utilize shared decision making with their partner, and may be influenced by their partner to seek better health behaviours than men who are not married (Li et al, 2017; Merrill, 2001). It has also been shown that if married men have a family history of prostate cancer, they are more likely to get screened (Wallner et al, 2008). We were unable to assess family history of prostate cancer in our study. Factors related to family physician visits and medical history can also affect frequency of screening, however we did not have this information available. All of these factors are related to screening behaviours and to account for potential screening bias, we adjusted hazard ratios for these factors. Age was also included in the adjustments as it is well established that the risk of prostate cancer increases with increased age and screening is more likely in older men (Bashir, 2016; Beaulac et al, 2006). Some of the results attenuated, but overall there was a less than 10% change in hazard ratios. With screening bias, it is asserted that increased screening leads to increased incidence and reduced mortality over time. In this study we observed no associations between employment in white collar work and prostate cancer mortality, which supports screening bias.

Our study found consistent elevated risks for jobs in administration and related occupations and industries. These types of jobs included workers in government, senior management, office, business, finance, law, and education. Some studies have previously shown similar elevated risks in men employed in white collar jobs (Buxton et al, 1999; Bairati et al, 2000; Norman et al, 2002; Zeegers et al, 2004; Sauve et al, 2016). As white collar jobs are recognized as having few chemical exposures, findings may reflect other factors of physical activity, socioeconomic factors, and screening. Men employed in these occupations are likely to have sedentary work environments with lower levels of occupational physical activity (Norman et al, 2002). Although physical activity could not be assessed in our study, lower levels of physical activity may be linked to androgen metabolism and reduced immune responses failing to prevent tumor formation (Norman et al, 2002). Many of these white collar jobs are typically associated with higher education and income which is often associated with informed decision making and better accessibility to health resources, including prostate cancer screening (Zeegers et al, 2004). When looking at education and income levels and men with prostate cancer in white collar jobs, we observed a non-significantly elevated risk for senior management workers who had a university degree (highest education category). However this was not statistically significant and we did not see any other associations related to education or income across white collar or administrative jobs. Based on our findings, further evidence is needed on physical activity and screening related factors and patterns in white collar and administrative workers to better understand how these factors are involved in prostate cancer risk.

Men employed in agriculture were at increased risk of prostate cancer diagnosis and mortality, which is consistent with previous literature (Cerhan et al, 1998; Ragin et al, 2013; LeMasters et al, 2006). Exposure to pesticides and diesel engine exhaust from farm equipment are suspected contributing risk factors. Exposure to pesticides may affect hormone levels and function by disrupting endocrine activity and increasing estrogen levels leading to tumor promotion (Buxton et al, 1999; Christensen et al, 2010; Jones et al, 2015). The Agriculture Health Study (AHS) has consistently reported elevated risks for prostate cancer among pesticide applicator occupations with mixed findings for specific pesticides linked to prostate cancer (Alavanja et al, 2005; Mahajan et al, 2006; Koutros et al, 2008; Barry et al, 2012; Jones et al, 2015; Christensen et al, 2010). Family history of prostate cancer is also recognized as a potential modifier for specific pesticide exposures like fonofos and aldrin and prostate cancer risk, but not for other pesticide exposures (Alavanja et al, 2005; Mahajan et al, 2006; Koutros et al, 2008; Barry et al, 2012; Jones et al, 2015; Christensen et al, 2010). We observed a reduced risk in the mining industry across both age groups, which is consistent with previous findings (Girschik et al, 2010). Few studies in the past have examined prostate cancer risk in natural resource based jobs, aside from agriculture, and these studies observed mixed findings (Sauve et al, 2016; Sritharan et al, 2016; Sass-Kortsak et al, 2007). Given the limited evidence, further investigation into these natural resource based occupations is needed to understand what chemical exposures or lifestyle factors are involved.

Significantly elevated risks were observed for firefighters and police officers, with non-significantly elevated risk in armed forces and other protective services. Protective services occupations involve exposure to diesel exhaust, dust and particulate matter, chemical agents, radiation and other mixed agents. They may also experience disruption of the circadian rhythm from shift work and they can be under constant psychological stress which may impact biological processes leading to the development of cancer (Sharma-Wagner et al, 2000; Wirth et al, 2013; Pukkala et al, 2014). Specifically, police officers may spend extensive periods driving or near vehicles which can lead to increased exposure to vehicle exhaust (Wirth et al, 2013). A recent Montreal case-control study reported a similar elevated risk in police officers (Sauve et al, 2016). Firefighters, in a highly hazardous job, are exposed to fires that release carcinogenic substances and toxins (Pukkala et al, 2014). Potential exposures in firefighting include mixtures of particulate, gases and fumes, diesel exhaust, and polychlorinated biphenyls (LeMasters et al, 2006; Bates et al, 2007; Tsai et al, 2015). Based on existing evidence, IARC classified firefighting as possibly carcinogenic to humans (Group 2B) (IARC, 2010). Screening may also be an important factor in firefighting occupations. It is speculated that there may have been targeted screening in firefighters in the 1990s, however there is no documentation available on screening by occupation for this time period (Tsai et al, 2015). For men in the armed forces, we observed a non-significantly elevated risk, although other international studies have found significant elevated risks (Leavy et al, 2006; Zhu et al, 2009). Men in the armed forces are involved in high risk environments and are exposed to many different types of agents. They are also more likely to get screened compared to men in other jobs. Specifically, the Canadian national defense and armed forces require frequent health examinations which may lead to better access to health resources and screening (National Defense and the Canadian Armed Forces, 2016). Given our findings and other recent evidence on prostate cancer risk in protective services, it is necessary to understand and compare job-specific exposures in each individual job (firefighting, police, armed forces) while also determining the impact of screening or availability of health resources in these jobs.

Few elevated risks were observed in occupations of construction and transportation. Previous studies have reported elevated risks associated with employment in construction and transportation, with some evidence linked to whole body vibrations, diesel exhaust, and polycyclic aromatic hydrocarbons (PAH) (Aronson et al, 1996; Sass-Kortsak et al, 2007; Nadalin et al, 2012; Jones et al, 2014). However, some studies have also reported mixed results across construction and transportation workers similar to our findings (Keller et al, 1993; Krstev et al, 1998; Sritharan et al, 2017). Our findings could be related to differences in prostate cancer screening in these jobs. A recent presentation identified that men in construction and transportation jobs were less likely to get screened than men in management jobs (Peters et al, 2016).

Based on our findings in occupation groups, we were interested in understanding if prostate cancer rates in the discussed occupations groups were similar to that of prostate cancer rates in Canadian men over the time period of the cohort. Across most provinces in Canada, prostate cancer incidence began to accelerate in 1990 and marked peaks of incidence were observed in both 1993 and 2001, followed by a steady decline (Dickinson et al, 2016). This pattern is aligned with the introduction of PSA testing in the 1990s and a surge of PSA testing and over-diagnosis in 2001 in Canada (Dickinson et al, 2016). We investigated if observed prostate cancer rates across specific occupations in our study showed similar patterns to the trend recognized across Canada. Occupations of government/management and education/law showed peaks that were during similar time periods as recognized across Canada (Figure 1). Observed prostate cancer rates in these occupations were also higher than the overall 1991 working cohort. These findings may be attributed to increased screening behaviours leading to increased diagnosis of prostate cancer among these workers. Protective services occupations show few peaks during the time of increased PSA testing and during other time periods (Figure 1). It is difficult to determine if the rates observed in protective services are due to screening or other factors. Observed prostate cancer rates in construction and transportation occupations were lower than the overall working cohort and there were no identified prominent peaks during the time of increased screening (Figure 1). Construction and transportation workers may have decreased screening activity leading to fewer prostate cancer cases identified, however further evidence is needed. Future studies should compare risk of prostate cancer in blue collar work and white collar work, while evaluating actual screening rates in these jobs.

Increased prostate cancer screening has also shown to reduce mortality from prostate cancer (Dickinson et al, 2016). Occupations related to white collar work, protective services, and construction and transportation showed no association to prostate cancer mortality in this study. Whereas, agriculture work was found to have an elevated risk of mortality. This may be indicative of screening differences by type of occupation, specifically showing that there may be increased prostate cancer screening in white collar and protective services jobs, and a lack of screening in agricultural workers. However, interpretation of findings is limited and further investigation into mortality from prostate cancer and occupation is needed.

Our study has some limitations and strengths. It only contains employment information at one point in time in 1991 and does not have data on employment duration. It also lacks information on family history of prostate cancer and physical activity, which may act as confounders or effect modifiers. There was no information on screening behaviours, although we accounted for factors related to screening. This study also had no information on aggressiveness of prostate cancer cases, but our analysis was able to capture cases in younger men which are usually rare and likely to be aggressive forms. Also, this study makes multiple comparisons which can lead to some chance findings. There are also distinct strengths in this study. It is one of the largest Canadian cohorts with information on occupation and prostate cancer, and other non-occupational factors. The large sample size provided the ability to detect a large number of prostate cancer cases with increased power and less likelihood of type I error. The large sample also captured cases under the age of 50 years which is generally difficult to obtain.

In this study, we observed elevated risks of incidence in jobs related to administration and management, agriculture, protective services and decreased risks in construction and transportation in men aged 25-74 years. Also, an elevated risk of mortality was observed in agriculture management workers. Findings show that there may be different factors involved such as job-specific exposures, lifestyle factors, and screening behaviours. Future studies should focus on the identified occupation groups in this study to pinpoint job-specific exposures while reporting on the screening behaviours of these workers. Further investigation is also needed on occupation and aggressive forms of prostate cancer, especially in younger age groups. This will provide better direction on the relationship between occupation, related exposures, and screening patterns.

Chapter 7. Prostate cancer in firefighting and police work: a systematic review and meta-analysis of epidemiologic studies

This chapter has been published:

Sritharan J, Pahwa M, Demers PA, Harris S, Cole DC & Parent ME. (2017b). Prostate cancer in firefighting and police work: a systematic review and meta-analysis of epidemiologic studies. Environmental Health 16: 124.

7.1 Abstract

Background*:* We conducted a systematic review and meta-analysis to evaluate potential associations between firefighting and police occupations, and prostate cancer incidence and mortality.

Methods: Original epidemiological studies published from 1980 to 2017 were identified through PubMed and Web of Science. Studies were included if they contained specific job titles for ever/never firefighting and police work and associated prostate cancer risk estimates with 95% confidence intervals (CI). Study quality was assessed using a 20-point checklist. Prostate cancer meta-risk estimates (mRE) and corresponding 95% CIs were calculated for firefighting and police work separately and by various study characteristics using random effects models. Between-study heterogeneity was evaluated using the I^2 score. Publication bias was assessed using Begg's and Egger's tests.

Results: A total of 26 firefighter and 12 police studies were included in the meta-analysis, with quality assessment scores ranging from 7-19 points. For firefighter studies, the prostate cancer incidence mRE was 1.17 (95% CI=1.08-1.28, I^2=72%) and the mortality mRE was 1.12 (95% CI=0.92-1.36, I^2=50%). The mRE for police incidence studies was 1.14 (95% CI=1.02-1.28; I^2=33%); for mortality studies, the mRE was 1.08 (95% CI=0.80-1.45; I^2=0%). By study design, mREs for both firefighter and police studies were similar to estimates of incidence and mortality.

Conclusion: Small excess risks of prostate cancer among firefighters and police workers were found from firefighter studies with moderate to substantial heterogeneity and a relatively small number of police studies, respectively. There is a need for further studies to examine police workers and to assess specific exposures in firefighting.

7.2 Introduction

Prostate cancer is one of the most commonly diagnosed cancers in men worldwide but its etiology remains poorly understood (IARC, 2016; Canadian Cancer Society, 2015; Dy et al, 2017; Plato & Concepcion, 2014; Bashir, 2015). The only established risk factors for prostate cancer are older age, positive family history of prostate cancer, and African-American ethnicity (IARC, 2016; Canadian Cancer Society, 2015; Plato & Concepcion, 2014; Bashir, 2015). There is some evidence linking prostate cancer to differences in socioeconomic status, increased height, increased obesity, reduced physical activity, and active smoking and alcohol use (Dy et al, 2017; Bashir, 2015; Singh & Jemal, 2017; Zuccolo et al, 2008; Zhao et al, 2016; Parikesit et al, 2016; Freedland & Aronson, 2004). There is growing evidence that occupation may be a risk factor, and previous studies have shown increased risks associated with employment in agriculture/farming, management and administration, rubber production, metal work, and transportation (Zeegers et al, 2004; Sauve et al, 2016; Sritharan et al, 2017a; Parent & Siemiatycki, 2001). Some studies have also suggested associations between prostate cancer risk and employment in protective services occupations (Zeegers et al, 2004; Sauve et al, 2016; LeMasters et al, 2006; Wirth et al, 2013; IARC, 2010; Pukkala et al, 2014).

Protective services occupations include firefighting, police, military, and other groups (ex. security guards). Previous epidemiological studies have demonstrated consistent associations between firefighting and different types of cancer, with some evidence for prostate cancer (LeMasters et al, 2006). In 2007, the International Agency for Research on Cancer (IARC) classified firefighting as “possibly” carcinogenic to humans (IARC Group 2B) (IARC, 2010). IARC’s evaluation was based on evidence from 42 epidemiological studies, including two previous meta-analyses on firefighting and cancer (LeMasters et al, 2006; Howe & Burch, 1990).Based on studies published at the time, IARC evaluated multiple cancer sites and identified statistically significant increased risks of prostate cancer, testicular cancer, and non-Hodgkin lymphoma (IARC, 2010). Since the IARC evaluation, 11 new studies have been published that included assessments of prostate cancer risk in firefighters. Relatively less is known about prostate cancer risk in police occupations, as this group is often understudied and findings have been inconsistent (Zeegers et al, 2004; Sauve et al, 2016; Sritharan et al, 2018; Wirth et al, 2013; Vena et al, 2014; Finkelstein, 1998).

Only one meta-analysis, published over a decade ago, focused on firefighting and cancer risks that included prostate cancer (LeMasters et al, 2006). This study found a significant association with prostate cancer incidence (summary risk estimate: 1.28, 95% CI: 1.15-1.43) based on evidence from 26 cohort and 6 case-control studies (LeMasters et al, 2006). Recently, a narrative review examined cancer risk in police work. Eight studies reported on prostate cancer risk in police work, with mixed findings (Wirth et al, 2015). The objective of the present systematic review and meta-analysis was to evaluate the quality of the epidemiological evidence on firefighting and police employment in association with prostate cancer incidence and mortality, and to conduct a quantitative synthesis. Based on the availability of epidemiologic literature, this meta-analysis focused on firefighting and police work, and not protective services as a whole.

7.3 Methods

7.3.1 Search Strategy

A search was conducted on PubMed and Web of Science to identify epidemiological studies published between January 1980 and December 2017 in English or French about employment in firefighting and police occupations, and risk of prostate cancer. Various combinations of MeSH terms were used to search for studies that included firefighter and police occupations (firefighting OR firefighter OR fire fighter OR fire OR police OR police officer OR policeman OR policemen) and that reported on associations with prostate cancer risk (prostate OR prostate neoplasm OR neoplasm OR cancer). Cited references in individual papers and review papers that resulted from the search were used to identify any additional studies.

7.3.2 Inclusion Criteria

To be included in the meta-analysis, articles must have reported results for original case-control or cohort studies that contained specific job titles related to ever/never firefighting and police work and that examined associated prostate cancer incidence and/or mortality using any type of relative risk estimator (hazard ratio (HR), odds ratio (OR), relative risk (RR), standardized mortality ratio (SMR), or standardized incidence ratio (SIR)) with corresponding 95% confidence intervals. Reviews, meta-analyses, editorials, experimental, and ecological studies were excluded. For any articles with overlapping study populations, only the most recently published study with prostate cancer incidence and/or mortality results was included. Furthermore, studies were excluded if reported risk estimates were only based on internal comparisons between different occupational groups rather than based on comparisons to the general population. Titles and abstracts were initially screened for eligibility, and for those eligible, full-text articles were reviewed.

7.3.3 Data Extraction

Information on author(s), date of publication, title, country of study, study design, number of cases/deaths and controls/non-cases, data collection method, effect sizes and 95% CIs for prostate cancer, and covariates was extracted from and tabulated for each study included in the meta-analysis. Effect sizes and 95% CIs recorded from included studies were for ever vs. never firefighter or police employment in models that were adjusted for the maximum number of potentially confounding variables.

7.3.4 Quality Assessment

The quality of each study included in the meta-analysis was independently assessed by two authors (JS and MP) using a modified quality assessment checklist by Downs and Black (Downs & Black, 1998). Checklist items that were irrelevant to observational studies were omitted, resulting in a maximum of 20 achievable points for reporting (9 points), external validity (2 points), internal validity (bias and confounding) (8 points), and power (1 point) (Downs & Black, 1998). Any disagreement of ratings was discussed and a consensus was arrived at mutually or by consulting a third author, if earlier consensus could not be reached.

7.3.5 Statistical Analysis

Reported ORs, HRs, RRs, SIRs, and SMRs were considered as RRs in meta-analyses and used in forest plots. A random effects model was used to calculate meta-risk estimates (mREs) in all meta-analyses due to potential variance in effect sizes between the included studies. mREs were calculated separately for firefighting and police occupations and prostate cancer risk. mREs were calculated for subgroups based on the following characteristics: incidence versus mortality, study design (i.e. cohort versus case-control, and administrative linkage-based studies, defined as large studies that used multiple linked administrative databases, e.g. census data and cancer statistics.

For each mRE, heterogeneity was evaluated using the I^2 statistic. The I^2 statistic is a percentage that describes the variation between studies that is not due to chance (Higgins & Thompson, 2002). Two-sided p-values for the I^2 statistic were reported. Ninety-five percent confidence intervals for the I^2 statistic were calculated to address small numbers of included studies ($N<5$) in some subgroup meta-analyses. In addition, the Galbraith plot was used to visualize if individual studies fell within or outside of the 95% confidence region. Studies outside of the 95% confidence region can contribute to high heterogeneity. These studies were removed in sensitivity analyses to evaluate the impact of decreased heterogeneity on mREs (Bax et al, 2009).

Begg's test and Egger's test were used to assess publication bias. Begg's test uses the correlation between ranks of effect sizes and variances, whereas Egger's test uses a funnel plot to plot the effect estimates against sample size (Begg & Mazumdar, 1994; Egger et al, 1997). All statistical analyses were performed using STATA version 14.2 (StataCorp LLC, College Station, USA).

7.4 Results

The literature search resulted in 366 unique studies published in English or French. Based on the screening of titles and abstracts, 318 (87%) were excluded due to non-observational/non-human studies, missing job titles, missing effect estimates for prostate cancer, duplicate studies, or irrelevancy to the objective of this meta-analysis. Of the remaining 48 studies that were obtained in full text, 17 were excluded because they did not include reports of relative risks for prostate cancer with 95% CIs, had overlapping study populations, or were studies of military workers. As a result, 31 unique studies were included (Figure 8).

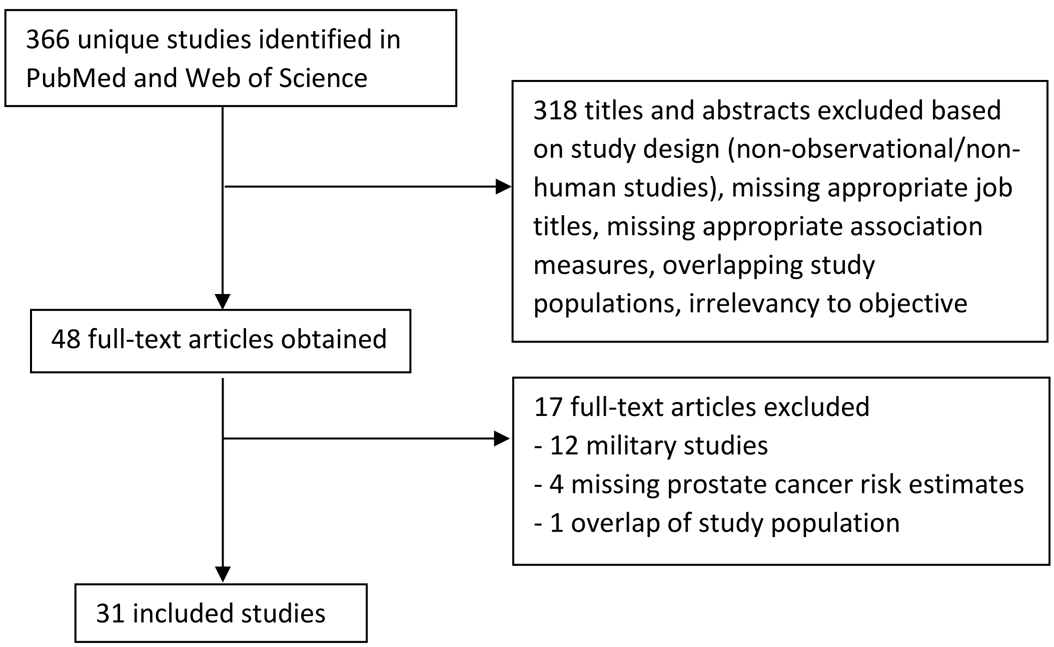

Figure 8. Flow chart of study selection in this meta-analysis.
This flow diagram illustrates how firefighting and police studies were selected for the meta-analysis, with the reasons for excluded studies, and final total number of included studies.

Of these, 24 were cohort and seven were case-control studies. Nineteen studies only included investigations of firefighters (Table 11) and five focused on police workers (Table 12); seven contained investigations of both firefighters and police workers (Table 13). In all studies that included firefighters (N=26), there were 5712 incident cases of prostate cancer and 428 deaths from prostate cancer. In all studies that included police workers (N=12), there were 1510 incident cases and 49 deaths. The characteristics of each included study are summarized in Tables 11 (firefighters), 12 (police workers), and 13 (both). Covariates included in the risk estimates selected from each of the seven case-control studies are shown in Table 14.

Of all the firefighter studies, 2 pairs of studies (Ma et al., 2005 & Ma et al., 2006; Demers et al., 1992 & Demers et al., 1994) examined the same respective populations but reported on different prostate cancer outcomes (incidence and mortality). In the meta-analyses of prostate cancer incidence and mortality in firefighters, respective results from both pairs of studies were retained and used. Two studies (Daniels et al., 2014 and Tornling et al., 1994) published results for both prostate cancer incidence and mortality, and each estimate was used. For the police studies, Demers et al., 1992 & Demers et al., 1994 reported on the same populations with different outcomes of incidence and mortality, and each estimate was used. Each incidence and mortality outcome was used only in their respective categories and not included together for any meta-risk estimates.

Table 11. Characteristics of included studies on firefighting and prostate cancer risk (N=19)

Author/Year	Location of Study	Study Design	Incidence or Mortality	Follow-up period	Number of Cases/Deaths	Cohort Size/Number of Controls[a]	Prostate Cancer Risk Estimates for Ever versus Never Employment[b]
Glass et al, 2016[33]	Australia	Cohort	Incidence	1980-2011	478	30, 057	SIR 1.31, 95% CI 1.19-1.43
Brice et al, 2015[34]	France	Cohort	Mortality	1979-2008	17	10, 829	SMR 0.54, 95% CI 0.31-0.86
Daniels et al, 2014[31]	USA	Cohort	Incidence Mortality	1950-2009	1261 cases 282 deaths	29, 993 29, 993	SIR 1.03, 95% CI 0.98-1.09; SMR 1.09, 95% CI 0.96-1.22
Pukkala et al, 2014[18]	Denmark, Finland, Iceland, Norway and Sweden	Cohort (linkage)	Incidence	1961-2005	660	16, 422	SIR 1.13, 95% CI 1.03-1.22
Ahn et al, 2012[35]	Korea	Cohort	Incidence	1996-2007	9	33, 416	SIR 1.32, 95% CI 0.60-2.51
Ma et al, 2006[28]	USA	Cohort	Incidence	1981-1999	209	34, 796	SIR 1.10, 95% CI 0.95-1.42
Ma et al, 2005[27]	USA	Cohort	Mortality	1972-1999	21	34, 796	SMR 1.08, 95% CI 0.67-1.65
Baris et al, 2001[36]	USA, USA	Cohort	Mortality	1925-1986	31	7, 789	SMR 0.96, 95% CI 0.68-1.37
Bates et al, 2001[37]	New Zealand	Cohort	Incidence	1977-1995	11	4, 221	SIR 1.08, 95% CI 0.50-1.90
Tornling et al, 1994[32]	Sweden	Cohort	Incidence Mortality	1951-1986	28 cases 14 deaths	1, 116 1, 091	SMR 114, 95% CI 76-165 SMR 121, 95% CI 66-202
Aronson et al, 1994[38]	Canada	Cohort	Mortality	1950-1989	16	5, 373	SMR 132, 95% CI 76-215
Giles et al, 1993[39]	Australia	Cohort	Incidence	1980-1989	5	2, 865	SIR 2.09, 95% CI 0.67-4.88
Guidotti, 1993[40]	Canada	Cohort	Mortality	1927-1987	8	3, 328	SMR 146.1, 95% CI 63.1-287.9
Beaumont et al, 1991[41]	USA	Cohort	Incidence	1940-1982	8	3, 066	RR 0.38, 95% CI 0.16-0.75
Grimes et al, 1991[42]	USA	Cohort	Mortality	1969-1988	4	205	PRR 2.6, 95% CI 1.4-5.0
Vena & Friedler, 1987[43]	USA	Cohort	Mortality	1950-1979	5	470	SMR 0.71, 95% CI 0.23-1.65
Tsai et al, 2015[44]	USA	Case-control (linkage)	Incidence	1988-2007	1397	3, 996	OR 1.45, 95% CI 1.25-1.69
Kang et al, 2008[45]	USA	Case-control (linkage)	Incidence	1986-2003	577	285, 964	SMOR 1.05, 95% CI 0.88-1.24
Krstev et al, 1998[46]	USA	Case-control	Incidence	1986-1989	12	981	OR 3.34, 95% CI 1.13-9.91

[a]cohort size represents the total sample size in only cohort studies, and the number of controls is only applicable to case-control studies

[b]HR – hazard ratio, SIR – standardized incidence ratio, SMR – standardized mortality/morbidity ratio, RR – relative risk, PRR – proportionate risk ratio, OR – odds ratio

- NR – not reported

Table 12. Characteristics of included studies on police work and prostate cancer risk (N=5)

Author/Year	Location of Study	Study Design	Incidence or Mortality	Follow-up Period	Number of Cases/Deaths	Cohort Size/Number of Controls[a]	Prostate Cancer Risk Estimates for Ever versus Never Employment[b]
Vena et al, 2014[20]	USA	Cohort	Mortality	1980-2005	31	3, 424	SMR 1.18, 95% CI 0.80-1.67
Gu et al, 2011[47]	USA	Cohort	Incidence	1976-2006	104	2, 234	SIR 0.88, 95% CI 0.72-1.07
Finkelstein, 1998[21]	Canada	Cohort	Incidence	1964-1995	85	22, 197	SIR 1.16, 95% CI 0.93-1.43
Forastiere et al, 1994[48]	Italy	Cohort	Mortality	1973-1991	7	3, 868	SMR 0.77, 95% CI 0.31-1.50
Bouchardy et al, 2002[49]	Switzerland	Case-control	Incidence	1980-1993	129	8, 997	OR 1.20, 95% CI 1.00-1.50

[a]cohort size represents the total sample size in only cohort studies, and the number of controls is only applicable to case-control studies
[b]HR – hazard ratio, SIR – standardized incidence ratio, SMR – standardized mortality/morbidity ratio, RR – relative risk, OR – odds ratio

Table 13. Characteristics of included studies on both firefighting and police work and prostate cancer risk (N=7)

Author/Year	Location of Study	Study Design	Incidence or Mortality	Follow-up Period	Number of Cases/Deaths	Cohort size or Number of Controls[a]	Prostate Cancer Risk Estimates for Ever versus Never Employment[b]
Sritharan et al, 2018[13]	Canada	Cohort (linkage)	Incidence	1991-2011	165 firefighters 325 police	1,100,000 1,100,000	HR 1.17, 95% CI 1.01-1.36 HR 1.22, 95% CI 1.09-1.36
Zeegers et al, 2004[11]	Netherlands	Cohort (linkage)	Incidence	1986-1993	709 firefighters 693 police	58, 279 58, 279	RR 0.59, 95% CI 0.05-6.33 RR 1.62, 95% CI 0.62-4.27
Demers et al, 1994[29]	USA	Cohort	Incidence	1974-1989	66 firefighters 28 police	2, 447 1, 878	SIR 1.40, 95% CI 1.10-1.70 IDR 1.10, 95% CI 0.70-1.80
Demers et al, 1992[30]	USA	Cohort	Mortality	1945-1989	30 firefighters 11 police	4, 546 3, 676	SMR 1.34, 95% CI 0.90-1.91 SMR 1.02, 95% CI 0.51-1.82
Sritharan et al, 2017a[50]	Canada	Case-control	Incidence	1995-1998	38 firefighters 35 police	22 26	OR 1.67, 95% CI 0.94-2.95 OR 1.15, 95% CI 0.66-1.99
Sritharan et al, 2016[51]	Canada	Case-control	Incidence	1994-1997	53 firefighters 12 police	155 30	OR 0.73, 95% CI 0.53-1.01 OR 0.82, 95% CI 0.41-1.63
Sauve et al, 2016[12]	Canada	Case-control	Incidence	2005-2009	26 firefighters 45 police	16 30	OR 1.72, 95% CI 0.88-3.37 OR 1.60, 95% CI 1.00-2.40

[a]cohort size represents the total sample size in only cohort studies, and the number of controls is only applicable to case-control studies
[b]HR – hazard ratio, SIR – standardized incidence ratio, SMR – standardized mortality/morbidity ratio, RR – relative risk, IDR – incidence density ratio, OR – odds ratio

Table 14. Covariates adjusted for in firefighter and police case-control studies

Author (Year)	*Age*	*Ethnicity*	*Family history of prostate cancer*	*Socioeconomic status proxy (income or education)*	*Physical activity*	*Obesity (BMI)*	*Height*	*Smoking*	*Alcohol Intake*
Sritharan et al (2017a)	Y	Y	Y	Y	Y	Y	N	Y	N
Sauve et al (2016)	Y	Y	Y	Y	Y	Y	N	N	Y
Sritharan et al (2016)	Y	Y	Y	N	N	N	N	N	N
Tsai et al (2015)	Y	Y	N	N	N	N	N	N	N
Kang et al (2008)	Y	N	N	N	N	N	N	Y	N
Bouchardy et al (2002)	Y	N	N	Y	N	N	N	N	N
Krstev et al (1998)	Y	Y	N	N	N	N	N	N	N

7.4.1 Quality Assessment

The overall quality assessment of all 31 included studies ranged from 5 to 19 points (Table 15). Scores were similar for firefighter, police, and firefighter and police studies across the different quality assessment categories. The mean score for reporting was 6 out of 9, based on clear and detailed reporting of aims/hypotheses, outcomes measures, participant information, confounder information, and loss to follow-up. Studies were generally found to be externally valid, and there was minimal bias. Studies of firefighters had higher scores for confounding factors than studies of police workers. Only one study reported a power calculation. Since all other studies did not report power estimations, it was unclear if these studies had sufficient power to detect statistically significant effects.

Table 15. Quality assessment of included firefighter and police studies

Quality Assessment Category	**Maximum Attainable Score**	**Studies on firefighters (n=19)**		**Studies on police workers (n=5)**		**Studies on both firefighters and police workers (n=7)**		**All studies (n=31)**
		Range	**Mean**	**Range**	**Mean**	**Range**	**Mean**	**Mean**
Reporting	9	4-9	6.0	1-8	5.4	4-8	6.1	5.9
External Validity	2	1-2	1.8	0-2	1.6	1-2	1.6	1.7
Internal Validity: Bias	4	3-4	3.8	3-4	3.8	4	4	3.8
Internal Validity: Confounding	4	2-4	3.2	1-4	2.8	3-4	3.6	3.2
Power	1	0	0	0	0	0-1	0.1	0.0
Total	20	10-19	14.8	5-18	13.6	12-18	15.4	14.6

7.4.2 Firefighter and Prostate Cancer Meta-Analyses

There were significantly elevated prostate cancer risks for firefighting occupations for incidence outcomes, cohort studies, and administrative linkage-based studies. For incidence studies, the mRE was 1.17 (95% CI: 1.08-1.28; I^2=72%, 95% CI: 55-82%, p-value <0.001; 19 studies) (Figure 9); for mortality studies, it was 1.12 (95% CI: 0.92-1.36; I^2=50%, 95% CI: 0-76%, p-value=0.04; 10 studies) (Figure 10). In cohort studies, the prostate cancer mRE was 1.14 (95% CI: 1.03-1.26; I^2=67%, 95% CI: 46-80%, p-value <0.001; 18 studies) (Figure 11). The meta-analysis of case-control studies resulted in an mRE of 1.27 (95% CI: 0.95-1.69; I^2=78%, 95% CI: 53-90%, p-value <0.001; 6 studies) (Figure 12). The mRE for census or administrative linkage-based studies was 1.19 (95% CI: 1.06-1.34; I^2=61%, 95% CI: 0-85%, p-value=0.04; 5 studies) (Figure 13).

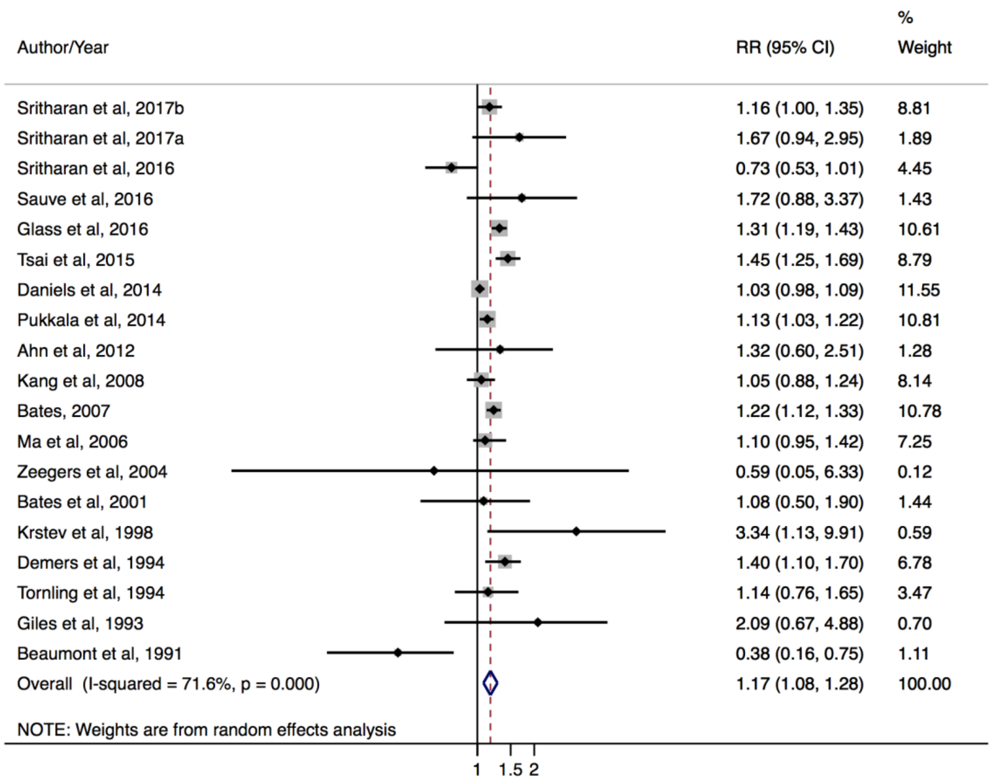

Figure 9. Forest plot and mRE of all prostate cancer incidence studies on firefighters.

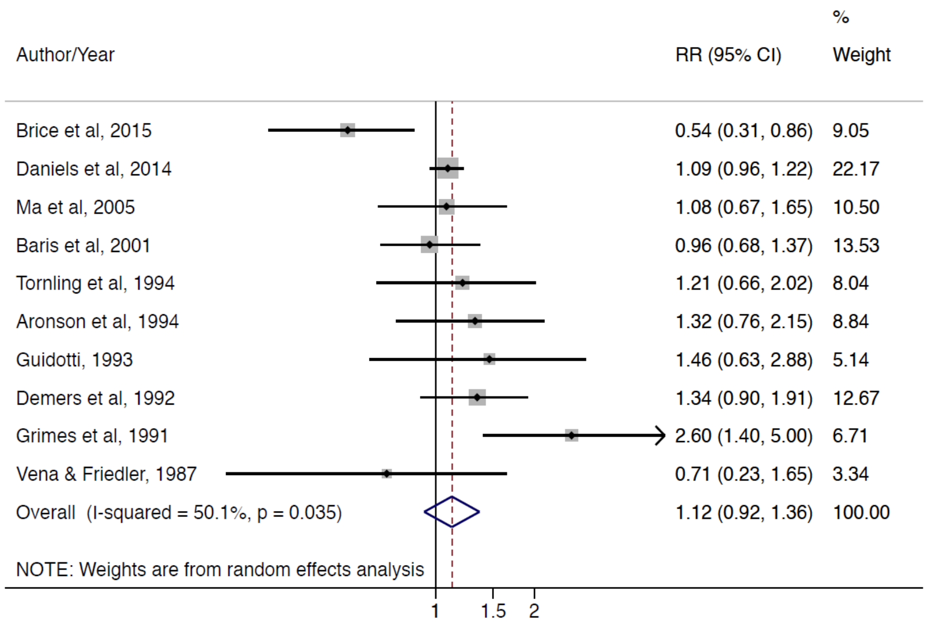

Figure 10. Forest plot and mRE of all prostate cancer mortality studies on firefighters.

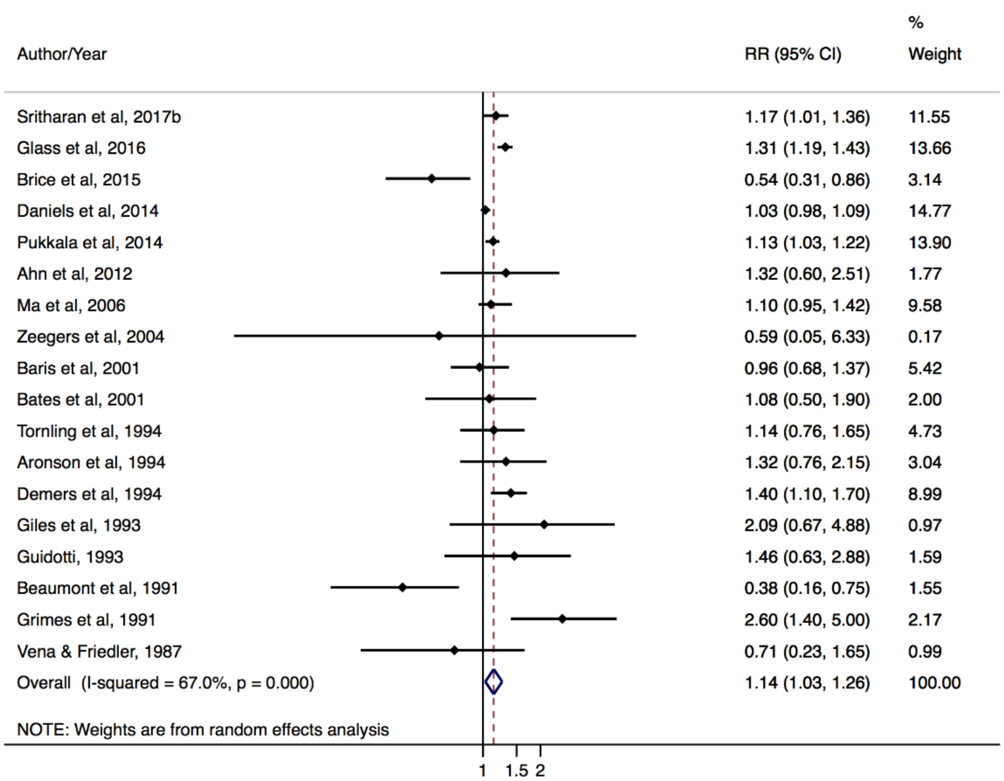

Figure 11. Forest plot and mRE of all cohort studies on firefighters.

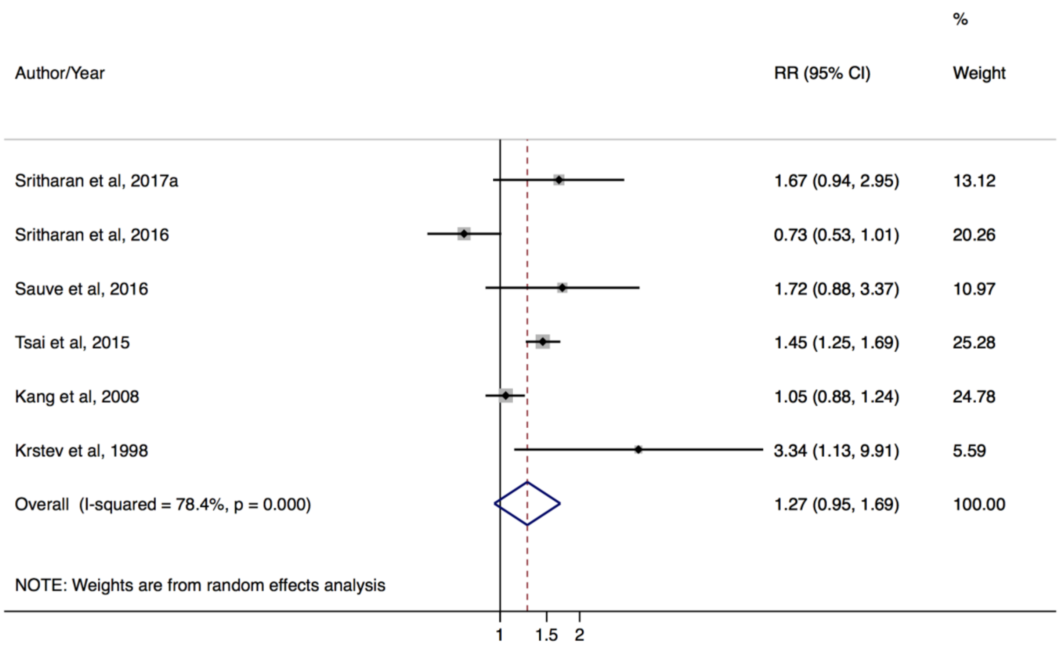

Figure 12. Forest plot and mRE of all case-control studies on firefighters.

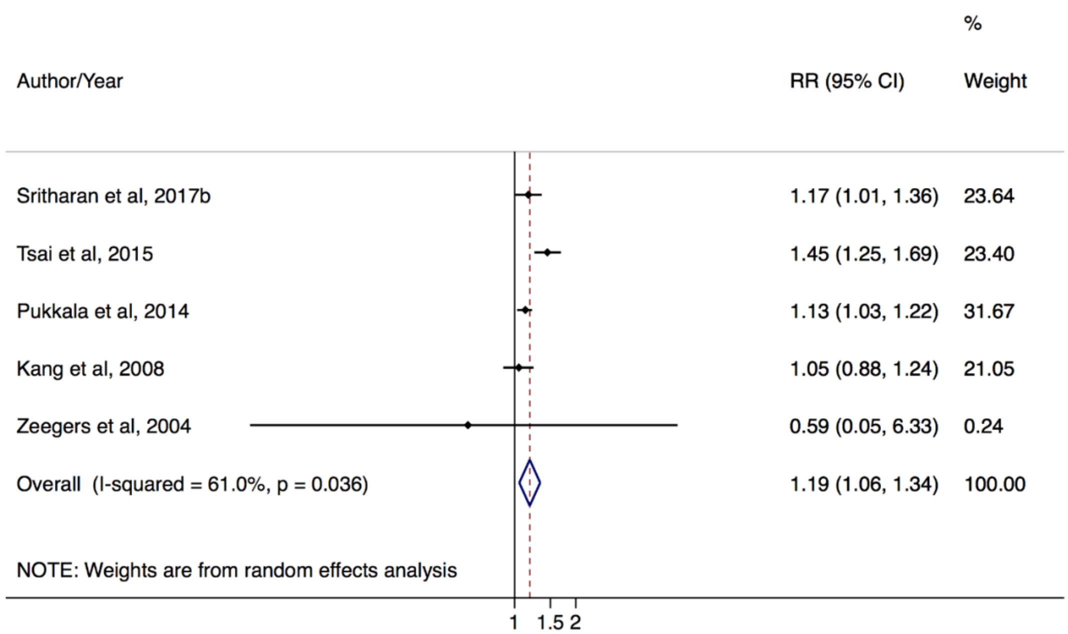

Figure 13. Forest plot and mRE of all administrative linkage-based studies on firefighters.

7.4.3 Police Work and Prostate Cancer Meta-Analyses

There were significantly elevated prostate cancer risks for police occupations by incidence outcomes and in case-control studies. The mRE for prostate cancer incidence studies was 1.14 (95% CI: 1.02-1.28; I^2=33%, 95% CI: 0-74%, p-value=0.16; 9 studies) (Figure 14) while the mRE for prostate cancer mortality studies was 1.08 (95% CI: 0.80-1.45; I^2=0%, 95% CI: 0%-90%, p-value=0.62; 3 studies) (Figure 15). The mRE for case-control studies was higher compared to the mRE for cohort studies (case-control studies: mRE=1.22, 95% CI: 1.03-1.44; I^2=0% (95% CI 0%-85%, p-value=0.42; 4 studies) (Figure 16) versus cohort studies: mRE= 1.10, 95% CI: 0.96-1.26; I^2=37%, 95% CI: 0-79%, p-value=0.15; 7 studies) (Figure 17). There were no administrative linkage-based studies of police workers and prostate cancer risk.

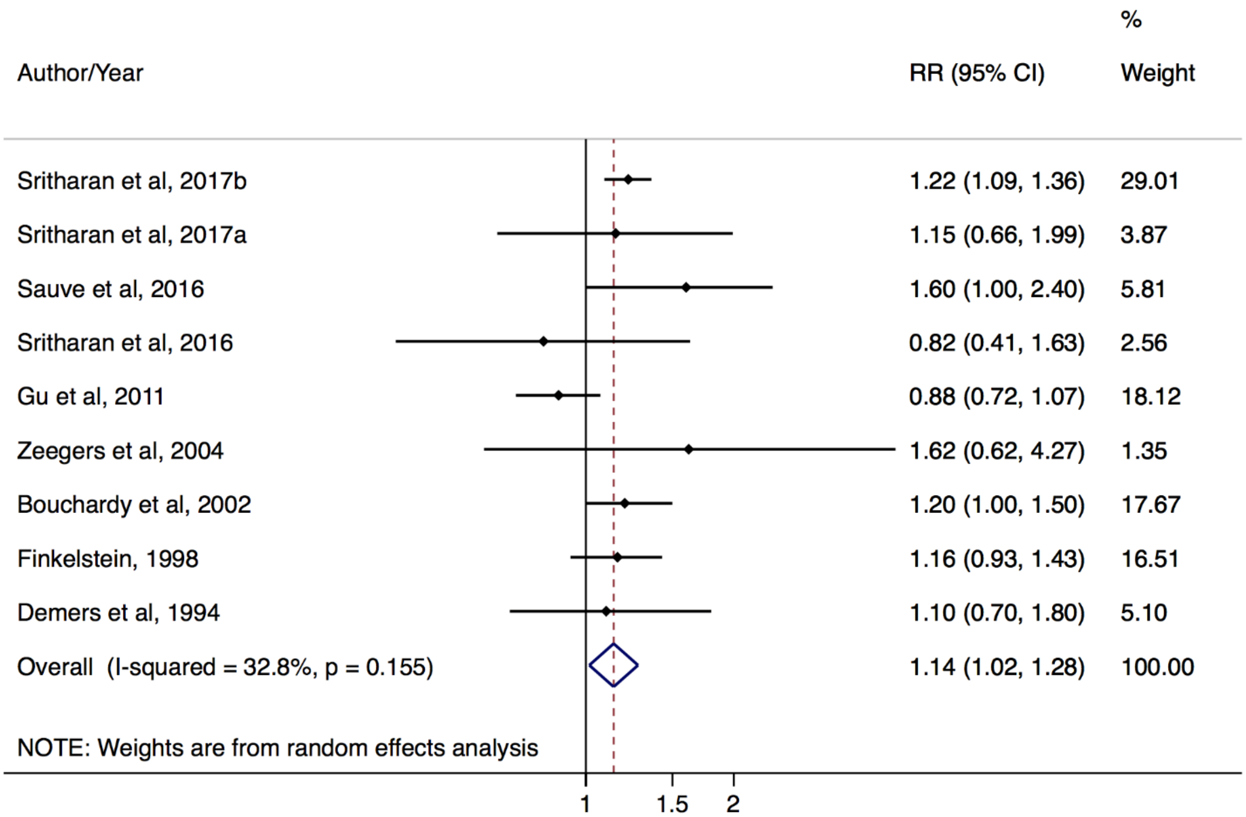

Figure 14. Forest plot and mRE of all prostate cancer incidence studies on police workers.

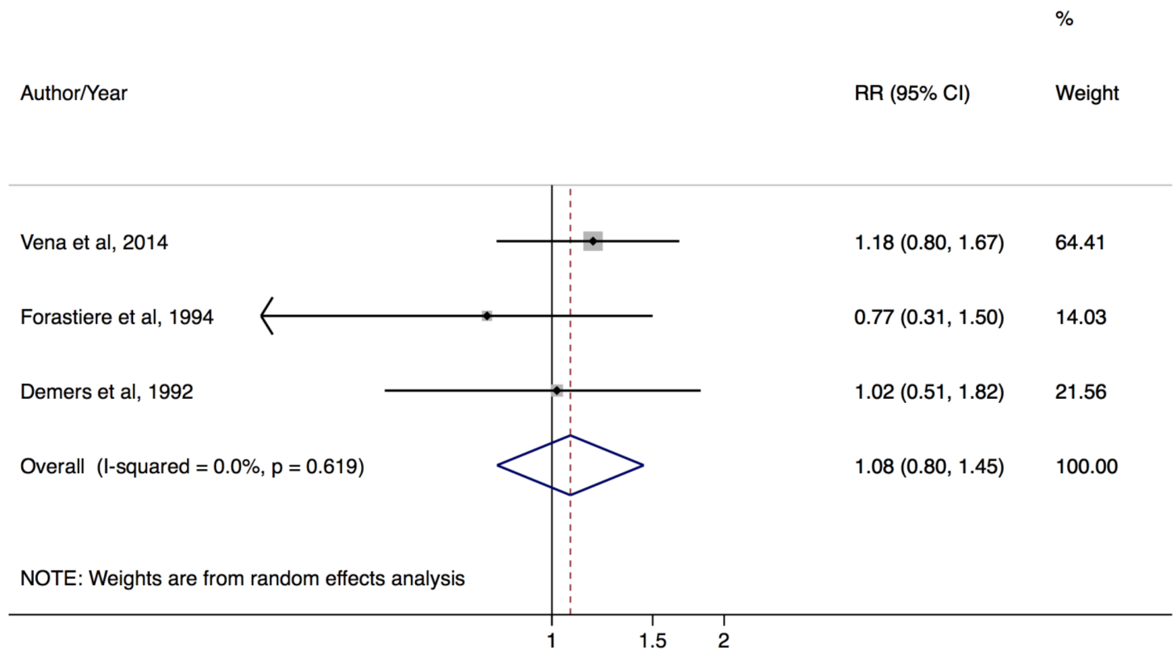

Figure 15. Forest plot and mRE of all prostate cancer mortality studies on police workers.

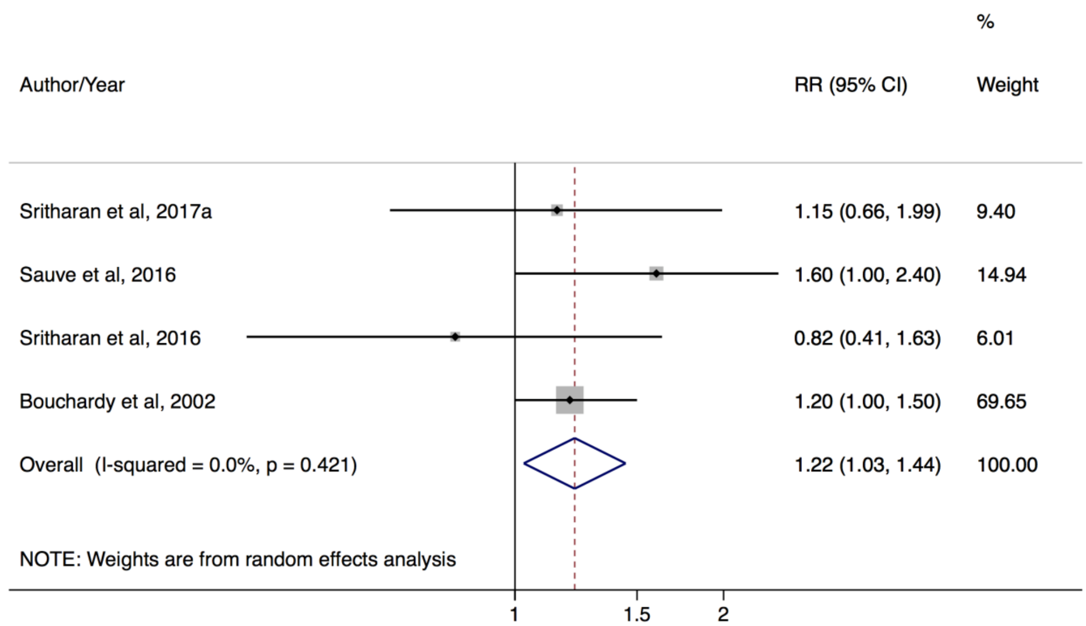

Figure 16. Forest plot and mRE of all case-control studies on police workers.

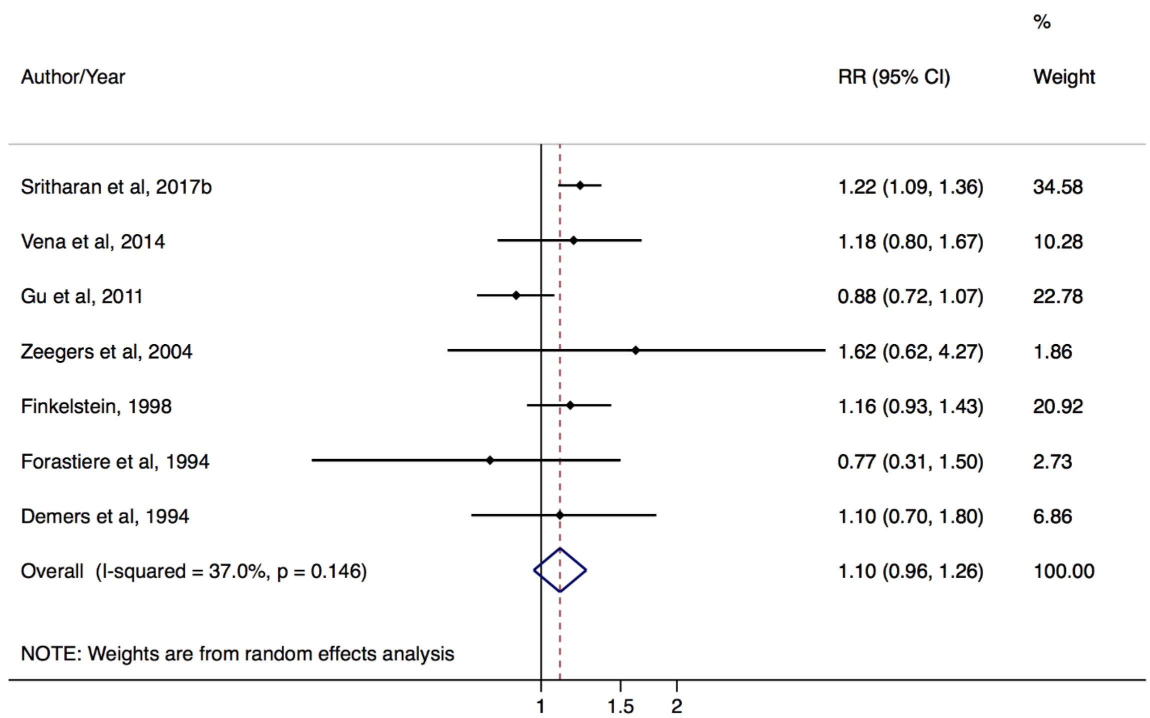

Figure 17. Forest plot and mRE of all cohort studies on police workers.

Figures 9-17 Legend. The forest plots display the author and year reference for all studies included in each estimate on the left side, followed by the relative risk estimate and corresponding 95% confidence intervals from each study and the weight based on sample size on the right side. Each estimate is also shown down the center of this forest plot, with corresponding 95% confidence intervals represented by bars that cross over the estimates. The weight of each study based on sample size is also presented as grey boxes over each estimate down the center of the forest plot. The overall heterogeneity value is represented by the I-squared percent with the corresponding p-value on the left side, and the overall meta-risk estimate is shown on the right side, also presented as the center diamond.

7.4.4 Between-Study Heterogeneity

There was high heterogeneity (72%) for the meta-analysis of all 19 firefighter incidence studies. As a sensitivity analysis, the Galbraith plot was used and one study (Beaumont et al., 1991), appeared outside of the 95% confidence region. Removal of this study resulted in a minimal change in heterogeneity (72 versus 69%, respectively). For the meta-analysis of the 10 mortality studies, there was moderate heterogeneity (50%). High heterogeneity was observed for the six case-control studies (78%), 18 cohort studies (67%) and the five administrative linkage-based studies (61%). When plotting these subgroups using the Galbraith plot, no studies appeared outside of the 95% confidence region.

For police studies, heterogeneity ranged from none to moderate (0-50%). Moderate heterogeneity was observed for the nine incidence studies (33%) and seven cohort studies (37%), but no heterogeneity (0%, 95% CI: 0-90%) was observed for the mortality (three studies) and case-control (four studies) subgroups. I^2 values of 0% are biased and imprecise, likely because of the small number of studies in these subgroups (n<5) (von Hippel, 2015). Using the Galbraith plot, none of the police studies appeared outside of the 95% confidence region.

7.4.5 Publication Bias

There was no evidence of publication bias according to Begg's test (p=0.86) and Egger's test (p=0.11) for the meta-analysis of all 19 firefighter incidence studies. No publication bias was evident for the 9 police incidence studies (Begg's test: p=0.60, Egger's test: p=0.68). There were also no statistically significant findings for publication bias for mortality studies, case-control, cohort, and administrative linkage-based studies.

7.5 Discussion

In this meta-analysis of 31 epidemiological studies of protective services workers, nearly identical and small statistically significant excess risks of prostate cancer were found for ever working in firefighting and police work. Statistically significant and borderline prostate cancer mREs were found for firefighters in separate evaluations of incidence studies, cohort studies, and administrative linkage studies, as well as in each meta-analysis of police worker incidence studies and case-control studies. Most studies were of average quality, with opportunities for improvement in reporting and study power assessment. As expected, case-control studies compared to cohort studies generally had more information on variables that can act as potential confounders of the firefighter/police work and prostate cancer associations. All case-control studies reported prostate cancer risk estimates that were adjusted for age; most were also adjusted for ethnicity. Fewer case-control studies adjusted risk estimates for family history of prostate cancer and potentially confounding variables such as socioeconomic status, physical activity, height, obesity, active smoking, and alcohol consumption. Overall, findings from this meta-analysis support positive associations found between prostate cancer risk and firefighting in the epidemiological literature, and indicate a potential relationship with police work as well.

There are a few hypotheses that may explain why employment in protective services occupations could be associated with increased prostate cancer risk. Firefighting and police jobs are inherently dangerous occupations that involve stressful, and, at times, life-threatening, situations with exposure to multiple hazards (LeMasters et al, 2006; Wirth et al, 2013; IARC, 2010). Psychological stressors can influence biological processes and lead to decreased immune function, increased pro-inflammatory cytokine secretion, and cancer progression (Wirth et al, 2013). Shift work, which is common in protective services work, was significantly associated with increased prostate cancer risk in a recent meta-analysis of eight case-control and cohort studies (Rao et al, 2015). Firefighters are also exposed to toxins released by fire and smoke including benzene , 1,3 butadiene, formaldehyde and at times can be exposed to other compounds such as radiation, diesel exhaust, asbestos, metals (arsenic and cadmium), and PAHs (LeMasters et al, 2006; Ma et al, 2006; IARC, 2010). The chemical reactions during combustion and the age and type of building or material on fire can contribute to exposure to these compounds (IARC, 2010). Police work involves fewer chemical exposures compared to firefighting, although exposure to ionizing radiation from radar devices is a concern for overall cancer risk (Zeegers et al, 2004; Sauve et al, 2016). Firefighters and police workers may also be exposed to air pollution on the job, as ambient concentrations of ultrafine particles and NO_2 have been previously linked to prostate cancer risk (Weichenthal et al, 2017; Parent et al, 2013). Of the described chemical exposures, only x and gamma radiation, arsenic compounds, and cadmium compounds have been linked to prostate cancer by IARC based on limited evidence in non-occupational settings. However, IARC has classified benzene, ionizing radiation, diesel exhaust, asbestos, arsenic compounds, cadmium compounds, and air pollution as all Group 1 carcinogens, based on evidence for other cancer sites (IARC, 2017). There is a need to further examine these chemical exposures in both firefighting and police work to understand if these exposures are involved in prostate cancer risk.

Evaluating potential associations between shift work and prostate cancer is an active area of ongoing research (Flynn-Evans et al, 2013; Parent et al, 2012; Papantoniou et al, 2015). Shift work can disrupt the body's endogenous circadian rhythm (sleep-wake cycle) and contribute to increased susceptibility to acute and chronic diseases. However, the biological mechanisms that may be involved in prostate and other cancers have not been established (Howe & Burch, 1990; Fekedulegn et al, 2013). One hypothesis is that night shift work can lead to decreased melatonin that can then lead to continuous testosterone production, influencing the growth and differentiation of prostate cancer cells (IARC, 2010). In addition, decreased sunlight exposure in night shift workers reduces the production of vitamin D, thereby compromising the effects of vitamin D on suppressing the production of prostate cancer cells (IARC, 2010).

Psychological stress also has been linked to cancer progression, but there is limited evidence for how this impacts cancer initiation (Moreno-Smith et al, 2010). Firefighting and police work involve constant stressors that can potentially affect cancer progression, particularly prolonged stress over years of employment in these jobs (Violanti et al, 1998). A recent study on stress at work and cancer outcomes found that the highest prevalence of stress at work was reported among firemen when compared to other types of occupations (Blanc-Lapierre et al, 2016).

Another factor that may influence our meta-analysis results is prostate cancer screening. Although prostate specific antigen (PSA) testing varies across different countries and within countries, it is believed that protective services workers have frequent and better access to health resources compared to other workers, including access to cancer screening (Daniels et al, 2014). In North America, for example, firefighters are provided with health information and recommendations on what to consider when completing a health examination with their primary physician, including recommendations for prostate cancer screening (International Association of Firefighters, 2017). However, it is up to each fire department to disseminate this information and ultimately up to each firefighter to request screening from their primary physician. In this meta-analysis we found slightly lower mortality mREs compared to incidence mREs for firefighters and police officers. As increased screening of prostate cancer leads to the identification of more early stage cases (increased incidence), this may be indicative of a screening effect. However, the mREs for both incidence and mortality were so similar that it was difficult to attribute these differences to screening. Also, prostate cancer screening may not be of high importance in firefighting compared to other cancers (ex. brain, bladder, and colon) and health conditions that have been consistently associated with firefighting. We evaluated study estimates based on different follow-up periods defined as pre-PSA period (prior to 1990 before the PSA test was introduced), during the introduction of PSA testing (early 1990s), and after the introduction of PSA testing (late 1990s and onwards). Although we included studies from different nations, most of the studies were North American so we loosely defined the time periods based on North America. We identified a number of pre-PSA period firefighter studies and observed a meta-risk estimate of 1.26 (95% CI 0.96-1.67) for these studies. For firefighter studies that had follow-up periods during and after the introduction of PSA testing, we observed a meta-risk estimate of 1.13 (95% CI 1.02-1.25). It was challenging to define firefighter study follow-up periods as post PSA testing (late 1990s onwards) since most of these studies had follow-up periods that overlapped the early 1990s when PSA testing began. We identified only a few firefighter studies that had later follow-up periods (late 1990s and early 2000s) and observed a meta-risk estimate of 1.58 (95% CI 1.09-2.29) for these studies. Overall, we observed an elevated risk for firefighter studies that were conducted before the introduction of PSA testing, and a statistically significant elevated risk for firefighter studies that took place during and after the introduction of PSA testing. These findings may be representative of the increased screening that took place over this time period. We attempted to evaluate police studies as well but were limited as almost all included police studies had follow-up periods overlapping periods with and without PSA testing.

Our findings of a slight excess risk of prostate cancer in firefighting and police services should be cautiously interpreted. As expected, there was considerable heterogeneity between studies, particularly in subgroup meta-analyses of police workers and prostate cancer risk that involved small numbers of studies. This makes it challenging to interpret mRE values with precision (von Hippel, 2015). Heterogeneity was likely due to differences in study design and populations studied, follow-up years, occupational exposure assessment and job coding, and adjustment of relative risk values for known or potential covariates. Specifically, there were differences in how the study populations were defined, in terms of paid or unpaid work, full time vs. part time, and eligible employment duration. Some heterogeneity may also be attributed to different follow-up periods in each study, especially those overlapping the pre and post PSA era. The variation in age distribution across included studies could also contribute to heterogeneity based on differences in how studies stratified by age. Some studies had relatively younger populations than other studies and we observed a similar elevated meta-risk estimate for these younger population studies as we did for overall estimates. Publication bias was also considered, but was not recognized as a significant factor as a majority of the included studies were cohort designs. The cohort studies generally looked at multiple cancer sites as outcomes, so it is unlikely that publication bias would have been of concern based on solely prostate cancer results.

A major strength of this meta-analysis is that it was the first to assess prostate cancer risk in both firefighting and police work, replete with subgroup analyses and assessments of study quality, heterogeneity, and publication bias. This meta-analysis captured all previously and newly published studies since the IARC evaluation of firefighting in 2007, and also quantitatively evaluated prostate cancer risk in police studies which had not been done before. Firefighting and police work should be priority areas for investigation because these occupations frequently involve exposure to multiple chemical, biological, physical, and psycho-social hazards. Exposure to some hazards may be associated with increased risk of prostate cancer, although the strength and consistency of associations varies across studies and there are substantial research gaps. Altogether, this research can be used to help identify opportunities for further investigation on how occupation is associated to prostate cancer risk.

Other occupations of interest with respect to prostate cancer risk are military workers. While we initially sought to include military studies in this meta-analysis, they were ultimately not included because these studies were primarily based on specific historical events (ex. Gulf war) or internal comparisons between military groups (Strand et al, 2017; Yi, 2013; Armed Forces Health Surveillance Center, 2012; Strand et al, 2011; Rogers et al, 2011; Cypel & Kang, 2010; Young et al, 2010; Storm et al, 2006; Yamane, 2006; Akhtar et al, 2004; Silva et al, 2000; Watanabe & Kang, 1996; Darby et al, 1990; Leavy et al, 2006; Sanderson et al, 2004; Giri et al, 2004). This made it difficult to compare findings to other studies that did not focus on single events or that compared workers to the general population. Future assessments can separately consider military studies.

Overall, the slight excess risks of prostate cancer in firefighting and police services found in this meta-analysis of 31 studies were generally robust to subgroup analyses by outcome (incidence and mortality) and study design. Our findings are important as they show the importance of prostate cancer incidence and mortality among protective services workers, and as this is the first meta-analysis to include both firefighting and police work and prostate cancer risk. The observed findings suggest that screening may not entirely explain our findings, but further investigation into actual screening rates and screening behaviours in firefighting and police work is warranted. Also, further investigations should be designed to assess specific exposures such as benzene, radiation, diesel exhaust, arsenic and cadmium compounds, PAHs, asbestos, and air pollution which are involved in firefighting. Little evidence on how they may relate to prostate cancer risk has been accrued. There is also a need for future studies to examine prostate cancer risk in police work given the small number of studies on police workers published to date. By addressing these important issues in future studies, there will be better understanding on prostate cancer risk in firefighting and police work.

Chapter 8. General Discussion

The research presented in this thesis provides evidence that occupation is an important risk factor for prostate cancer in Canadian men. The primary focus of this thesis was to investigate the relationship between occupation and prostate cancer risk and to understand how non-occupational factors play a role in this relationship. The following section will provide a discussion on the main findings of the thesis, while outlining important themes that emerged from our research, investigation into potential job-specific exposures, and contribution to the literature.

8.1 Research Aims and Hypotheses Revisited

8.1.1 Study 1: Hypotheses Revisited

Natural resource based industries are important for Canada, as Canada is one of the few developed nations that places significant importance on the primary industry sector. Natural resource based industries were and still remain primary contributors to economic and population growth in Northern Ontario and Canada (Northern Development Ministers Forum, 2015). Northern Ontario covers almost 90% of Ontario’s land mass with key industries being mining and forestry (Northern Development Ministers Forum, 2015). It is also expected that men employed in natural resource based work remain in these jobs for a majority of their working life, which may be representative of consistent job-related exposures over time. There are few studies that exist in this region on occupation and prostate cancer and our findings indicate that future research needs to continue examining prostate cancer risk in the Northern Ontario region and across Canada (Lightfoot et al, 2000; Lightfoot et al, 2004; Darlington et al, 2007; Sass-Kortsak et al, 2007).

The purpose of the study in Northeastern Ontario (Chapter 4, Sritharan et al, 2016) was to investigate if employment in natural resource based work and job-related exposures was associated with prostate cancer risk in men aged 45-84 years. Findings from previous studies have shown some association between exposures involved in natural resource based occupations and prostate cancer risk (Parent et al, 2001; Parent et al, 2009; Boers et al, 2005, Doolan et al, 2014). At the start of this study, the aim was to investigate many different occupations, but given the importance of natural resource based occupations in the Northeastern Ontario region and the small sample size, focus was narrowed to only these related occupations in this study. Risk of prostate cancer had not been thoroughly studied in natural resource based workers before, and these workers may be exposed to higher levels of carcinogens than other workers. It was hypothesized that associations would be observed for agriculture and mining work in this study. Findings confirmed associations for agriculture occupations but were limited for mining occupations. An elevated risk was observed for incidental work related to mining, however this was not statistically significant and this mining occupation only included a subset of all mining workers in the study. Other associations in natural resource based work were recognized, particularly for forestry, logging, wood, and paper related occupations. These are important natural resource based occupations that share common exposures such as diesel exhaust, whole body vibrations, wood dust, and wood preservative chemicals (Sass-Kortsak et al, 2007; Magagnotti et al, 2013; Vallieres et al, 2015).

Strong associations in natural resource based work were observed not only for ever employment but also with duration of employment. Consistent evidence with duration of employment showed that men were employed in the same jobs for more than 10 years which reflects a long exposure period. For job-specific exposures, no associations were observed for prostate cancer, though exposure information was limited since it was unrelated to job titles and was broadly reported by participants. The limited information on job-specific exposures is an important gap in occupational research. As there is no substantial evidence on specific exposures associated with prostate cancer risk, it is challenging to narrow down which exposures to focus on. By identifying occupations linked to prostate cancer, there can be improved understanding of specific exposures that are associated with these occupations leading to better surveillance of workplace exposures. This study can also be replicated in other high natural resource based regions within Canada and abroad to compare risk estimates across population groups. It would be ideal to compare findings with much larger population groups to increase the sample size and power. Also, as over 90% of the participant population in this study identified as being Caucasian, there was no room to stratify the analysis by ethnicity, which is a strong risk factor for prostate cancer. Further investigation into natural resource based work in other parts of Canada could help to identify if associations are similar across different ethnic groups which could provide better understanding on how ethnicity is involved in the relationship between occupation and prostate cancer risk.

This first study was relatively small in terms of the number of cases and controls and was specific to a small region, but the results of the study contribute to knowledge on occupational risk factors for prostate cancer. The objectives of this study were realistic and this study provided valuable findings that were used for publication. Although existing data were used, a significant amount of time was needed to thoroughly clean and organize the data, and create new variables from existing variables. An advantage to using existing population data (secondary analyses) to understand complex relationships is that it provided more time to develop research approaches and test hypotheses, rather than spending substantial time and funding to collect primary data (Cheng et al, 2014). More importantly, using existing data from previous years gives us the opportunity to use current and updated knowledge on prostate cancer and account for new evidence on prostate cancer risk to assess associations that were not previously considered. This first study is consistent with existing evidence on different natural resource based occupations, while also providing new knowledge specific to Northern Ontario, and Canada as a whole.

8.1.2 Study 2: Hypotheses Revisited

The second study of the thesis, using the NECSS, (Chapter 5, Sritharan et al, 2017a) involved a much larger dataset than the first study, with data collected from 1737 cases and 1803 controls across eight Canadian provinces. The NECSS was initiated to allow researchers to investigate multiple environmental factors and multiple cancer sites (Johnson et al, 1998). With the advantage of a larger population based dataset, a large sample size of men aged 50-74 years was investigated to understand the relationship between occupation, industry, and prostate cancer. As a result, 43 occupations and 66 industries were classified and investigated with duration of employment and potential job-specific exposures. This study data set had the unique advantage of including multiple co-variates for analysis, allowing the inclusion of known and potential risk factors for prostate cancer. Findings from this study supported the hypothesis that there would be increased risks among agriculture workers and other natural resource based occupations, however not for mining workers. It was also hypothesized that new associations for occupations that were not commonly linked to prostate cancer would be observed and findings showed associations for white collar jobs, protective services, and construction workers. No associations were observed for any job-specific exposures, however the means used to assess exposure in this study were limited and non-specific to the jobs held by participants.

In this study, screening bias was a potential concern. As previously mentioned, the screening behaviours of men are associated with multiple factors, including occupation (Richardson et al, 2007; Littlejohns et al, 2016). No specific screening history data was collected in this study so the aim was to explore factors that may be related to screening bias based on the multiple covariates available. In this study screening behaviours among men may vary by occupation and other factors such as age, ethnicity, family history of prostate cancer, socioeconomic status, and marital status. However, adjusting for these potential screening factors in the NECSS did not significantly alter the identified associations between occupation, industry, and prostate cancer incidence. Since the findings did not significantly change with adjustment of screening related factors, findings may not be affected by screening bias. Additional information on participant screening practices is needed to actually confirm if any screening bias existed in this study. Associations observed for agriculture occupations strengthen findings observed in the Northeastern Ontario study. Strong associations between prostate cancer and occupation groups that are of growing interest were identified. Some of these groups had been linked to prostate cancer in the previous literature, but this study provided evidence from a Canadian context. Based on the findings of this second study, further investigation is needed to confirm associations between occupation and prostate cancer, job-specific exposures, and screening patterns.

8.1.3 Study 3: Hypotheses Revisited

The third study, CanCHEC (Chapter 6, Sritharan et al, 2018), involved one of the largest Canadian cohorts to date. The cohort contained data from participants across all Canadian provinces and territories with a large sample size of 1.1 million men (Peters et al, 2013). Similar to the previous two studies (Chapters 4 and 5), data were available on men with prostate cancer aged 50-74 years; what was unique with the CanCHEC was that the study also contained data on men with prostate cancer aged 25-49 years which is generally more difficult to obtain as prostate cancer is rare in younger men. The CanCHEC had more power to assess associations across a wider age group and larger population group. This cohort study design was different from the previous two case-control studies as it involved the linkage of administrative data - the Canadian Cancer Database, the Canadian Mortality Database, and the Tax Summary Files (Peters et al, 2013). These linked databases made it possible to follow men who completed the 1991 census to observe how many of them developed prostate cancer and did not develop prostate cancer. There were also important demographic and lifestyle co-variates in this dataset which were collected in the 1991 census and retrieved through the linkage. The linkage provided data on age, ethnicity, socioeconomic status (income and education), and marital status which may be linked to prostate cancer risk and screening behaviours.

The CanCHEC findings (Chapter 6) were somewhat consistent with the NECSS study (Chapter 5), strengthening overall findings in this thesis. Increased prostate cancer risks were observed in white collar, agriculture, and protective services occupations and industries. Decreased risks were observed in construction and transportation occupations and industries, whereas in the NECSS study only a decreased risk in construction managers was observed with no association across other related occupations. Previous studies from the literature presented mixed findings in construction and transportation jobs. Further assessment is needed to understand why decreased risks were observed in construction and transportation workers in the CanCHEC analysis and to further investigate what factors are involved related to exposures and screening behaviours.

Using CanCHEC, age-standardized rates were calculated to help understand prostate cancer patterns. The age-standardized rates for each follow-up year were then compared to the general population prostate cancer rates over the same years. Based on historical prostate cancer rates, there is evidence of significant surges of prostate cancer incidence in the early 1990s and early 2000s coinciding with increased PSA testing during these same time periods (Dickinson et al, 2016). In the CanCHEC, patterns of prostate cancer over this same time period were examined to recognize if patterns from the general population were similar to the CanCHEC working population. These patterns were also examined by occupation group to compare occupation groups to one another, which had not been done in previous published studies. Findings showed that prostate cancer rates varied by occupation group, similar to the hazard ratios observed. Age-standardized prostate cancer rates were highest in white collar jobs and lowest in construction and transportation jobs when compared to the overall working cohort. White collar jobs had a few similar prostate cancer peaks when compared with the general population of Canada, whereas construction and transportation jobs did not have similar peaks as compared to the general population. Protective services jobs had increased incidence during various years but trends did not follow the same pattern as the general population. Elevations in incidence across these different occupation groups were not clearly defined making it difficult to interpret further. No obvious patterns were identified, demonstrating the complexity of screening bias in this study.

With CanCHEC, it was hypothesized that there would be significant increased prostate cancer risks in white collar and agriculture workers. Findings were supportive of these hypotheses. It was also hypothesized that patterns of prostate cancer rates by occupation group would be similar to that of the general Canadian population with peaks representative of increased screening periods. Prostate cancer rates were highest for white collar jobs and lowest in some blue collar jobs (construction and transportation) which may be indicative of possible differences in screening behaviours by occupation gradient. However, findings were not as clear and concise as expected, and patterns varied significantly. Again, this study reiterates the importance of including information on screening history and further investigating specific occupations identified in this study.

8.1.4 Study 4: Hypotheses Revisited

For the fourth study (Chapter 7, Sritharan et al, 2017b) a meta-analysis was conducted to examine specific protective services occupations, since there were consistent increased risks of prostate cancer in these workers in the other thesis population studies. Also, based on the existing literature, it was evident that there was limited understanding of prostate cancer risk in these groups (LeMasters et al, 2006; Wirth et al, 2013). It was difficult to interpret all studies on protective services occupations due to heterogeneity and use of different comparison groups, and for this reason, only firefighting and police work were evaluated. Military work was excluded from the meta-analysis. Firefighting and police work proved to be interesting groups because of the potential job-specific chemical exposures and factors of shift work, psychological stress, and screening behaviours. The existing literature was systematically reviewed and a methodological approach was followed to include quality studies in the analysis. All existing and updated firefighter and police studies that evaluated prostate cancer risk were assessed, making it the first meta-analysis on prostate cancer to include both firefighting and police epidemiological studies. Also, no previous quantitative meta-analysis existed on police work and prostate cancer, so this was the first meta-analysis on police work and prostate cancer risk.

Findings in the meta-analysis supported the hypothesis of an excess risk of prostate cancer in both firefighting and police work. Overall, findings supported the hypothesis that there would be increased risks across subgroups of firefighters and police workers. It was also hypothesized that incidence and mortality would be representative of the screening effect, where increased screening would result in increased incidence and decreased mortality estimates. However, findings did not support this hypothesis as mortality and incidence estimates were very similar, with elevated risks. Since estimates for both incidence and mortality in this meta-analysis were similar, these findings did not support the hypothesis that there is screening effect involved. Heterogeneity was also recognized as an important factor in firefighting and police studies, given the differences in employment type, duration, exposure assessment, age at diagnosis, and follow-up time periods. As all estimates across firefighting and police work subgroups were so similar, it is important for future studies to look into specific chemical exposures, shift work, stress, and screening rates. Results from this meta-analysis suggest that men in these high risk jobs are affected by prostate cancer and require further investigation into job-specific exposures, prevention strategies, and screening practices.

8.2 Overarching Themes in the Four Studies

Each of the four studies presented in this thesis were built upon one another with achievable study aims and defined hypotheses. All four studies addressed important knowledge gaps surrounding the relationship between occupation and prostate cancer. The results of these studies demonstrate strong associations between prostate cancer risk and administrative, natural resource based, construction, transportation, and protective services occupations (Figure 18). The results of the meta-analysis also show elevated risks of prostate cancer mortality in protective services occupations. The studies also indicate the importance of other factors such as screening patterns, sedentary behaviour, stress, and other factors that have been linked to prostate cancer previously, as shown in Figure 18. The findings of this thesis support the broad hypothesis that occupation is associated with prostate cancer risk, while outlining the need for further research in specific areas of exposure assessment methods to identify job-related exposures. Overarching themes from the thesis related to potential job exposures and other factors will be discussed in the following paragraphs leading into a discussion on job-specific exposures.

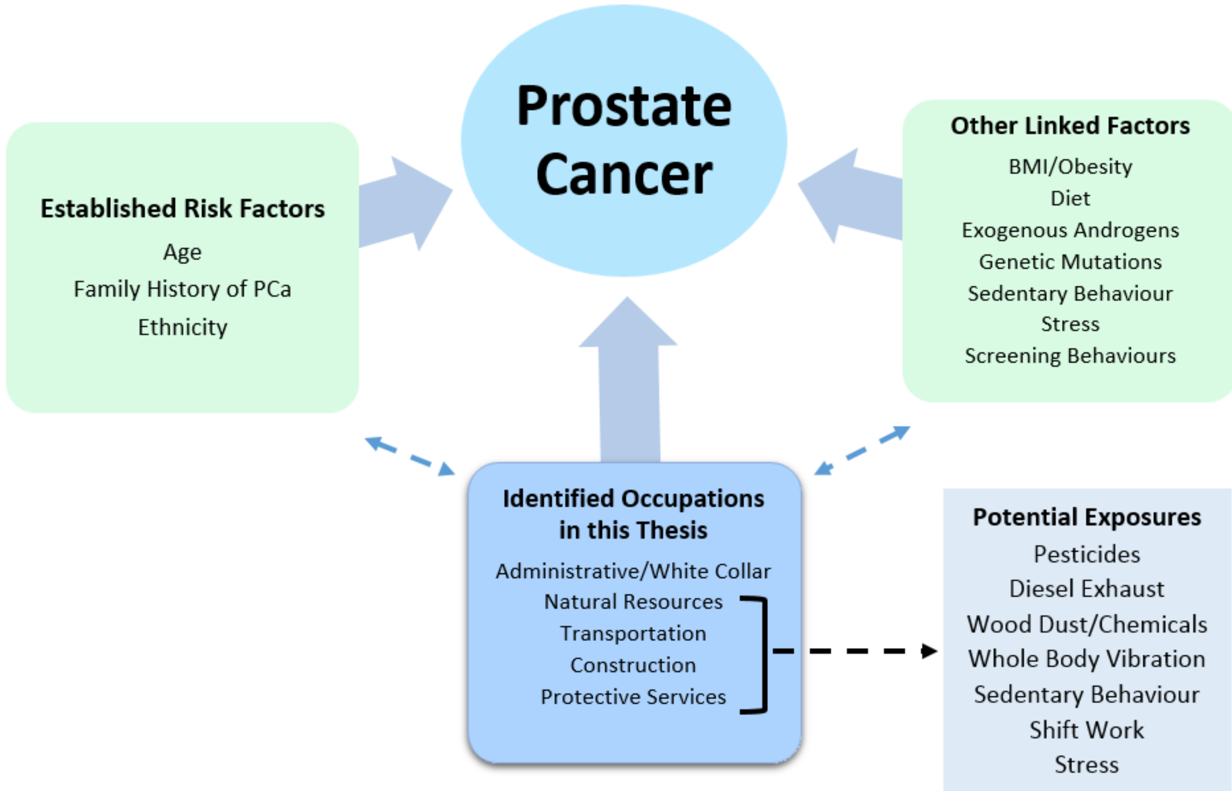

Figure 18. Diagram of identified occupations in this thesis among other risk factors for prostate cancer.
This diagram provides an illustration of the established risk factors, other linked risk factors, and identified occupations in this thesis related to prostate cancer risk. The identified occupations are also related to established risk factors and other linked risk factors. Specific identified occupations in this thesis are also related to potential exposures as shown in this diagram.

Based on the evidence in the literature it was expected that there would be significant associations between natural resource based work and prostate cancer risk. Previous studies on mining work and prostate cancer have shown inconsistent findings, but all three population studies showed no risk of prostate cancer in mining related occupations. Findings in mining work do not support the risk of prostate cancer in these jobs, however other associations were observed that warrant further research. The Northeastern Study (Chapter 4) provided consistent associations across most natural resource based work, while the NECSS and CanCHEC studies (Chapters 5 and 6) showed the recurring theme of agriculture and farming associated with prostate cancer risk. As the Northeastern Ontario region involves significant natural resource based work, the findings of this study may not necessarily reflect risks across Canada. Findings in agriculture and farming in the three population studies in this thesis are relevant because agricultural and farming workers are generally thought to have healthier lifestyles. They are often recognized as being more physically active with increased sun exposure leading to increased vitamin D levels (Rafnsson, 2007). Since studies in this thesis have shown consistent increased risks in these workers, findings may be related to job-specific exposures. Agriculture workers continue to be exposed to chemical agents such as pesticides and diesel exhaust (Rafnsson, 2007). Other common natural resource based work also include these exposures, among whole body vibrations, wood dust, wood preservative chemicals, and shift work.

Similar findings were also observed in construction and transportation groups in the NECSS and CanCHEC studies (Chapters 5 and 6) and these findings warrant further investigation. In the NECSS, decreased risks were observed in construction managers and brick and cement workers and no association was observed for other construction and transportation workers. In the CanCHEC, decreased risks were observed in construction managers only in men 50-74 years, similar to findings in the NECSS, and increased risks in construction managers in men aged 25-49 years. Findings in the CanCHEC also showed decreased risks in construction trades and in transportation occupations. Although some of the findings were borderline statistically significant, decreased risks in these blue collar jobs were still consistent. There are overlapping exposures in construction, transportation, and natural resource based workers such as diesel exhaust and whole body vibrations which may contribute to the few increased risks observed. On the other hand, decreased associations identified in these blue collar jobs may be related to increased physical activity and sun exposure, and decreased prostate cancer screening.

Another interesting theme in the NECSS and CanCHEC studies (Chapters 5 and 6) was the increased risks observed in white collar jobs. Increased risks were observed for occupations related to management, office, legal work, finance, and non-significantly elevated for other occupations related to education, government services, and business. The only difference between these studies was that there was a significantly decreased risk in senior management and government officials in the NECSS study and a significantly increased risk in this same occupation in the CanCHEC. The few existing studies in the literature that have reported on prostate cancer risk in white collar and administrative level work have shown mixed findings. It is unclear why there are prostate cancer risk differences in these occupations, but it is important to clarify differences in job titles classified as white collar work versus other administrative work (e.g. clerical). Even though there are few chemical exposures involved in these types of jobs, sedentary behaviour and physical activity may be significant factors. White collar jobs involve mounted sedentary behaviour compared to the high level of physical activity in blue collar jobs such as construction and transportation (Lynch et al, 2014; Krstev et al, 1998). A few studies have compared sedentary occupations to physically active occupations, with inconsistent findings (Orsini et al, 2009; Lacey et al, 2001; Lynch et al, 2014). Men employed in white collar jobs are also likely to have better access and flexibility of resources related to prostate cancer screening than men employed in blue collar jobs. This may lead to increased screening rates in men in white collar jobs leading to an increased number of identified cases.

Another theme observed in the NECSS and CanCHEC studies (Chapters 5 and 6) was the consistent elevated risks of prostate cancer in protective services workers. Based on these two studies and other recent studies that observed similar findings (Sauve et al, 2016), risk of prostate cancer in firefighting and police work were evaluated using a meta-analysis approach. Based on consistent findings in protective services groups in this thesis, further assessment of potential chemical exposures such as diesel exhaust and whole body vibrations is warranted. Some protective services groups differ in terms of chemical exposures, like men in police work are exposed to fewer chemical agents than firefighters. Given the minimal understanding on which specific exposures are actually involved in different protective service groups, improvements need to be made in exposure assessment. Further understanding is also needed on other factors such as shift work, sedentary behaviour/physical activity, stress, and screening behaviours (Wirth et al, 2013). Given the similar incidence and mortality estimates in the meta-analysis (Chapter 7), it appears that screening may not have been an influential factor but more information is needed on the individual screening practices of these workers. Aside from utilizing questionnaires for self-reported data, exposure assessment tools need to be used to adequately assess specific exposures. It would be ideal to develop job exposure matrices to understand exposures and associated risks in protective services. There will be distinct challenges in applying these tools given that each group of protective workers is not in the same environment on a daily basis and these workers can experience different levels of exposures, shift work, and stress at any given time.

Protective services workers are recognized as first responders and are aimed at protecting the lives of others. As these jobs provide an important service to the community, this should be a priority research area in the future. Protective services workers are a high risk group for many possible health conditions as a result of work-related responsibilities (Kaikkonen et al, 2017). Although these workers are often recognized as being resilient and healthy, it is clear that prostate cancer is still an important issue among these workers (chapters 4-7). It is recommended that future studies address the potential chemical exposures involved in each protective services occupation, while also including screening and lifestyle factors.

8.3 Investigation into Job-Specific Exposures

Investigation of job-specific exposures is necessary across the occupations identified in the four core studies. The thesis studies involved the use of questionnaires and interviews to collect data from participants, which are common methods of data collection in population based studies. Questionnaires and interviews from thesis studies included demographic and lifestyle factors, occupational history, and occupational exposures. Questionnaires are important in assessing information on employment and exposures, especially when there is limited knowledge on exposures associated with prostate cancer risk (Nieuwenhuijsen, 2005). Although questionnaires are ideal tools to collect data in large studies, there is a need to use other exposure assessment tools alongside questionnaires. As the studies in this thesis included multiple occupations, it would have been overwhelming to include many different exposures, but now with identified occupations associated with prostate cancer risk, additional exposure assessment tools are necessary. Use of job exposure matrices are effective for estimating occupational exposures when complete job histories are available and when there is consistency in exposures linked to jobs (Checkoway et al, 2007). Job exposure matrices have been used to examine pesticide exposure and health effects such as cancer, with findings showing similar associations in epidemiological studies

(Carles et al, 2017). Similar to pesticide exposure, job-exposure matrices can be developed for other identified exposures.

Efforts should be focused on determining what kind of exposures are involved in the identified jobs while accounting for related occupational and non-occupational factors as discussed. Future research based on our findings and suggestions can develop research strategies that involve multiple exposure assessment tools, specific to occupations identified in this thesis, while understanding how other factors influence the relationship between occupation and prostate cancer risk. This will help to determine potential mechanistic effects involved in the occupational etiology of prostate cancer while also leading to better prevention strategies in the future. Further investigation into related exposures will be discussed in the following paragraphs.

8.3.1 Pesticides

Of the potential exposures involved in the identified occupations in this thesis, pesticides have been repeatedly assessed in the past. In the thesis studies, pesticide exposure was assessed based on reported data, unrelated to job titles, so this was quite limited and uninformative. Based on evaluations by IARC, some pesticides have been classified as Group 1 (carcinogenic to humans), and primarily as Group 2A (probably carcinogenic to humans) and Group 2B (possibly carcinogenic to humans). Specifically, lindane and pentachlorophenol were classified as Group 1, dichlorodiphenyltrichloroethane (DDT), glyphosate, malathion, and diazinon were classified as Group 2A and 2,4-D, chlorothalonil, dichlorvos, 2-methyl-4-chlorophenoxyacetic acid (MCPA), methylchlorophenoxypropionic acid (MCPP), para-dichlorobenzene, tetrachlorvinphos, parathion were classified as Group 2B (IARC, 2015). Of these pesticide exposures, only malathion has been associated with prostate cancer in the IARC evaluations. Also, a recent meta-analysis has shown a weak association between pesticides and prostate cancer risk, with significant differences in the quality of exposure assessment across included studies (Lewis-Mikhael et al, 2016).

There is growing evidence showing that men who have a family history of prostate cancer are at an increased risk for prostate cancer when exposed to pesticides (Lewis-Mikhael et al, 2016). These findings reiterate the importance of examining occupational pesticide exposures, in interaction with non-occupational factors (e.g. family history of prostate cancer). Studies in the literature heavily weigh towards an increased risk of prostate cancer based on pesticide exposure, with some studies showing no association at all. Given that across all three thesis population studies (Chapters 4-6) increased risks in agriculture workers were observed, this should still be an important area to assess exposures while considering how non-occupational factors (family history of prostate cancer) play a role. To do this, questionnaires can be used to identify self-reported pesticide exposure and non-occupational factors, while also investigating the type of pesticides used on farms and other agricultural work environments through exposure assessment tools. Further sample sizes need to be large enough to have power to detect interactions.

8.3.2 Diesel Engine Exhaust

Diesel engine exhaust is another potential exposure among agriculture and other natural resource based work, construction, transportation, and protective services. Diesel exhaust exposure is highly relevant to natural resource based work because men in these jobs may operate vehicles throughout the day. Few studies have examined diesel exhaust exposure in forestry workers with limited findings (Magagnotti et al, 2013), however it is still necessary to examine these workers further. In Canada, transportation and construction industries are the largest occupational groups exposed to diesel exhaust, especially those employed as truck drivers or heavy equipment operators (Sass-Kortsak et al, 2007; Carex Canada, 2016). The three studies in this thesis could not assess diesel exhaust exposure in transportation and construction workers. But findings from the three studies showed decreased prostate cancer risks or no association in transportation and construction workers. Firefighters and military workers can also be exposed to diesel exhaust from idling vehicles and when spending long periods of time in or near fire trucks and military vehicles. Men in police work involved as first responders are often near ambulance vehicles and those involved in traffic related work may be exposed to diesel exhaust. Diesel exhaust was classified by IARC as Group 1, carcinogenic to humans (IARC, 2013), although this classification was not based on prostate cancer but rather on other cancer types, primarily lung cancer. Reported diesel exhaust in the thesis studies (Chapters 4 and 5) did not show any association with prostate cancer risk, however this was based on limited exposure data. Assessing diesel exhaust exposure can be difficult since it is often combined with other ambient contaminants and there are currently no standard practices for estimating exposure (Carex Canada, 2016). There is no single marker of diesel exhaust exposure but components such as respirable particulate matter, nitrogen oxide or dioxide, and carbon monoxide are used (Pronk et al, 2009). Cancer is primarily associated with particulate matter, making it an important marker for future prostate cancer studies. Area sampling or personal sampling can be done selectively by submicron, respirable, or inhalable size to capture exposures at an individual level and within the work environment. Sampling generally results in low air volume samples and a large number of samples is needed (Pronk et al, 2009). Focusing on jobs identified in this thesis that specifically involve diesel exhaust exposure can provide better direction and specificity when assessing exposure levels.

8.3.3 Whole Body Vibrations

Workers exposed to diesel exhaust can also be exposed to whole body vibrations (WBV), which has not been evaluated for carcinogenicity by IARC. WBV is common across many natural resource based occupations, construction, transportation, and even firefighting and military work (Mayton et al, 2014). The vibrations occur when individuals are operating vehicles or equipment, and the vibrations or shock is transmitted to the whole body (Mayton et al, 2014). WBV has been considered in some natural resource based occupations, construction, and transportation, however it has not been evaluated in protective services occupations. Previous studies have shown mixed findings for risk of prostate cancer and occupational exposure to WBV resulting in lack of conclusiveness (Nadaline et al, 2002; Sass-Kortsak et al, 2007; Jones et al, 2014; Young et al, 2009). Typically, questionnaires are used to assess WBV exposure based on the type of job individuals report because it can be quite expensive and limiting to evaluate exposure using vibration measurement tools. Instrumentation through the seating or standing area of the vehicle or equipment can be used to capture vibration measurements. Other factors that are also considered in this exposure assessment are the features of the vehicle or equipment (make, age, weight, power source), operating conditions (load weight), and driver conditions (speed, road conditions) (Nitti & De Santis, 2010). Given our occupational findings in this thesis, there is a need to assess WBV in the identified jobs using available tools.

8.3.4 Wood Industry Related Exposures

Wood dust is another common exposure in construction, forestry, logging, pulp and paper mill and other paper and wood related occupations. Wood dust is one of the most common occupational exposures and was classified as a Group 1 carcinogen by IARC (Vallieres et al, 2015). It is primarily involved in adverse conditions related to the nasal passage and lung function (Vallieres et al, 2015) and has not been linked to prostate cancer risk. Wood dust acts as a respiratory irritant as the particles from the dust are likely to enter the human body by inhalation (Fritschi et al, 2006). Based on the associations recognized in the thesis studies across construction, forestry, logging, pulp and paper mill, and wood occupations (Chapters 4-6), it is relevant to investigate wood dust exposure as a potential risk factor. It is also common across furniture occupations but no associations were observed in the thesis studies between furniture occupations and risk of prostate cancer. Wood dust concentration can be assessed across different occupations to compare levels and questionnaire and interview methods can be used to assess occurrence, frequency, and level of exposure (Vallieres et al, 2015). These components can help to determine the intensity of exposure, however self-reported data are still difficult to verify without actual measurements of concentrations. Better exposure assessment methods are needed. Elevated risks in pulp and paper work were only observed in the Northeastern Ontario study (Chapter 4), with no associations observed in the other thesis studies. IARC previously evaluated pulp and paper manufacturing and lumber and sawmill industries and classified them as Group 3, meaning these industries were not classifiable in terms of carcinogenicity (IARC, 2013).

Wood preservative chemicals are another potential exposure in wood related occupations, primarily in wood treatment employment. These chemicals can be heterogeneous involving creosote, containing multiple PAHS, and pentachlorophenol (PCP) (Dahlgren et al, 2007). These toxic compounds can be expelled as low level air and dust exposures which can affect workers who are in their work environment daily. Aside from gathering reported information from workers, these toxins can also be assessed by collecting air and soil samples within and around the workplace. Also, biological blood samples can be collected from workers to analyze levels of PCP, PCBs, and polychlorinated dioxins (Dahlgren et al, 2007). Findings from these samples could then be compared to the toxic chemical reports provided by industries of interest to compare collected results to these reports. Although, potential reporting biases and quality issues in industry reports should be considered when utilizing them. Since some association was only observed in the Northeastern Ontario study (Chapter 4), and IARC did not identify pulp and paper manufacturing as carcinogenic, this may not be a priority area but it would still interesting to evaluate when investigating other wood related industries.

8.3.5 Other Exposures

Existing studies in the literature have shown limited evidence for rubber manufacturing industries and metal exposures (primarily arsenic and cadmium exposures), and these agents were also evaluated by IARC showing limited evidence for prostate cancer risk (IARC, 2017). Across two of the population studies in this thesis no associations were observed for rubber related occupations or industries or for metal related occupations or industries (Chapters 5 and 6). Findings did not support the association between prostate cancer and rubber or metal exposures, continuing to show that there is only limited evidence for these associations. As job titles involving rubber production and metal work were evaluated as surrogates for exposure, men who were directly exposed to specific metal exposures such as arsenic or cadmium could not be specifically evaluated. Future studies could explore these occupations in detail to thoroughly evaluate rubber or metal work and related exposures.

8.4 Other Occupational Factors

8.4.1 Shift Work

Shift work involving regular night or rotating shifts is common in occupations of manufacturing, health care, and accommodation (Carex Canada, 2016). However, no associations were identified between prostate cancer risk and these occupations in the thesis studies (Chapters 5 and 6). Shift work is also present in some natural resource based work, transportation, and protective services, however it has not been thoroughly investigated in these specific occupations. Evidence from IARC's evaluation in 2007 was primarily based on studies examining breast cancer in women working night shifts (Costa, 2010). But there is growing evidence that shift work is associated with increased prostate cancer risk (Rao et al, 2015) and there needs to be further investigation into specific occupations that are linked to prostate cancer risk and involve shift work. To achieve this, future studies should evaluate self-reported shift work in the identified occupations in this thesis. Information can be gathered by using workplace records to validate if the self-reported shift work information is accurate. By using these types of reported data, levels of shift work can be compared across the different jobs identified in this thesis. By comparing different occupations, this can lead to better understanding of differences in shift work by occupation and understand how this is related to prostate cancer risk.

8.4.2 Screening Behaviours

As previously discussed, men in white collar work tend to have higher education and income levels, leading to better accessibility to resources and screening than men in blue collar work (Cheng et al, 2009). As screening behaviours were challenging to interpret in the thesis studies, further understanding is needed as to whether men in white collar work adhere to screening practices. Sources could include self-reported data and hospital or physician reports. CanCHEC study findings (Chapter 6) demonstrated increased risks in some non-management level clerical and administrative jobs, similar to a recent Canadian population study by Sauve et al, 2016. Men in these non-management level jobs may not have the same income and education levels as their management counterparts and they may not necessarily have the same access and flexibility with healthcare resources. In order to understand these non-management level jobs better, similar factors in non-management and management level jobs would need to be investigated. These two groups (white collar jobs versus non-management administrative jobs) would be interesting to assess differences in influencing factors. For workplaces that involve both these groups, it would be interesting to examine the workplace health programs in place and to compare how employees in these two levels of jobs acknowledge or participate in these programs. Further evidence is also needed on differences in screening between white collar and blue collar work to thoroughly understand why there are differences by occupation. Through analysis of the CanCHEC, it was observed that men in white collar work had the highest prostate cancer rates and men in blue collar work related to construction and transportation had the lowest prostate cancer rates. Given the changes in PSA recommendations and the interpretation of these recommendations by health care providers, there is a need to study screening behaviours thoroughly by occupation. Further information is needed on actual PSA screening rates to identify if men in specific occupation groups have significant differences in screening behaviours.

8.4.3 Vitamin D and Physical Activity

Aside from potential reduced screening behaviours, reduced risks of prostate cancer in outdoor workers including construction, transportation, or natural resources, may involve the protective effects of vitamin D from increased sun exposure and increased physical activity (John et al, 2005; Krstev et al, 1998). Over 90% of circulating 25-OHD (25-hydroxyvitamin D) stems from casual sun exposure and occupational sun exposure among outdoor workers that are involved in frequent outdoor activities

(John et al, 2005). Although the existing epidemiologic evidence is still quite limited on vitamin D exposure and prostate cancer risk, further evidence is needed on vitamin D levels and sun exposure in men who work primarily outdoors, to understand their risk for prostate cancer. Also, detailed information on the frequency and duration of outdoor work involved in the identified jobs is needed while accounting for what work these men do in the winter months when there is limited sun exposure. With knowledge that increased sun exposure may increase the risk of skin cancer in outdoor workers, it is also necessary to understand if these workers use any protective measures limiting sun exposure (John et al, 2005).

Physical activity is another protective factor that is thought to decrease risk of prostate cancer. Both occupational and leisure physical activity was adjusted for in the NECSS (Chapter 5) and findings were still statistically significant with these adjustments. In the Northeastern Ontario and CanCHEC studies there was no physical activity information available so this factor was not accounted for (Chapters 4 and 6). Decreased risks in travel clerks and sports and recreation were also observed, consistent by occupation and industry in the NECSS study. This is interesting because these workers may also have higher physical activity compared to other occupations. However, no association was recognized in these workers in the CanCHEC. Based on these limited findings, further evidence is needed on both occupational and leisure physical activity to evaluate accurate occupational physical activity levels and to understand how leisure physical activity plays a role in the overall physical activity of workers. Not only is there a need to understand physical activity levels, but also other accompanying lifestyle factors such as diet and sedentary work environments in order understand these potential influencing factors.

8.4.5 Psychological Stress

Psychological stress is another factor that varies by occupation and plays a role in the development of cancer. Psychological stress can arise from everyday activities, but the main source of stress in Canadian workers is from the workplace (Crompton, 2011). Psychological stress stems from job strain which is defined as high demand and low control work (Heikkila et al, 2013). This is especially important for work that involves high stress environments, such as firefighting and police work, and where workers identify their job as a primary source of stress, like those in white collar jobs (Crompton, 2011). Previous literature on job strain has focused primarily on breast cancer, among other cancers, but the role that workplace stress plays in the development of cancer is still conflicting (Blanc-Lapierre et al, 2017). A recent meta-analysis found no association between workplace stress and the most common cancers of prostate, breast, colorectal, and lung (Heikkila et al, 2013). Important limitations of this meta-analysis and other studies on stress are that job strain was determined at baseline or only at one point in time leading to potential misclassification of levels of stress in different workplaces over time e.g. with re-organization. It is also challenging to assess carcinogenic effects from stress, as focus tends to be on other conditions related to cardiovascular or mental health. There is also often significant heterogeneity across studies that assess job stress and cancer, stemming from differences in how demand and control factors are measured (Heikkila et al, 2013; Blanc-Lapierre et al, 2017). There is a need to investigate stress across different occupations, related to the risk of prostate cancer. Assessment of stress should be based on lifetime work history to account for entire work profiles, while also considering important time periods related to stress (10 years before cancer diagnosis, at diagnosis, at follow-up), and the effects of the duration of workplace stress (Blanc-Lapierre et al, 2017).

To effectively understand how stress plays a role in different occupations, it is not only important to evaluate lifetime work history but to also assess job-related chemical exposures alongside stress (Blanc-Lapierre et al, 2017). This will provide a better illustration of work circumstances and workplace exposures that may lead to job stress. It is practical to use questionnaires and interviews to assess workplace stress and lifetime occupational history. There are issues of over-reporting and response bias with collecting these types of data, but this is common with reporting tools. Information on few known and potential prostate cancer risk factors can also influence psychological stress, and these factors should be accounted for in future studies (Blanc-Lapierre et al, 2017). This will provide a unique understanding of workplace stress, while ensuring that other potential factors related to both stress and prostate cancer are considered.

8.5 Knowledge Translation and Communication

Most men spend a third of their adult life in work hours which not only impacts societal and economic growth, but also affects the well-being and health of these working men (WHO, 1994). Moreover, as little is known on prostate cancer risk factors and prevention, there is a need to provide better knowledge translation and communicate workplace risks to those at risk for prostate cancer. Results from the four studies are not only significant for researchers and academics, but also for workplace health and safety representatives, occupational hygienists and physicians, policy makers, and primarily for the men employed in the identified occupations in Chapters 4 to 7. Findings in this thesis are preliminary and will lead to future investigations on understanding the relationship between occupation and prostate cancer to identify specific exposures and other non-occupational factors. Investigating the relationship between occupation and prostate cancer further can influence decisions around workplace health. Identified exposures and associations can lead to improved workplace health and safety to control or reduce exposure levels. This could also help inform not only occupational physicians but also general practitioners involved in the health of men employed in the identified occupations. Ultimately, improved evidence and understanding of occupations associated to prostate cancer can lead to changes in workplace compensation. In Ontario, the Workplace Safety and Insurance Board (WSIB) provides workers compensation coverage. WSIB benefits both the workers and employers by providing detailed guidelines for compensation based on the specific injury, illness, or occupation. Recently, both Ontario and British Columbia have added prostate cancer to the list of occupational diseases that are presumed to be related to firefighting (British Columbia Workers Compensation Act, 2017; WSIB, 2017). Individuals who have worked at least 15 years in firefighting are eligible in both provinces for compensation through their workplace compensation board. These workers are eligible for workers' compensation benefits without requiring evidence that their diagnosis of prostate cancer is work-related.

Alongside improvements in workplace health, there needs to be better communication to understand and provide knowledge to employed men at risk of prostate cancer. There are common barriers involved in addressing workplace health in men. There are differences in how men individually deal with their health concerns and how they approach health resources, as they are less likely to seek out care compared to women (Ross et al, 2011). Personal factors such as demographic related issues, socioeconomic status, family history and genetic history, language, personal beliefs, and current health status can affect how men perceive prostate cancer risk (Ross et al, 2011). There are also health resource factors involved such as the structure, delivery, accessibility, and availability of health care. Additionally, there are also issues related to prostate cancer involving differences in screening recommendations and in information dissemination (Ross et al, 2011). Although prostate cancer screening has changed rapidly over the years and there are varying recommendations publically available, there is still a lack of consistent information and strategies for prostate cancer prevention. Without knowledge and understanding on prostate cancer etiology, it can be challenging for employed men to make informed decisions on prostate cancer prevention, screening, and diagnostic information (Ross et al, 2011). This is why knowledge translation is particularly important for prostate cancer. Better understanding of exposures and risk factors can lead to stronger evidence, which can provide health professionals and men with the most up to date and accurate information on prevention. The Canadian Cancer Society (CCS) provides up to date and detailed information on all causes of prostate cancer, including potential occupational risk factors. CCS has included pesticides, cadmium, and chemicals in rubber manufacturing as possible risk factors for prostate cancer, which is widely available on their website (Canadian Cancer Society, 2016). With increasing evidence for the association between occupation and prostate cancer, it is important for organizations like CCS to provide up to date evidence that is publically available.

Prevention is especially important for men who are considered to be at high risk for prostate cancer and for men who are less likely to have access to prostate cancer services. Men are at a higher risk based on older age, having a family history of prostate cancer, and if they are of African American descent (Canadian Cancer Society, 2015). Research has shown that there is a lack of information dissemination among high risk men, which is contradictory since these men are at a higher risk and should receive more information on prevention and resources than men not at high risk (Ross et al, 2011). Knowledge translation and communication are equally important for men who are less likely to seek our prostate cancer information and resources based on a number of factors. Men with lower socioeconomic status (lower income and education) may be limited in resources with less accessibility and utilization of medical services (Zeegers et al, 2004). With limited resources, these men are less likely to benefit from prostate knowledge and information, detection, and treatment (Liu et al, 2001). Our studies and previous literature have shown that men employed in blue collar jobs had lower prostate cancer incidence rates than other occupations, which may be indicative of limited access to prostate cancer resources (Peters et al, 2016; Sritharan et al, 2018). These high risk groups should be a priority area for prevention, in order to focus on how to reduce their risk of prostate cancer. By communicating prostate cancer knowledge and evidence effectively, there can be better utilization of prevention strategies especially for men at high risk or for men with limited availability of resources.

8.6 Strengths and Limitations

8.6.1 Strengths

There are significant overarching strengths that span across the major study chapters (4-7) in this thesis. This thesis presents findings on prostate cancer, an often understudied area with limited understanding for risk factors and prevention. A major strength of this thesis was the utilization and availability of prostate cancer data, allowing for increased evidence and better understanding of risk factors for prostate cancer. Findings from this thesis provide strong evidence on occupation associated to prostate cancer, addressing gaps in knowledge. This thesis also addresses both known and potential risk factors related to prostate cancer that are both occupational and non-occupational. With prostate cancer being the second most common cancer diagnosis in Canadian men and risk significantly increasing with age, the studies in this thesis are important in providing evidence that is aimed at prostate cancer prevention.

Another major strength of this thesis was the use of available studies spanning across Canada. There are very few population based studies in Canada that have information on prostate cancer and occupation and one of the important strengths of this thesis was the ability to obtain multiple large Canadian population studies on prostate cancer and occupation. These population studies also had the advantage of including multiple covariates for analysis related to occupational and non-occupational factors which was necessary for each of the analyses in this thesis. Having large Canadian population datasets available for analysis is lower cost and allows for time sensitive analyses with use of different approaches (Cheng et al, 2014). With the availability of existing data, there was more time to prepare, clean, and organize the data, with efficient and consistent analysis. All three population studies in this thesis were comparable and representative of the Canadian population, adding to the limited literature specific to Canada. Different types of studies were included in this thesis - two case-control studies, one cohort study, and a meta-analysis. In occupational epidemiology, case-control and cohort studies are among the strongest types of studies, providing the strengths of having prostate cancer cases and controls and a cohort where prostate cancer develops in some participants over time (Checkoway et al, 2007; Song & Chung, 2011). An important strength of the case-control studies, unlike the cohort in this thesis, was the availability of lifetime occupational history. This information provides concise and detailed job title information on all jobs the participants held in their lifetime, which can act as potential exposure surrogates and allows for more accuracy with exposure groups. Lifetime occupational history can improve the strength of association between occupation groups and prostate cancer risk as it provides information on duration of employment. The meta-analysis approach provided a sound, epidemiological evaluation of existing studies. It was unique in that it provided an update of previous firefighter meta-analyses but also is the only published meta-analysis to look at both firefighting and police work and prostate cancer risk.

Another significant strength of this thesis was the consistency observed across the three population studies. Findings across the three studies are important for Canada and prostate cancer research as evidence was shown for major occupation groups with understanding on non-occupational factors potentially linked to prostate cancer. Consistency in findings provides stronger evidence from across Canada, which strengthens existing evidence and provides new areas where future research should focus. The three population studies led to the targeted meta-analysis on protective services occupations and prostate cancer, which further indicates where future investigations should focus. These studies also showed consistency in identification of non-occupational factors related to socioeconomic status and screening, placing importance on the need to investigate these factors further.

8.6.2 Limitations

There are also limitations involved in this thesis approach. A common limitation in using existing data is that the design of the existing questionnaires used in the studies cannot be modified or adjusted. (Cheng et al, 2014). Another limitation in using existing data is that the specific nuances with the data that involved the original researchers may not be known during secondary analysis (Cheng et al, 2014). However, the existing data used across the thesis chapters were analyzed in collaboration with the original researchers which contributed to understanding of study specific issues or nuances. Studies in this thesis also lacked in-depth exposure assessment which has emerged as an important part of occupational epidemiology. However, more in-depth exposure assessment is quite difficult to achieve with prostate cancer given the limited evidence for what exposures are linked to prostate cancer and the limitations in exposure methods. Further assessment of exposures is possible by using a job exposure matrix but this requires pinpointing what exposures are the most relevant, increased time and funding, and the availability of appropriate quantification methods. Without appropriate exposure assessment, it can be difficult to understand the underlying mechanisms involved in the exposure-outcome relationship. The studies in this thesis could not advance understanding on what specific mechanisms are involved in occupational risk factors and prostate cancer risk, although common mechanisms are proposed.

All three of the population studies and most epidemiologic population studies use reported job titles as surrogates for potential exposures which is another limitation in this thesis. Job title information can be difficult to interpret if the jobs are broadly categorized or if exposures are highly variable across different jobs (Sun et al, 2003). This can be especially difficult if job titles are categorized using different classification systems or tools. In the thesis studies, the most detailed job titles available and similar classification systems were used to allow for comparability across the studies. The same classification systems were used in the Northeastern Ontario and CanCHEC studies in Chapters 4 and 6 (SIC 1991 and SOC 1980), and an updated classification system was used in the NECSS study in Chapter 5 (NOC-S-2006 and NAICS 2002). Although there are differences in job title coding for Chapter 5, the re-categorization of job titles based on the most detailed 4-digit coding provided similar groupings for both classification systems. The re-categorization of job titles ultimately ensured that each specific job title was carefully evaluated in each of the three studies to overcome the limitations of using job title information.

Multiple testing is often recognized as a limitation in large studies that examine multiple job titles, leading to chance findings and increased false positives. Some studies in the literature have used approaches such as the Bonferroni method to provide conservative estimates, ultimately reducing the number of false positives. However, this method can be too conservative and may actually increase the number of false negative findings. For the purpose of this thesis, multiple testing was used to examine many different job groups and observe patterns across multiple Canadian datasets. The studies in this thesis were used to understand how occupation and prostate cancer are related and what groups showed similar patterns of risk. Given that findings were consistent across the three studies in this thesis and given that findings were consistent to other published literature, multiple testing may not have been a significant limitation in this thesis.

Other limitations included the lack of screening behavior information and detailed prostate cancer information (ex. aggressiveness measured by the Gleason score) across all studies in this thesis. Although these issues could not be assessed in the Northeastern Ontario Study (Chapter 4), these issues were investigated in the NECSS and CanCHEC (Chapters 5 and 6). In the NECSS, variables such as age, family history of prostate cancer, ethnicity, marital status, and socioeconomic status (education and income) were accounted for to try to adjust for potential factors related to screening behaviours. In the CanCHEC, the age-standardized rates were calculated to understand screening patterns by occupation group over time. Findings from both these studies provided some insight into screening behaviours but were difficult to interpret in detail. Through Chapter 7, the meta-analysis showed little evidence for screening bias as incidence and mortality estimates in protective services occupations were quite similar, warranting the need for further understanding on screening practices in these occupations. The strategies used in these thesis chapters helped to understand screening issues related to prostate cancer, but further investigation is necessary on actual screening rates in employed men to validate findings. Aggressiveness of prostate cancer using the Gleason score has been rarely assessed in past occupational studies, including the studies in these thesis because of limited information on prostate cancer diagnosis. Very few Canadian studies could thoroughly assess aggressiveness using the Gleason score (Sauve et al, 2016) and have shown that there may be differences in occupation by aggressiveness of prostate cancer but further investigation is needed. Overall, there were similar limitations observed across the four core studies, which can be overcome in future approaches by including detailed prostate cancer information (Gleason score), actual screening status or screening history, job specific information, and thorough exposure assessment.

8.7 Contribution to the Literature

The results from this thesis provide important consistent evidence on occupation associated to prostate cancer risk and build upon evidence from previous studies. Although the mechanism of how these occupations and their exposures are linked to prostate cancer is not entirely known, there is an important link between the type of occupation(s) one holds and their risk for prostate cancer. Strong evidence was observed for specific occupations related to administrative, natural resources (specifically agriculture), construction and transportation, and protective services. With knowledge that these types of occupations are likely linked to prostate cancer risk, further communication and prevention strategies should be put forth. This is not only important for the health of employed men, but also for specific communities that rely on major industries such as Northern Ontario. With improved knowledge on occupational risks and better communication of findings - researchers, health and safety practitioners, and clinicians can work together to understand occupational risk factors for prostate cancer. This can lead to appropriate reporting of occupational factors and changes in the workplace, ultimately leading to better prostate cancer prevention strategies.

Findings from this thesis demonstrate that the relationship between occupation and prostate cancer is complex, involving multiple non-occupational factors such as age, family history of prostate cancer, ethnicity, socioeconomic status, and screening behaviours. This relationship is also influenced by job-specific exposures which are overlapping and quite heterogeneous across occupations, adding to the difficulty of teasing a-part specific exposure data. Future studies should focus on using appropriate exposure assessment methods in the identified occupations to pinpoint exactly what exposures are involved, while considering known and potential factors associated with prostate cancer. Potential occupational exposures/factors to focus on in future studies are pesticides, diesel exhaust, whole body vibrations, wood dust/chemicals, and shift work, while also considering factors of stress and sedentary behaviour. This will help to understand the specific exposures involved in these occupations and strengthen the evidence for occupational risk factors for prostate cancer. This thesis provides valuable Canadian research that strengthens the understanding on the occupational etiology of prostate cancer and provides direction for future research. As prostate cancer will continue to be a significant disease among aging men, there will always be a need to understand the etiology of prostate cancer.

Chapter 9. Conclusions

The four connected studies in this thesis explore the occupational etiology of prostate cancer and contribute to the overall understanding of risk factors for prostate cancer. This thesis provides new and supporting evidence for the association between occupation and prostate cancer, while highlighting the complexity of prostate cancer and associated risk factors. The results of this thesis show that specific occupations are associated with prostate cancer risk and provide consistent associations that strengthen and support some of the results from previous studies. There was consistency in associations between administrative, natural resource based work, construction, transportation, and protective services occupations and prostate cancer risk. Firefighting and police work, in particular, were found to be associated with a slight excess risk of prostate cancer as a meta-risk estimate, indicating the importance of further study in these protective services groups.

Findings from this thesis illustrate the importance of job-specific exposures that overlap many of the identified occupations. Exposures such as pesticides, diesel exhaust, whole body vibrations, wood dust and chemicals, require further investigation using improved exposure assessment methods. Furthermore, other non-chemical factors in this thesis have been shown to influence the relationship between occupation and prostate cancer risk. Factors related to shift work, physical activity and sedentary behaviour, psychological stress, and importantly, screening behaviours are essential to consider in future prostate cancer research. Even though there were limitations in this thesis related to reporting of exposures and other factors, this thesis has provided valuable insight on these factors showing that these factors play an important role in prostate cancer risk. With better understanding of these factors, the current evidence stemming from this thesis and existing literature can be strengthened. Given that prostate cancer will continue to be an important form of cancer among men worldwide, and given that there are still no established preventable risk factors, this thesis is important in providing stronger evidence and knowledge into the occupational etiology of prostate cancer.

Chapter 10. Future Directions

As this thesis has provided improved understanding on the occupational etiology of prostate cancer, significant research questions have also surfaced from each study in this thesis, with overlapping themes that should be investigated in future studies. Two important themes that should be addressed in future studies are exposure assessment and screening behaviours. The studies in this thesis identified consistent patterns between prostate cancer risk and specific occupation groups that have identifiable exposures. Future exposure assessment studies can use these identified occupations to investigate related exposures using validated exposure assessment methods. Exposure assessment requires feasible and time consuming tools and resources, but by achieving valid and reliable exposure assessment, associations observed in the thesis studies could be better understood. The studies in this thesis had limited detailed prostate cancer screening information as well. Future studies should evaluate actual screening patterns by retrieving information through linked physician/clinic data or self-reported data. There may be limited data available on PSA tests done in the physician’s office but this information would be useful to understand how many men are actually screened, the age at which they began screening, and if they have been advised by their primary physician to get screened. Further understanding is also needed on if screening recommendations and screening behaviours changed over time in employed men, given the controversy and conflicting recommendations around PSA testing and the lack of specificity from PSA testing. Also, very few studies in the past were able to account for prostate cancer grade using the Gleason score or were able to provide specific information related to prostate cancer diagnosis when looking at occupation (Sauve et al, 2016). These limitations were present in this thesis and should be addressed in future studies. Specific future directions related to each thesis study is discussed in the following sections.

The first study of this thesis presented detailed findings on prostate cancer risk based on occupations and industries common in the Northeastern Ontario region. The findings are reflective of the natural resource based occupations and industries that were prominent in Northern Ontario, related to economic and population growth (Statistics Canada, 2006). However, since the 1990s there has been a decline in employment in blue collar work and in population density in Northern Ontario (Southcott, 2008; Di Matteo, 2017). Given the changes in employment and population, it would be interesting to examine prostate cancer in natural resource based industry workers in Northern Ontario in the current time period to understand if prostate cancer risk patterns are consistent. Prostate cancer risk in this region can be examined with exposure assessment and prostate cancer screening behaviours, which was not done in Chapter 4. Ideally, a cohort study could be applied to examine men employed in natural resource based occupations to identify men diagnosed with prostate cancer with additional information on prostate cancer grade. The lifetime occupational history of these all men in the cohort would need to be collected to understand the duration and time of employment in natural resource based occupations. Exposure assessment methods would need to be used within the workplaces of natural resource based occupations to examine prominent exposures of pesticides, diesel exhaust, whole body vibrations, and wood dust. Men employed in natural resource based occupations who are diagnosed with prostate cancer can then be compared to employed men (in similar occupations and in other occupations) who were never diagnosed with prostate cancer or had no history of prostate cancer. Information on the screening behaviours of all men in the study would need to be collected to account for screening bias in both cases and non-cases. In order to achieve this, screening behaviour information can be collected by interviewing the participants, and then verifying their responses by examining their health records. The following are important research questions to address:

- *Are men who are employed or were employed in natural resource based occupations in Northern Ontario currently exposed or previously exposed to pesticides, diesel exhaust, whole body vibrations, and wood dust in the workplace? If so, what is the duration, frequency, and intensity of these exposures?*
- *Are men who are employed or were employed in natural resource based occupations in Canada more likely to seek out prostate cancer screening than men in other occupations? Do their screening patterns differ from men in other occupations?*
- *Do associations between natural resource based occupations and prostate cancer differ by prostate cancer grade measured by the Gleason score? Were men who were diagnosed with a higher grade of prostate cancer more likely to have worked in natural resource based occupations than men with low grade prostate cancer?*

Findings in the second and third studies of this thesis (Chapters 5-6) show there are clear differences in occupations that are associated with prostate cancer risk. There was strong evidence for white collar, natural resource based, construction and transportation, and protective services occupations in the two studies. These findings, when compared to other recent studies with similar findings, indicate the importance of acknowledging multiple covariates involved in the relationship between occupation and prostate cancer risk. This includes demographic information and lifestyle factors, among occupational factors. Chapters 4-6 show the importance of including confounders of age, ethnicity, and family history of prostate cancer and future studies should continue to include these factors. Other screening related factors should also be considered, along with actual screening rates of participants. The studies in this thesis had limited information on these factors, but with feasible funding and time, these factors could be investigated in depth. More time and funding to appropriately link the datasets, clean and organize variables, and analyze the data would be necessary.

A large prostate cancer cohort study could be initiated or created through linked databases to include a multitude of important factors described in this thesis and one that has a long follow-up period given the long latency period for prostate cancer. The established cohort study should include a large Canadian sample size with the focus solely on prostate cancer risk factors and outcomes of incidence and mortality. This approach would be similar to the recent large Montreal case-control study by Marie-Elise Parent and co-investigators known as "*Case-control study of environmental, occupational, lifestyle factors and genetic susceptibility biomarkers in the etiology of prostate cancer*". The Montreal study includes an abundance of information on multiple prostate cancer covariates, screening history, and biomarkers; it is however limited to only the Montreal region. Replicating this type of study with a cohort design in a larger population would require increased funding, time, and resources, but by doing so, important questions that emerged from this thesis and re-occurring study themes could be further evaluated. An interview and questionnaire process to collect information on detailed occupational history and prostate cancer screening behaviours of participating men could be used. Linked information, similar to CanCHEC, from census data or other large cohorts (e.g. Canadian Partnership for Tomorrow Project), tax summary files, cancer registries, and mortality data could aid in retrieving all necessary information on population participants and prostate cancer outcomes. Detailed information from the data sources such as demographic information from census or population data, migration and residential information from the tax summary files, detailed prostate cancer diagnosis information from the cancer registries, and cause of death information from mortality data would be valuable. These different datasets could also be linked to existing cohorts that already capture a large population. The linked data would strengthen and verify the accuracy of information collected from questionnaires and solely focus on prostate cancer. The large cohort study could be used to address the following questions:

- *Are Canadian men in white collar, natural resource based, construction, transportation, and protective services occupations more likely to have been screened for prostate cancer in their lifetime or while employed in any of these occupations?*
- *Are there differences in grade of prostate cancer measured by the Gleason score, in diagnosed men who are employed or were employed in white collar, natural resource based, construction, transportation, and protective services occupations?*
- *Are demographic factors of income and education associated with the occupations of Canadian men, and in turn, are these factors linked to their prostate cancer screening behaviours?*
- *With recent PSA changes, did screening practices in men in white collar, natural resource based, construction, transportation, and protective services occupations change over different time periods of pre and post PSA periods?*

The fourth study (Chapter 7), a meta-analysis, was performed to address the associations observed in protective services in recent studies, including the three studies in this thesis. The meta-analysis conducted was the first to include both firefighting and law enforcement. Based on our findings, it is necessary to continue investigation into potential chemical and non-chemical exposures involved in firefighting and police work. Firefighters, in particular, are exposed to multiple exposures with varying duration and frequency levels and further understanding is needed. Appropriate exposure assessment with relevant monitoring and sampling tools are needed to capture exposures in the work environments of firefighters. In contrast, men in police work are exposed to very few chemical exposures, primarily diesel exhaust, and there is still a need to understand and assess this exposure further.

Aside from chemical exposures, lengthy and detailed employment history from each participant based on employment records and through in-person interviews is needed. This information can be helpful to classify different types of firefighters and police workers based on their specialization, frequency and duration of the job, and work hours. Other factors such as shift work and stress require reported information can be collected through an interview. For shift work, responses could be compared to their respective detailed employment history for verification. Psychological stress would also need to be assessed thoroughly and may even require a separate tool to evaluate this alongside job-specific exposures. The exposure assessment would go in hand with a questionnaire and interview process to strengthen the accuracy of captured exposures on the job. Also, data would need to be collected on prostate cancer screening history from their primary physician or hospital records and retrieve detailed information on prostate cancer diagnosis to identify men who were diagnosed and men who are non-cases. With screening history, information on grade of tumours in men who were diagnosed with prostate cancer could be retrieved. This would help to understand the relationship between high grade and low grade prostate cancer and occupation. These different elements can be captured through different study designs, particularly with a case-control or cohort approach to target different questions and to overcome shortcomings in these different study designs. Important questions to address in firefighting and police work include:

- *What chemical exposures (by duration and frequency) are involved in firefighting?*
- *Are men in police work exposed to diesel exhaust? How often are they exposed (duration and frequency)?*
- *Do men in firefighting and police work seek or receive prostate cancer screening as recommended in Canada?*
- *Are there differences by prostate cancer grade, measured by the Gleason score, among diagnosed men who are employed in firefighting or police work?*
- *Do men in firefighting and police work perceive their risk from stress and shift work on the job? How does psychological stress and shift work differ across these two protective services groups?*

The meta-analysis in this thesis did not include military workers but this occupation is another important protective services groups that needs to be further assessed. The thesis studies did show increased risks in military workers and there is a need to understand what types of complex exposures are involved in this occupation. Using a cohort study, military workers in Canada can be followed to identify exposures in their work environment, among other non-chemical factors (shift work, stress), and prostate cancer risk. It would be ideal to do the military study separate from firefighting and police work, as Canadian military workers have not been exclusively studied for prostate cancer risk before. Further understanding on how military workers perceive risk of prostate cancer is important, while also assessing if they recognize prostate cancer screening as a priority. Perceived risks from military worker participants can be compared to their respective screening history which can be collected through self-reported or physician data. Similar approaches mentioned in firefighting and police work would be used to assess men in the military. By collecting this information the following questions could be addressed:

- *What chemical exposures (by duration and frequency) are involved in military work?*
- *Do military workers seek or receive prostate cancer screening as recommended in Canada?*
- *Are there differences by prostate cancer grade, measured by the Gleason score, among diagnosed men who are employed in military work?*
- *Do military workers perceive their risk from stress and shift work on the job? How does psychological stress and shift work differ across these three protective services occupations?*

Additional meta-analyses could also be conducted to assess occupational groups that have shown inconsistent associations in the thesis studies. Specifically, construction and transportation occupations are groups that continued to show mixed findings in the thesis studies and in previous studies. Using a meta-analysis to evaluate construction and transportation occupations could provide strong evidence identifying if positive or negative associations exist collectively across studies. The following questions could be addressed in a future meta-analysis:

- *Are construction and transportation workers at an increased risk for prostate cancer incidence and mortality?*
- *Are there differences in prostate cancer risk by type of construction or transportation job title? Are there differences in prostate cancer risk by duration of employment in these jobs?*

By investigating both occupational and non-occupational factors described in these future directions, occupational groups associated with prostate cancer risk can be confidently identified, while also accounting for other commonly occurring factors. This is an exceedingly important area for future research as prostate cancer risk significantly increases with increasing age and given the increased life expectancy, prostate cancer will continue to be a concern (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2015). The suggested future directions are not only applicable to Canada, but also to other industrialized nations that have high prostate cancer rates. Findings in industrialized nations can also be compared to nations with low prostate cancer rates, to understand how factors affecting prostate cancer differ by nation (Kimura, 2012). By understanding these issues with prostate cancer, there can be improved substantial evidence on risk factors, prevention, and understanding of prostate cancer screening impacts. Findings would steer future research to better understand the etiology of prostate cancer.

References

‘t Mannetje A & Kromhout H. (2003). The use of occupation and industry classifications in general population studies. International Journal of Epidemiology, 32(3): 419-428.

Agency for Toxic Substances & Disease Registry. (2014). Polychlorinated biphenyls (PCBs) toxicity, what are routes of exposure for PCBs? ATSDR; Atlanta: USA. https://www.atsdr.cdc.gov/csem/csem.asp?csem=30&po=6 (accessed November 30, 2016)

Ahn YS, Jeong KS & Kim KS. (2012). Cancer morbidity of professional emergency responders in Korea. American Journal of Industrial Medicine, 55: 768-778.

Akhtar FZ, Garabrant DH, Ketchum NS & Michalek JE. (2004). Cancer in the US air force veterans of the Vietnam war. Journal of Occupational and Environmental Medicine, 46(2): 123-136.

Alavanja MC, Sandler DP, Lynch CF, Knott C, Lubin JH, Tarone R, Thomas K, Dosemeci M, Barker J, Hoppin JA & Blair A. (2005). Cancer incidence in the Agriculture Health Study. Scandinavian Journal on Work, Environment, and Health, 31(Suppl 1): 39-45.

Alavanja MCR, Blair A, Merkle S, Teske J, Eaton B, & Reed B. (1989). Mortality among forest and soil conservationists. Archives of Environmental Health, 44(2): 94-101.

Alavanja MCR, Samanic C, Dosemeci M, et al. (2003) Use of agricultural pesticides and prostate cancer risk in the agricultural health study cohort. American Journal of Epidemiology, 157(9): 800-814.

Albright F, Stephenson RA, Agarwal N, Teerlink CC, Lowrance WT, Farnham JM & Albright LAC. (2015). Prostate cancer risk prediction based on complete prostate cancer family history. Prostate, 75(4): 390-398.

Allot EH, Masko EM & Freedland SJ. (2013). Obesity and prostate cancer: weighing the evidence. European Urology, 63(5): 800-809.

American Cancer Society. (2015). Prostate cancer overview. American Cancer Society. Accessed on October 14, 2016 from http://www.cancer.org/acs/groups/cid/documents/webcontent/003072-pdf.pdf (accessed February 8, 2017)

American Cancer Society. (2016). What causes prostate cancer? American Cancer Society. Accessed on October 13, 2016 from http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-what-causes (accessed February 8, 2017)

Andriole GL, Crawford ED, Grubb RL, Buys SS, Chia D, Church TR et al. (2009). Mortality results from a randomized prostate-cancer screening trial. The New England Journal of Medicine, 360: 1310-1319.

Andriole GL, Crawford ED, Grubb RL, Buys SS, Chia D, Church TR et al. (2012). Prostate cancer screening in the randomized prostate, lung, colorectal, and ovarian cancer screening trial: mortality results after 13 years follow up. Journal of the National Cancer Institute, 104(2): 125-132.

Araki H, Watanabe H, Mishina T & Nakao M. (1983). High-risk group for benign prostatic hypertrophy. Prostate, 4(3): 253-64.

Armed Forces Health Surveillance Center. (2012). Incidence diagnoses of cancers and cancer-related deaths, active component, U.S. armed forces, 2000-2011. Medical Surveillance Monthly Report, 19(6): 18-22.

Aronson KJ, Howe GR, Carpenter M & Fair ME. (1999). Surveillance of potential associations between occupations and causes of death in Canada, 1965-91. Occupational and Environmental Medicine, 56(4): 265-269.

Aronson KJ, Siemiatycki J, Dewar R & Gerin M. (1996). Occupational risk factors for prostate cancer: results from a case-control study in Montreal, Quebec, Canada. American Journal of Epidemiology, 143(4): 363-373.

Aronson KJ, Siemiatycki J, Dewar R & Gérin M. (1996). Occupational risk factors for prostate cancer: results from a case-control study in Montréal, Québec, Canada. American Journal of Epidemiology, 143(4):363-73.

Aronson KJ, Tomlinson GA & Smith L. (1994). Mortality among fire fighters in metropolitan Toronto. American Journal of Industrial Medicine, 26: 89-101.

Augustsson K, Michaud DS, Rimm EB, Leitzmann MF, Stampfer MJ, Willet WC & Giovannucci E. (2003). A prospective study of intake of fish and marine fatty acids and prostate cancer. Cancer Epidemiology Biomarkers & Prevention, 12(1): 64-7.

Bairati I, Larouche R, Meyer F, Moore L & Fradet Y. (2000). Lifetime occupational physical activity and incidental prostate cancer (Canada). Cancer Causes Control, 11(8): 759-64.

Ballard T, Lagorio S, De Angelis G & Verdecchia A. (2000). Cancer incidence and mortality among flight personnel: a meta-analysis. Aviation, Space, and Environmental Medicine, 71(3): 216-224.

Band PR, Abanto Z, Bert J, Lang B, Fang R, Gallagher RP & Le ND. (2011). Prostate cancer risk and exposure to pesticides in British Columbia farmers. Prostate, 71: 168-183.

Band PR, Le ND, Fang R, Deschamps M, Coldman AJ, Gallagher RP & Moody J. (1996). Cohort study of air Canada pilots: mortality, cancer incidence, and leukemia risk. American Journal of Industrial Medicine, 143(2): 137-143.

Band PR, Le ND, Fang R, Threlfall WJ & Gallagher RP. (1999). Identification of occupational cancer risks in British Columbia. Part II: A population-based case-control study of 1516 Prostatic cancer cases. Journal of Occupational & Environmental Medicine, 41(4):233-47.

Baris D, Garrity TJ, Telles JL, Heineman EF, Olshan A & Zahm SH. (2001). Cohort mortality study of Philadelphia firefighters. American Journal of Industrial Medicine, 39: 463-476.

Barry KH, Koutros S, Lubin JH, Coble JB, Barone-Adesi F, Beane Freeman LE, Sandler DP, Hoppin JA, Ma X, Zheng T & Alavanja MCR. (2012). Methyl bromide exposure and cancer risk in the agriculture health study. Cancer Causes and Control, 23(6): 807-818.

Bashir MN. (2015). Epidemiology of prostate cancer. Asian Pacific Journal of Cancer Prevention, 16: 5137-5141.

Bates MN, Fawcett J, Garrett N, Arnold R, Pearce N & Woodward Al. (2001). Is testicular cancer an occupational disease of fire fighters? American Journal of Industrial Medicine, 40: 263-270.

Bates MN. (2007). Registry-based case-control study of cancer in California Firefighters. American Journal of Industrial Medicine, 50:339-344.

Bax L, Ikeda N, Fukui N, Yaju Y, Tsuruta H & Moons KGM. (2009). More than numbers: the power of graphs in meta-analysis. American Journal of Epidemiology, 169(2): 249-255.

Beaulac JA, Fry RN & Onysko J. (2006). Lifetime and recent prostate specific antigen (PSA) screening of men for prostate cancer in Canada. Canadian Journal of Public Health, 1-6.

Beaumont JJ, Chu GST, Jones JR, Schenker MB, Singleton JA, Plantanida LG & Reiterman M. (1991). An epidemiologic study of cancer and other causes of mortality in San Francisco firefighters. American Journal of Industrial Medicine, 19: 357-372.

Begg CB & Mazumdar M. (1994). Operating characteristics of a rank correlation test for publication bias. Biometrics, 50(4): 1088-1101.

Beral V, Inskip H, Fraser P, Booth M, Coleman D & Rose G. (1985). Mortality of employees of the United Kingdom atomic energy authority, 1946-1979. British Medical Journal (Clinical Research Ed), 291(6493): 440-447.

Bertin G & Averbeck D. (2006). Cadmium: cellular effects, modifications of biomolecules, modulation of DNA repair and genotoxic consequences (a review). Biochimie, 88; 1549-1559.

Blanc-Lapierre A, Rousseau MC, Weiss D, El-Zein M, Siemiatycki J & Parent ME. (2016). Lifetime report of perceived stress at work and cancer among men: a case-control study in Montreal, Canada. Preventative Medicine, 96: 28-35.

Boers D, Zeegers MPA, Swaen GM, et al. The influence of occupational exposure to pesticides, polycyclic aromatic hydrocarbons, diesel exhaust, metal dust, metal fumes, and mineral oil on prostate cancer: a prospective cohort study. Occupational and E

Boivin DB & Boudreau P. (2014). Impacts of shift work on sleep and circadian rhythms. Pathologie Biologie, 62: 292-301.

Bollman RD, Beshiri R & Mitura V. (2006). Northern Ontario’s communities: economic diversification, specialization, and growth. Ottawa: Statistics Canada. http://www.statcan.gc.ca/pub/21-601-m/21-601-m2006082-eng.pdf (accessed November 2015)

Born J, Hawes R & Whitehead J. (2010). Results from the health and lifestyle information survey of Canadian forces personnel 2008/2009. Ottawa, ON: Department of National Defense. http://publications.gc.ca/collections/collection_2011/dn-nd/D2-293-2010-eng.pdf (accessed January 19, 2017)

Botelho F, Pina F, Figueiredo L, Cruz F & Lunet N. (2012). Does baseline total testosterone improve the yielding of prostate cancer screening? European Journal of Cancer, 48(11): 1657-1663.

Bouchardy C, Schuler G, Minder C, Hotz P, Bousquet A, Levi F, Fisch T, Torhorst J & Raymond L. (2002). Cancer risk by occupation and socioeconomic group among men – a study by the association of swiss cancer registries. Scandinavian Journal of Work, Environment & Health, 28 Suppl: 1: 1-88.

Bratt O, Garmo H, Adolfsson J, Bill-Axelson A, Holmberg L, Lambe M & Stattin P. (2010). Effects of prostate-specific antigen testing on familial prostate cancer risk estimates. Journal of the National Cancer Institute, 102(17): 1336-1343.

Brice A, Jean-Luc M, Frederic M, Stephane D, Gaelle C, Simone MP, Christian L, Ellen I & Patrick B. (2015). French firefighter mortality: analysis over a 30-year period. American Journal of Industrial Medicine, 58: 437-443.

British Columbia Workers Compensation Act. (2017). Firefighters' occupational disease regulation. Victoria, British Columbia. http://www.bclaws.ca/Recon/document/ID/freeside/11_125_2009 (accessed March 2, 2018).

Brownson RC, Chang JC, Davis JR & Bagby JR. (1988). Occupational risk of prostate cancer: a cancer registry-based study. Journal of Occupational Medicine, 30(6): 523-526.

Bruschweiler ED, Danuser B, Huynh CK, Wild P, Schupfer P, Vernez D, Boiteux P & Hopf NB. (2012). Generation of polycyclic aromatic hydrocarbons (PAHs) during woodworking operations. Frontiers in Oncology, 2(148): 1-8.

Buja A, Lange JH, Perissinotto E, Rausa G, Grigoletto F, Canova C & Mastrangelo G. (2005). Cancer incidence among male military and civil pilots and flight attendants: an analysis on published data. Toxicology and Industrial Health, 21(10): 273-282.

Buxton JA, Gallagher RP, Le ND, Band PR & Bert JL. (1999). Occupational risk factors for prostate cancer mortality in British Columbia, Canada. American Journal of Industrial Medicine, 35(1): 82-86.

Bylsma LC & Alexander DD. (2015). A review and meta-analysis of prospective studies of red and processed meat, meat cooking methods, heme iron, heterocyclic amines and prostate cancer. Nutrition Journal, 14: 125.

Caini S, Gandini S, Dudas M, Bremer V, Severi E & Gherasim A. (2014). Sexually transmitted infections and prostate cancer risk: a systematic review and meta-analysis. Cancer Epidemiology, 38(4): 329-38.

Caldwell E. (2011). Building capacity for northern Ontario agriculture. Sault Ste. Marie, Canada: Innovation Centre. http://www.fonom.org/sites/default/files/4%20May%209%20-%201020am%20RAIN.pdf (accessed November 2015)

Canadian Cancer Society's Advisory Committee on Cancer Statistics. (2015). Canadian Cancer Statistics 2015, special topics: predictions of the future burden of cancer in Canada. Toronto, ON: Canadian Cancer Society.
https://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2015-EN.pdf (accessed February 15, 2017)

Canadian Cancer Society. (2015). Prostate cancer statistics. Toronto, Canada: Canadian Cancer Society. http://www.cancer.ca/en/cancer-information/cancer-type/prostate/statistics/?region=on (accessed June 16, 2016)

Canadian Cancer Society. (2017). Prostate cancer statistics. Toronto, Canada: Canadian Cancer Society. http://www.cancer.ca/en/cancer-information/cancer-type/prostate/statistics/?region=on (accessed June 6, 2017)

Canadian Cancer Society. (2016). What is prostate cancer? Toronto, Canada: Canadian Cancer Society. http://www.cancer.ca/en/cancer-information/cancer-type/prostate/prostate-cancer/?region=on (accessed on October 14, 2016)

Canadian Cancer Society. (2016). Risk factors for prostate cancer. Toronto, Canada: Canadian Cancer Society. http://www.cancer.ca/en/cancer-information/cancer-type/prostate/risks/?region=on

Canadian Task Force on Preventative Health Care. (2014). Screening for prostate cancer (2014). Ottawa, Canada: CTFPHC. http://canadiantaskforce.ca/ctfphc-guidelines/2014-prostate-cancer/ (accessed November 7, 2016)

Cancer Care Ontario. (2014). Occupation and environment. Toronto, Canada: CCO. https://www.cancercare.on.ca/cms/One.aspx? portalId=1377&pageId=323772 (accessed on February 9, 2017)

Cancer Research UK. (2017). Statistics on preventable cancers. http://www.cancerresearchuk.org/health-professional/cancer-statistics/risk/preventable-cancers (accessed October 4, 2011)

Carex Canada. (2016). Diesel engine exhaust. British Columbia, Canada: Carex Canada. https://www.carexcanada.ca/en/diesel_engine_exhaust/ (accessed March 14, 2017)

Carles C, Bouvier G, Lebailly P & Baldi I. (2017). Use of job-exposure matrices to estimate occupational exposure to pesticides: a review. Journal of Exposure Science & Environmental Epidemiology, 27: 125-140.

Carpenter L, Higgins C, Douglas A, Fraser P, Beral V & Smith P. (1994). Combined analysis of mortality in three United Kingdom nuclear industry workplaces, 1946-1988. Radiation Research, 138(2): 224-3.

Centers for Disease Control and Prevention. (2016). Prostate cancer rates by race and ethnicity. Atlanta, USA: Division of Cancer Prevention and Control. https://www.cdc.gov/cancer/prostate/statistics/race.htm. (accessed May 8, 2017)

Cerhan JR, Cantor KP, Williamson K, Lynch CF, Torner JC & Burmeister LF. (1998). Cancer mortality among Iowa farmers: recent results, time trends, and lifestyle factors (United States). Cancer Causes Control, 9(3): 311-319.

Charles LE, Loomis D, Shy CM, Newman B, Millikan R, Nylander-French LA & Couper D. (2003). Electromagnetic fields, polychlorinated biphenyls, and prostate cancer mortality in electric utility workers. American Journal of Epidemiology, 157(8): 683-691.

Chavarro JE, Stampfer MJ, Hall MN, Sesso HD & Ma J. (2008). A 22-y prospective study of fish intake in relation to prostate cancer incidence and mortality. The American Journal of Clinical Nutrition, 88(5): 1297-1303.

Checkoway H, DiFerdinando G, Hulka BS & Mickey DD. (1987). Medical, life-style, and occupational risk factors for prostate cancer. Prostate, 10(1): 79-88.

Checkoway H, Pearce N & Kriebel D. (2007). Selecting appropriate study designs to address specific research questions in occupational epidemiology. Occupational & Environmental Medicine, 64(9): 633-638.

Chen C, Xun P, Nishijo M, Carter S & He K. (2016). Cadmium exposure and risk of prostate cancer: a meta-analysis of cohort and case-control studies among the general and occupational populations. Scientific Reports, 6: 25814.

Cheng I, Witte JS, McClure LA, Shema SJ, Cockburn MG, John EM & Clarke CA. (2009). Socioeconomic status and prostate cancer incidence and mortality rates among the diverse population of California. Cancer Causes Control, 20(8): 1431-1440.

Cheng HG & Phillips MR. (2014). Secondary analysis of existing data: opportunities and implementation. Shanghai Archives of Psychiatry, 26(6): 371-375.

Christensen CH, Platz EA, Andreotti G, Blair A, Hoppin JA, Koutros S, Lynch CF, Sandler DP & Alavanja MC. (2010). Coumaphos exposure and incident cancer among male participants in the agriculture health study (AHS). Environmental Health Perspectives, 118(1): 92-96.

Cogliano VJ, Baan R, Straif K, Grosse Y, Lauby-Secretan B, Ghissassi FE, Bouvard V, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L & Wild CP. (2011). Preventable exposures associated with human cancers. Journal of National Cancer Institute, 103:1-13.

Costa G. (2010). Shift work and health: current problems and preventive actions. Safety and Health at Work, 1(2): 112-123.

Crompton, S., 2011. What's stressing the stressed? Main sources of stress among workers. Ottawa, Canada; Statistics Canada. Catalogue no. 11-008-X. http://www.statcan.gc.ca/pub/11-008-x/2011002/article/11562-eng.pdf (accessed September 25, 2017)

Cross AJ, Peters U, Kirsh VA, Andriole GL, Reding D, Hayes RB & Sinha R. (2005). A prospective study of meat and meat mutagens and prostate cancer risk. Cancer Research, 65(24): 11779-11784.

Cypel Y & Kang H. (2010). Mortality patterns of army chemical corps veterans who were occupationally exposed to herbicides in Vietnam. Annals of Epidemiology, 20(5): 339-346.

Dahlgren J, Takhar H, Schecter A, Schmidt R, Horsak R, Paepke O, Warshaw R, Lee A & Anderson-Mahoney P. (2007). Residential and biological exposure assessment of chemicals from a wood treatment plant. Chemosphere, 67: S279-S285.

Daniels RD, Bertke S, Dahm MM, Yiin JH, Kubale TL, Hales TR, Baris D, Zahm SH, Beaumont JJ, Waters KM & Pinkerton LE. (2015). Exposure-response relationships for select cancer and non-cancer health outcomes in a cohort of US firefighters from San Francisco, Chicago and Philadelphia (1950-2009). Occupational & Environmental Medicine, 72(10): 699-706.

Daniels RD, Kubale TL, Yiin JH, Dahm MM, Hales TR, Baris D, Zahm SH, Beaumont JJ, Waters KM & Pinkerton LE. (2014). Mortality and cancer incidence in a pooled cohort of US firefighters from San Francisco, Chicago and Philadelphia (1950-2009). Occupational and Environmental Medicine, 71(6): 388-397.

Darby SC, Muirhead CR, Doll R, Kendall GM & Thakrar B. (1990). Mortality among United Kingdom servicemen who served abroad in the 1950s and 1960s. British Journal of Industrial Medicine, 47: 793-804.

Darlington GA, Kreiger N, Lightfoot N, Purdham J & Sass-Kortsak A. (2007). Prostate cancer risk and diet, recreational physical activity and cigarette smoking. Chronic Diseases in Canada, 27(4):145-153.

De Coster S & van Larebeke N. (2012). Endocrine-disrupting chemicals: associated disorders and mechanisms of action. Journal of Environmental and Public Health, Volume 2012, ID 713696: 1-52.

Dennis LK & Dawson DV. (2002). Meta-analysis of measures of sexual activity and prostate cancer. Epidemiology, 13(1): 72-79.

De Pergola G & Silvestris F. (2013). Obesity as a major risk factor for cancer. Journal of Obesity, 2013: 29156.

De Vocht F, Sobala W, Wilczynska U, Kromhout H, Szeszenia-Dabrowska N & Peplonska B. (2009). Cancer mortality and occupational exposure to aromatic amines and inhalable aerosols in rubber tire manufacturing in Poland. Cancer Epidemiology, 32: 94-102.

Demers PA, CHeckoway H, Vaughn TL, Weiss NS, Heyer NJ & Rosenstock L. (1994). Cancer incidence among firefighters in Seattle and Tacoma, Washington (United States). Cancer Causes Control, 5(2): 129-135.

Demers PA, Heyer NJ & Rosenstock L. (1992). Mortality among firefighters from three northwestern United States cities. British Journal of Industrial Medicine, 49: 664-670.

Demichelis, F., & Standford, J. L. (2015). Genetic predisposition to prostate cancer: update and future perspectives. Urologic Oncology, 33(2): 75-84.

Deneo-Pellegrini H, De Stefani E, Ronco A, and Mendilaharsu M. (1999). Foods, nutrients and prostate cancer: a case-control study in Uruguay. British Journal of Cancer, 80(3-4), 591–597.

Di Matteo L. (2017). Why are northern Ontario's cities really shrinking? Fraser Institute. https://www.fraserinstitute.org/blogs/why-are-northern-ontarios-cities-really-shrinking (accessed September 20, 2017)

Di Sebastiano KM & Mourtzakis M. (2014). The role of dietary fat throughout the prostate cancer trajectory. Nutrients, 6(12): 6095-6109.

Dickerman BA, Markt SC, Koskenvuo M, Hublin C, Pubkkala E, Mucci LA & Kaprio J. (2016). Sleep disruption, chronotype, shift work, and prostate cancer risk and mortality: a 30-year prospective cohort study of Finnish twins. Cancer Causes & Control, 27(11): 1361-1370.

Dickinson J, Shane A, Tonelli M, Connor Gorber S, Joffres M, Singh H & Bell N. (2016). Trends in prostate cancer incidence and mortality in Canada during the era of prostate-specific antigen screening. Canadian Medical Association Journal, 4(1): E73-E79.

Doolan G, Benke G & Giles G. (2014). An update on occupation and prostate cancer. Asian Pacific Journal of Cancer Prevention, 15(2): 501-516.

Dy GW, Gore JL, Forouzanfar MH, Naghavi M & Fitzmaurice C. (2017). Global burden of urologic cancers, 1990-2013. European Urology, 71: 437-336.

Eaton NE, Reeves GK, Appleby PN & Key TJ. (1999). Endogenous sex hormones and prostate cancer: a quantitative review of prospective studies. British Journal of Cancer, 80(7): 930-934.

Egger M, Smith GD, Scheider M & Minder C. (1997). Bias in meta-analysis detected by a simple, graphical test. BMJ, 315: 629-634.

Elghany NA, Shumacher MC, Slattery ML, West DW & Lee JS. (1990). Occupation, cadmium exposure, and prostate cancer. Epidemiology, 1(2): 107-115.

Erdurak K, Dundar PE, Ozyurt BC, Negri E, La Vecchia C, & Tay Z. (2014). Smoking, occupation, history of selected diseases and bladder cancer risk in Manisa, Turkey. European Journal of Cancer Prevention, 23(1): 58-61.

Fekedulegn D, Burchfiel CM, Hartley TA, Andrew ME, Charles LE, Tinney-Zara CA & Violanti JM. (2013). Shiftwork and sickness absence among police officers: the BCOPS study. Chronobiology International, 30(7): 930-941.

Finkelstein MM. (1998). Cancer incidence among Ontario police officers. American Journal of Industrial Medicine, 34(2):157-62.

Flynn-Evans EE, Mucci L, Stevens RG & Lockley SW. (2013). Shiftwork and prostate-specific antigen in the National Health and Nutrition Examination Survey. Journal of the National Cancer Institute, 105(17): 1292-1297.

Forastiere F, Perucci CA, Di Pietro A, Miceli M, Rapiti E, Bargagli A & Borgia P. (1994). Mortality among urban policemen in Rome. American Journal of Industrial Medicine, 26: 785-798.

Fowke JH, Schlundt D, Signorello LB, Ukoli FAM & Blot WJ. (2005). Prostate cancer screening between low-income African-American and Caucasian men. Urologic Oncology: Seminars and Original Investigations, 23(5): 333-340.

Fradet Y, Klotz L, Trachtenberg J & Zlotta A. (2009). The burden of prostate cancer in Canada. Canadian Urological Association Journal, 3(3 Suppl 2): S92-S100.

Fradet Y, Meyer F, Bairati I, Shadmani R & Moore L. (1999). Dietary fat and prostate cancer progression and survival. European Urology, 35(5-6): 388-391.

Fragar L, Depczynski J & Lower T. (2011). Mortality patterns of Australian male farmers and farm managers. Australian Journal of Rural Health, 19(4):179-184.

Freedland SJ & Aronson WJ. (2004). Examining the relationship between obesity and prostate cancer. Reviews in Urology, 6(2): 73-81.

Freedman DM, Dosemeci M & McGlynn K. (2002). Sunlight and mortality from breast, ovarian, colon, prostate, and non-melanoma skin cancer: a composite death certificate based case-control study. Occupational and Environmental Medicine, 59: 257-262.

Fritschi L, Glass DC, Heyworth JS, Aronson K, Girschik J, Boyle T, Grundy A & Erren TC. (2011). Hypotheses for mechanisms linking shiftwork and cancer. Medical Hypotheses, 77: 430-436.

Frumkin H. (2010). Environmental health, from global to local, second edition. San Francisco, USA: John Wiley & Sons.
https://books.google.ca/books?id=jA3CNU7i4Y0C&pg=PT173&lpg=PT173&dq=historical+occupational+studies&source=bl&ots=fT2RDKrXez&sig=Qe9HPIO4OlysuBLwb12RjREpyQk&hl=en&sa=X&ved=0ahUKEwiIssyb4ZnQAhVD9YMKHY2HBysQ6AEIGzAA#v=onepage&q=historical%20occupational%20studies&f=false

Gaines AR, Vidal AC & Freedland SJ. (2015). Vasectomy: potential links to an increased risk of aggressive prostate cancer? Expert Review of Anticancer Therapy, 15(10): 1123-1125.

Gann PH, Hennekens CH, Sacks FM, Grodstein F, Giovannucci EL & Stampfer MJ. (1994). Prospective study of plasma fatty acids and risk of prostate cancer. Journal of the National Cancer Institute, 86(4): 281–286.

Gann PH. Risk factors for prostate cancer. Rev Urol 2002, 4(Suppl 5): S3-S10.

Gapstur SM, Diver WR, Stevens VL, Carter BD, Teras LR & Jacobs EJ. (2014). Work schedule, sleep duration, insomnia, and risk of fatal prostate cancer. American Journal of Preventative Medicine, 46(3 Suppl 1): S26-33.

Gibbs GW & Labreche F. (2014). Cancer risks in aluminum reduction plant workers. Journal of Occupational and Environmental Medicine, 56 (5 Suppl); S40-S59.

Giles G, Staples M & Berry J. (1993). Cancer incidence in Melbourne metropolitan fire brigade members, 1980-1989. Health Reports Statistics Canada, 5(1): 1-38.

Giovannucci E, Rimm EB, Colditz GA, Stampfer MJ, Ascherio A, Chute CG & Willett WC. (1993). A prospective study of dietary fat and risk of prostate cancer. Journal of the National Cancer Institute, 85(19): 1571-1579.

Giri VN, Cassidy AE, Beebe-Dimmer J, Smith DC, Bock CH & Cooney KA. (2004). Association between agent orange and prostate cancer: a pilot case-control study. Urology, 63: 757-761.

Girschik, J., Glass, D., Ambrosini, G. L., & Fritschi, L. (2009). Could mining be protective against prostate cancer? A study and literature review. Occupational & Environmental Medicine, 67: (365-374).

Glass DC, Pircher S, Del Monaco A, Vander Hoorn S & Sim MR. (2016). Mortality and cancer incidence in a cohort of male paid Australian firefighters. Occupational and Environmental Medicine, 73: 761-771.

Golden RJ, Noller KL, Titus-Ernstoff L, Kaufman RH, Mittendorf R, Stillman R & Reese EA. (1998). Environmental endocrine modulators and human health: an assessment of the biological evidence. Critical Reviews in Toxicology, 28(2): 109-227.

Government of Canada. (2016). Canadian armed forces medical standards (CFP 154). Ottawa, Canada: Government of Canada. http://www.forces.gc.ca/en/about-policies-standards-medical-occupations/index.page (accessed October 5, 2016)

Grimes G, Hirsch D & Borgeson D. (1991). Risk of death among Honolulu fire fighters. Hawaii Medical Journal, 50(3): 82-85.

Gu JK, Charles LE, Burchfiel CM, Andrew ME & Violanti JM. (2011). Cancer incidence among police officers in a U.S. northeast region: 1976-2006. International Journal of Emergency Mental Health, 13(4): 279-289.

Guidotti TL. (1993). Mortality of urban firefighters in Alberta, 1927-1987. American Journal of Industrial Medicine, 23: 921-940.

Gwini S, Macfarlane E, Del Monaco A et al. (2012). Cancer incidence, mortality, and blood lead levels among workers exposed to inorganic lead. Annals of Epidemiology, 22, 270-6.

Hammer GP, Emrich K, Naserlack M, Blettner M & Yong M. (2015). Shift work and prostate cancer incidence in industrial workers: a historical cohort study in a German chemical company. Deutsches Arzteblatt International, 112(27-28): 463-470.

Hassan E. (2005). Recall bias can be a threat to retrospective and prospective research designs. The Internet Journal of Epidemiology, 3(2).

Hayes JH & Barry MJ. (2014). Screening for prostate cancer with the prostate-specific antigen test: a review of current evidence. JAMA, 311(11): 1143-1149.

Health and Safety Authority. (2015). Summary of workplace injury, illness, and fatality statistics, 2014-2015. Dublin, Ireland: HSA. http://www.hsa.ie/eng/Publications_and_Forms/Publications/Corporate/HSA_Statistics_Report_2014-2015.pdf (accessed February 20, 2018)

Heikkila K, Nyberg ST, Theorell T, Fransson EI, Alfredsson L, Bjorner JB, et al. (2013). Work stress and risk of cancer: meta-analysis of 5700 incident cancer events in 116 000 European men and women. BMJ, 346 (f165).

Higgins JPT & Thompson SG. (2002). Quantifying heterogeneity in a meta-analysis. Statistics in Medicine, 21: 1539-1558.

Hoffman RM, Gilliland FD, Eley JW, Harlan LC, Stephenson RA, Stanford JL, Albertson PC, Hamilton AS, Curtis Hunt W & Potosky AL. (2000). Racial and ethnic differences in advanced-stage prostate cancer: the prostate cancer outcomes study. Journal of National Cancer Institute, 93(5): 388-395.

Hosain GMM, Sanderson M, Du Xl, Chan W & Strom SS. (2012). Racial/ethnic differences in predictors of psa screening in a tri-ethnic population. Central European Journal of Public Health, 19(1): 30-34.

Howe, C.J, Cole, SR, Lau, B, Napravnik, S, & Eron, JJ. (2016). Selection bias due to loss to follow up in cohort studies. Epidemiology (Cambridge, Mass.), 27(1), 91–97.

Howe GR & Burch JD. (1990). Fire fighters and risk of cancer: an assessment and overview of the epidemiologic evidence. American Journal of Epidemiology, 132: 1039-1050.

Howe GR & Lindsay JP. (1983). A follow-up study of a ten-percent sample of the Canadian labour force: Cancer mortality in males, 1965-1973. Journal of the National Cancer Institute, 70(1): 37-44.

Hsing AW & Chokkalingam AP. (2006). Prostate cancer epidemiology. Frontiers in Bioscience, 1(11): 1388-413.

Huang W, Hayes R, Pfeiffer R, Viscidi RP, Lee FK, Wang YF, Reding D, Whitby D, Papp JR & Rabkin CS. (2008). Sexually transmissible infections and prostate cancer risk. Cancer Epidemiology Biomarkers and Prevention, 17(9): 2374-2381.

Huncharek M, Muscat J & Kupelnick B. (2008). Dairy products, dietary calcium and vitamin D intake as risk factors for prostate cancer: a meta-analysis of 26,769 cases from 45 observational studies. Nutrition and Cancer, 60(4): 421–441.

Huvinen M & Pukkala E. (2013). Cancer incidence among Finnish ferrochromium and stainless steel production workers in 1967-2011: a cohort study. BMJ Open, 3(11): e003819.

Hystad P, Villeneuve PJ, Goldberg MS, Crouse DL, Johnson K & the Canadian Cancer Registries Epidemiology Research Group. (2015). Exposure to traffic-related air pollution and the risk of developing breast cancer among women in eight Canadian provinces: a case-control study. Environment International 74: 240-248.

IARC. (2015). IARC monographs volume 112: evaluation of five organophosphate insecticides and herbicides. Lyon, France: IARC. https://www.iarc.fr/en/media-centre/iarcnews/pdf/MonographVolume112.pdf (accessed January 3, 2017)

Industry Canada. (2011). Archived – final evaluation for the Northern Ontario development program. Ottawa: Government of Canada. ://www.ic.gc.ca/eic/site/ae-ve.nsf/eng/03336.html#ftn3 (accessed November 2015)

International Agency for Research on Cancer. (2014). World Cancer Report 2014. Lyon, France: IARC. http://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports/World-Cancer-Report-2014 (accessed July 28, 2016)

International Agency for Research on Cancer. (1987). Androgenic (anabolic) steroids (group 2A). IARC Monographs, Suppl 7, 96. https://monographs.iarc.fr/ENG/Monographs/suppl7/Suppl7-17.pdf (accessed March 12, 2017)

International Agency for Research on Cancer. (1993). Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. Lyon, France: IARC. http://monographs.iarc.fr/ENG/Monographs/vol58/mono58.pdf (accessed July 28, 2016)

International Agency for Research on Cancer. (2000). X- and y-radiation, volume 100D. Lyon, France; IARC. 103-229. http://monographs.iarc.fr/ENG/Monographs/vol100D/mono100D-7.pdf (accessed July 28, 2016)

International Agency for Research on Cancer. (2001). Ionizing radiation, part 2: some internally deposited radionuclides, volume 78. Lyon, France; IARC. 7-595. http://monographs.iarc.fr/ENG/Monographs/vol78/mono78.pdf (accessed July 28, 2016)

International Agency for Research on Cancer. (2010). Painting, firefighting, and shiftwork, volume 98. Lyon, France: IARC. http://monographs.iarc.fr/ENG/Monographs/vol98/index.php (accessed July 27, 2016)

International Agency for Research on Cancer. (2012a). Chemical agents and related occupations, volume 100F. Lyon, France: IARC. http://monographs.iarc.fr/ENG/Monographs/vol100F/index.php (accessed July 27, 2016)

International Agency for Research on Cancer. (2012b). Arsenic, metals, fibres, and dusts, volume 100C. Lyon, France: IARC. http://monographs.iarc.fr/ENG/Monographs/vol100C/index.php (accessed July 27, 2016)

International Agency for Research on Cancer. (2012c). Radiation, volume 100D. Lyon, France: IARC. http://monographs.iarc.fr/ENG/Monographs/vol100D/index.php (accessed July 27, 2016)

International Agency for Research on Cancer. (2012d). Cadmium and cadmium compounds, volume 59. Lyon, France; IARC. 119-237. http://monographs.iarc.fr/ENG/Monographs/vol100C/mono100C-8.pdf (accessed July 27, 2016)

International Agency for Research on Cancer. (2012e). Occupational exposures in the rubber-manufacturing industry, volume 100F. Lyon, France; IARC. 541-562. http://monographs.iarc.fr/ENG/Monographs/vol100F/mono100F-36.pdf (accessed July 27, 2016)

International Agency for Research on Cancer. (2013). IARC monographs on the evaluation of carcinogenic risks to humans. http://monographs.iarc.fr/ (accessed September 2 2015)

International Agency for Research on Cancer. (2014). Report of the advisory group to recommend priorities for IARC monographs during 2015-2019. Lyon, France: IARC. https://monographs.iarc.fr/ENG/Publications/internrep/14-002.pdf (accessed July 27, 2016)

International Agency for Research on Cancer. (2015). IARC monographs evaluate consumption of red meat and processed meat. Lyon, France; IARC. https://www.iarc.fr/en/media-centre/pr/2015/pdfs/pr240_E.pdf (accessed July 27, 2016)

International Agency for Research on Cancer. (2015). Malathion, volume 112. Lyon, France; IARC. 1-124. https://monographs.iarc.fr/ENG/Monographs/vol112/mono112-07.pdf (accessed July 27, 2016)

International Agency for Research on Cancer. (2015). Some organophosphate insecticides and herbicides: diazinon, glyphosate, malathion, parathion, and tetrachlorvinphos, volume 112. Lyon, France: IARC. http://monographs.iarc.fr/ENG/Monographs/vol112/in (accessed July 27, 2016)

International Agency for Research on Cancer. (2016). GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012. Lyon, France: IARC. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx (accessed May 5, 2017)

International Agency for Research on Cancer. (2017). List of classifications by cancer sites with sufficient or limited evidence in humans, Volume 1 to 118*. Lyon, France; IARC. http://monographs.iarc.fr/ENG/Classification/Table4.pdf (accessed February 12, 2017)

International Labour Organization. (2017). Labour force participation rate – ILO modelled estimates, July 2015. Geneva, Switzerland: ILO. http://www.ilo.org/ilostat/faces/oracle/webcenter/portalapp/pagehierarchy/Page3.jspx?MBI_ID=15&_adf.ctrl-state=hcz39covt_50&_afrLoop=47714487261639&_afrWindowMode=0&_afrWindowId=hcz39covt_47#! (accessed July 10, 2017)

Izawa JI, Klotz L, Siemens DR, Kassouf W, So A, Jordan J, Chetner M & Iansavichene A. (2011). Prostate cancer screening: Canadian guidelines 2011. Canadian Urological Association Journal, 5(4): 235-240.

Jack RJ & Oliver M. (2008). A review of factors influencing whole-body vibration injuries in forestry mobile machine operators. International Journal of Forest Engineering, 19(1): 51-65.

Jacobs EJ, Anderson RL, Stevens VL, Newton CC, Gansler T & Gapstur SM. (2016). Vasectomy and prostate cancer incidence and mortality in a large US cohort. Journal of Clinical Oncology, doi: 10.1200/JCO.2015.66.2361

Järup L, Bellander T, Hogstedt C & Spång G. (1998). Mortality and cancer incidence in Swedish battery workers exposed to cadmium and nickel. Occupational and Environmental Medicine, 55: 755–759.

John EH, Schwartz GG, Koo J, Van Den Berg D & Ingles SA. (2005). Sun exposure, vitamin D receptor gene polymorphisms, and risk of advanced prostate cancer. Cancer Research, 65(12): 5470-5479.

Johnson KC, Mao Y, Argo J, Duboi S, Semenciw R & Lava J. (1998). The national enhanced cancer surveillance system: a case-control approach to environment-related cancer surveillance in Canada. Environmetrics, 9(5): 495-504.

Jones MK, Harris MA, Peters PA, Tjepkema M & Demers PA. (2014). Prostate cancer and occupational exposure to whole-body vibration in a national population-based cohort study. American Journal of Industrial Medicine, 57(8): 896-905.

Jones RR, Barone-Adesi F, Koutros S, Lerro CC, Blair A, Lubin J, Heltshe SL, Hoppin JA, Alavanja MC & Beane Freeman LE. (2015). Incidence of solid tumours among pesticide applicators exposed to the organophosphate insecticide diazinon in the Agriculture Health Study: an updated analysis. Occupational and Environmental Medicine, 72(7): 496-503.

Joseph HJ & Hickey JR. (2004). Prostate cancer screening among military service members. Military Medicine, 169(4): 257.

Ju-Kun S, Yuan DB, Rao HF, Chen TF, Luan BS, Xu XM, Jiang FN, Zhong WD & Zhu JG. (2016). Association between CD exposure and risk of prostate cancer: a PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore), 95(6): e2708.

Kaikkonen P, Lindholm H, Lusa S. (2017). Physiological load and psychological stress during a 24-hour work shift among Finnish firefighters. Journal of Occupational & Envionmental Medicine, 59: 41-46.

Kang D, Davis LK, Hunt P & Kreibel D. (2008). Cancer incidence among male Massachusetts firefighters, 1987-2003. American Journal of Industrial Medicine, 51: 329-335.

Kawachi I, Pearce N & Fraser J. (1989). A new Zealand cancer registry-based study of cancer in wood workers. Cancer, 64(12): 2609-2613.

Keller JE & Howe HL. (1993). Cancer in Illinois construction workers: a study. American Journal of Industrial Medicine, 24: 223-230.

Kimura T. (2012). East meets west: ethnic differences in prostate cancer epidemiology between east Asians and Caucasians. Chinese Journal of Cancer, 31(9): 421-429.

Klap J, Schmid M & Loughlni KR. (2014). The relationship between total testosterone levels and prostate cancer: a review of the continuing controversy. The Journal of Urology, 193(2): 403-414.

Koh KA, Sesso HD, Paffenbarger Jr RS & Lee IM. (2006). Dairy products, calcium and prostate cancer risk. British Journal of Cancer, 95(11): 1582–1585.

Kohler LN, Garcia DO, Harris RB, Oren E, Roe DJ & Jacobs ET. (2016). Adherence to diet and physical activity cancer prevention guidelines and cancer outcomes: a systematic review. Cancer Epidemiology, Biomarkers, and Prevention, 25(7): 1018-1028.

Kotb AF, Beltagy A, Ismail AM, Hashad MM. (2015). Sexual activity and the risk of prostate cancer: review article. Archivio Italiano Di Urologia, 87(3): 214-215.

Koutros S, Beane Freeman LE, Lubin JH, Heltshe SL, Andreotti G, Barry KH, DellaValle CT, Hoppin JA, Sandler DP, Lynch CF, Blair A & Alavanja MC. (2013). Risk of total and aggressive prostate cancer and pesticide use in the Agriculture Health Study. American Journal of Epidemiology, 177(1): 59-74.

Koutros S, Cross AJ, Sandler DP, Hoppin JA, Ma X, Zheng T, Alavanja MCR & Sinha R. (2008). Meat and meat mutagens and risk of prostate cancer in the Agricultural Health Study. Cancer Epidemiology, Biomarkers & Prevention, 17(1): 80-87.

Koutros S, Langseth H, Grimsrud TK, Boyd Barr D, Vermeulen R, Potengen L, Wacholder S, Beane Freeman LE, Blair A, Hayes RB, Rothman, Engel LS. (2015). Prediagnositc serum organochlorine concentrations and metastatic prostate cancer: a nested case-control study in the Norwegian Janus serum bank cohort. Environmental Health Perspectives, 123: 9.

Koutros S, Mahajan R, Zheng T, Hoppin JA, Ma X, Lynch CF, Blair A & Alavanja MC. (2008). Dichlorvos exposure and human cancer risk: results from the Agriculture Health Study. Cancer Causes Control 2008, 19(1): 59-65.

Krishnadasan A, Kennedy N, Zhao Y, Morgenstern H & Ritz B. (2007). Nested case-control study of occupational chemical exposures and prostate cancer in aerospace and radiation workers. American Journal of Industrial Medicine, 50: 383-390.

Krstev S, Baris D, Stewart P, Dosemeci M, Swanson GM, Greenberg RS, Schoenberg JB, Schwartz AG, Liff JM & Hayes RB. (1998). Occupational risk factors and prostate cancer in U.S. blacks and whites. American Journal of Industrial Medicine, 34: 421-430.

Krstev S, Baris D, Stewart PA, Hayes RB, Blair A & Dosemeci M. (1998). Risk for prostate cancer by occupation and industry: a 24 state death certificate study. American Journal of Industrial Medicine, 34: 413-420.

Krstev S, Baris D, Stewart PA, Hayes RB, Blair A & Dosemeci M. (1998). Risk for prostate cancer by occupation and industry: a 24 state death certificate study. American Journal of Industrial Medicine, 34: 413-420.

Kruk J & Czerniak U. (2013). Physical activity and its relation to cancer risk: updating the evidence. Asian Pacific Journal of Cancer Prevention, 14(7): 3993-4003.

Kubo T, Oyama I, Nakamura T, Kunimoto M, Kadowaki K, Otomo H, Fujino Y, Fujimoto N, Matsumoto T & Matsuda S. (2011). Industry-based retrospective cohort study of the risk of prostate cancer among rotating-shift workers. International Journal of Urology, 18(3): 206-211.

Kubo T, Ozaka K, Mikami K, Wakai K, Fujino Y, Watanabe Y, Miki T, Nakao M, Hayashi K, Suzuki K, Mori M, Washio M, Sakauchi F, Ito Y, Yoshimura T & Tamakoshi A. (2006). Prospective cohort study of the risk of prostate cancer among rotating-shift workers: findings from the Japan collaborative cohort study. American Journal of Epidemiology, 164(16): 549-555.

Kurahashi N, Inoue M, Iwasaki M, Sasazuki S & Tsugane S. (2008). Dairy product, saturated fatty acid, and calcium intake and prostate cancer in a prospective cohort of Japanese men. Cancer Epidemiology Biomarkers and Prevention, 17(4): 930– 937.

Lacey JV Jr, Deng J, Dosemeci M, Gao Y, Mostofi FK, Sesterhenn IA, Xie T & Hsing AW. (2001). Prostate cancer, benign prostatic hyperplasia and physical activity in Shanghai, China. International Journal of Epidemiology, 30(2): 341-349.

Lam TV, Agovino P, Niu X & Roche L. (2007). Linkage study of cancer risk among lead-exposed workers in New Jersey. Science of the Total Environment, 372; 455-462.

Lassed S, Deus CM, Lourenco N, Dahdouh A, Rizvanov AA, Oliveira PJ & Zama D. (2016). Diet, lifestyles, family history, and prostate cancer incidence in an east Algerian patient group. BioMed Research International, ID 5730569, 1-9.

Le Marchand L, Kolonel LN, Wilkens LR, Myers BC & Hirohata T. (1994). Animal fat consumption and prostate cancer: a prospective study in Hawaii. Epidemiology, 5(3): 276–282.

Leavy J, Ambrosini G & Fritschi L. (2006). Vietnam military service history and prostate cancer. BMC Public Health, 6:75.

Lee E, Burnett CA, Lalich N, Cameron LL & Sestito JP. (2002). Proportionate mortality of crop and livestock farmers in the United States, 1984-1993. American Journal of Industrial Medicine, 42(5): 410-420.

Lee IP, Suzuki K, Lee SD & Dixon RL. (1980). Aryl hydrocarbon hydroxylase induction in rat lung, liver, and male reproductive organs following inhalation exposure to diesel emission. Toxicology and Applied Pharmacology, 52:181-186.

LeMasters GK, Genaidy AM, Succop P, Deddens J, Sobeih T, Barriera-Viruet H, Dunning K & Lockey J. (2006). Cancer risk among firefighters: a review and meta-analysis of 32 studies. Journal of Occupational and Environmental Medicine, 48(11): 1189-1201.

Levi F, Negri E, La Vecchia C & Te VC. (1988). Socioeconomic groups and cancer risk at death in the Swiss Canton of Vaud. International Journal of Epidemiology, 17(4): 711-717.

Lewis-Mikhael AM, Bueno-Cavanillas A, Guiron TO, Olmedo-Requena R, Delgado-Rodriguez M & Jimenez-Moleon JJ. (2016). Occupational exposure to pesticides and prostate cancer: a systematic review and meta-analysis. Occupational and Environmental Medicine, 73: 134-144.

Lewis-Mikhael AM, Olmedo-Requena R, Martinez-Ruiz V, Bueno-Cavanillas A & Jimenez-Moleon JJ. (2015). Organochlorine pesticides and prostate cancer, is there an association? A meta-analysis of epidemiological evidence. Cancer Causes Control, 26(10): 1375-1392.

LI CY & Sung FC. (1999). A review of the healthy worker effect in occupational epidemiology. Occupational Medicine, 49; 225-229.

Li J, Hall IJ, & Zhao G. (2017). Prostate cancer screening decision-making in three states: 2013 behavioral risk factor surveillance system analysis. Cancer Causes Control, 28: 235-240.

Licqurish S, Pillipson L, Chiang P, Walker J, Walter F & Emery J. (2016). Cancer beliefs in ethnic minority populations: a review and meta-synthesis of qualitative studies. European Journal of Cancer Care, 00: 1-13, doi:10.1111/ecc.12556.

Lightfoot N, Conlon M, Kreiger N, Sass-Kortsak A, Purdham J & Darlington G. (2004). Medical history, sexual, and maturational factors and prostate cancer risk. Annals of Epidemiology, 14(9):655-662.

Lightfoot N, Kreiger N, Sass-Kortsak A & Purdham J & Buchan G. (2000). Prostate cancer risk. Medical history, sexual, and hormonal factors. Annals of Epidemiology, 10(7):470.

Lin DW, Porter M & Montgomery B. (2009). Treatment and survival outcomes in young men diagnosed with prostate cancer: a population based cohort study. Cancer, 115(13): 2863-2871.

Lin PH, Aronson W & Freedland SJ. (2015). Nutrition, dietary interventions and prostate cancer: the latest evidence. BMC Medicine, 8; 13: 3.

Lindelof B, Krynitz B, Ayoubi S, Martschin C, Wiegleb-Edstrom D & Wiklund K. (2012). Previous extensive sun exposure and subsequent vitamin D production in patients with basal cell carcinoma of the skin, has no protective effect on internal cancers. European Journal of Cancer, 48; 1154-1158.

Littlejohns TJ, Travis RC, Key TJ & Allen NE. (2016). Lifestyle factors and prostate-specific antigen (PSA) testing in UK biobank: implications for epidemiological research. Cancer Epidemiology, 45: 40-46.

Liu L, Cozen W, Bernstein L, Ross RK & Deapen D. (2001). Changing relationship between socioeconomic status and prostate cancer incidence. Journal of National Cancer Institute, 93:705-709.

Loughlin KR. (2016). Can a vasectomy increase prostate cancer risk? Harvard University. http://www.harvardprostateknowledge.org/can-a-vasectomy-increase-prostate-cancer-risk (accessed October 13, 2015)

Lynch BM, Friedenreich CM, Kopciuk KA, Hollenbeck AR, Moore SC & Matthews CE. (2014). Sedentary behavior and prostate cancer risk in the NIH-AARP diet and health study. Cancer Epidemiology & Biomarkers, 23(5): 882-889.

Lynch BM. (2010). Sedentary behavior and cancer: a systematic review of the literature and proposed biological mechanisms. Cancer Epidemiology, Biomarkers & Prevention, 19(11): 2691-2709.

Ma F, Fleming LE, Lee DJ, Trapido E & Gerace TA. (2006). Cancer incidence in Florida professional firefighters, 1981 to 1999. Journal of Occupational and Environmental Medicine, 48(9): 883-888.

Ma F, Fleming LE, Lee DJ, Trapido E, Gerace TA, Lai H & Lai S. (2005). Mortality in Florida professional firefighters, 1972-1999. American Journal of Industrial Medicine, 47: 509-517

Ma F, Lee DJ, Fleming LE & Dosemeci M. (1998). Race-specific cancer mortality in US firefighters: 1984-1993. Journal of Occupational & Environmental Medicine, 40(12): 1134-1138.

MacFarlane E, Carey R, Keegel T, El-Zaemay S, & Fritschi L. (2013). Dermal exposure associated with occupational end use of pesticides and role of protective measures. Safety and Health at Work, 4(3): 136-141.

Magagnotti N, Picchi G, Sciarra G, Spinelli R. (2014). Exposure of mobile chipper operators to diesel exhaust. The Annals of Occupational Hygiene, 52: 217-226.

Mahajan R, Blair A, Lynch CF, Schroeder P, Hoppin JA, Sandler DP & Alavanja MC. (2006). Fonofos exposure and cancer incidence in the Agriculture Health Study. Environmental Health Perspectives, 114(12): 1838-1842.

Maltseva A, Serra C & Kogevinas M. (2016). Cancer risk among workers of a secondary aluminum smelter. Occupational Medicine (Oxford, England), 66(5): 412-414.

Markt SC, Grotta A, Nyren O, Adami HO, Mucci LA, Valdimarsdottir UA, Stattin P, Bellocco R & Lagerros YT. (2015). Insufficient sleep and risk of prostate cancer in a large Swedish cohort. Sleep, 38(9): 1405-1410.

Mayton AG, Jobes CC & Gallagher S. (2014). Assessment of whole-body vibration exposures and influencing factors for quarry haul truck drivers and loader operators. International Journal of Heavy Vehicle Systems, 21(3): 241-261.

Meng H, Hu W, Chen Z & Shen Y. (2014). Fruit and vegetable intake and prostate cancer risk: a meta-analysis. Asia-Pacific Journal of Clinical Oncology, 10(2): 133–140.

Merchand LL, Kolonel LN, Wilkens LR, Myers BC & Hirohata T. (1994). Animal fat consumption and prostate cancer: a prospective study in hawaii. Epidemiology, 5(3): 276–282.

Merletti F, Soskolne CL & Vineis P. (N/A). Chapter 28 – epidemiology and statistics. Encyclopaedia of Occupational Health and Safety, 4th Edition. http://www.ilocis.org/documents/chpt28e.htm (accessed July 10, 2017)

Merrill RM. (2001). Demographics and health-related factors of men receiving prostate-specific antigen screening in Utah. Preventative Medicine, 33: 646-652.

Michaud DS, Augustsson K, Rimm EB, Stampfer MJ, Willet WC & Giovannucci E. (2001). A prospective study on intake of animal products and risk of prostate cancer. Cancer Causes and Control, 12(6), 557–567.

Mitrou PN, Albanes D, Weinstein SJ, Pietinen P, Taylor PR, Virtamo J & Leitzmann MF. (2007). A prospective study of dietary calcium, dairy products and prostate cancer risk (Findland). International Journal of Cancer, 120(11): 2466-73.

Moreno-Smith M, Lutgendorf SK & Sood AK. (2010). Impact of stress on cancer metastasis. Future Oncology, 6(12): 1863-1881.

Morrison H, Savitz D, Semenciw R, Hukla B, Mao Y, Morison D & Wigle D. (1993). Farming and prostate cancer mortality. American Journal of Epidemiology, 137(3): 270-280.

Moul JW. (2005). Screening for prostate cancer in military populations. Military Medicine, 170(11): 905.

Muller RL, Gerber L, Moreira DM, Andriole G, Castro-Santamaria R & Freedland SJ. (2012). Serum testosterone and dihydrotestosterone and prostate cancer risk in the placebo arm of the Reduction by Dutasteride of Prostate Cancer Events trial. European Urology, 62: 757-764.

Nadalin V, Kreiger N, Parent ME, Salmoni A, Sass-Kortsak A, Siemiatycki J, Sloan M & Purdham J. (2012). Prostate cancer and occupational whole-body vibration exposure. Annals of Occupational Hygiene, 56(8): 968-974.

National Cancer Institute. (2009). Prostate cancer screening results from the prostate, lung, colorectal, and ovarian cancer randomized screening trial: questions and answers. U.S. Department of Health and Human Services. https://www.cancer.gov/types/prostate/research/plco-screening-results-qa (accessed November 7, 2016)

National Cancer Institute. (2014). Hormone therapy for prostate cancer. U.S. Department of Health and Human Sciences. http://www.cancer.gov/types/prostate/prostate-hormone-therapy-fact-sheet#q2 (accessed July 19, 2016)

National Defense and the Canadian Armed Forces. (2016). Canadian armed forces medical standards (CFP 154). Ottawa, Canada: Government of Canada. http://www.forces.gc.ca/en/about-policies-standards-medical-occupations/index.page (accessed October 5, 2016)

Nelles JL, Hu W & Prins GS. (2011). Estrogen action and prostate cancer. Expert Review of Endocrinology & Metabolism, 6(3):437-451.

Nieuwenhuijsen MJ. (2005). Design of exposure questionnaires for epidemiological studies. Occupational and Environmental Medicine, 62: 272-280.

Norman A, Moradi T, Dosemeci M, Rydh B, Nyren O & Wolk A. (2002). Occupational physical activity and risk for prostate cancer in a nationwide cohort study in Sweden. British Journal of Cancer, 86(1): 70-75.

Northern Development Ministers Forum. (2015). Ontario: key industries. http://www.focusnorth.ca/english/province/ontario.php (Accessed September 19, 2017)

Occupational Cancer Research Centre. (2015). About. Toronto, Canada: OCRC. Found at: http://www.occupationalcancer.ca/aboutocrc/ (accessed June 9, 2016)

Ontario Ministry of Health & Long Term Care. (2012). Cancer, prostate cancer and the PSA test. Toronto, Canada: Ontario Ministry of Health & Long Term Care. http://www.health.gov.on.ca/en/public/programs/cancer/prostate/#6 (accessed June 2, 2017)

Orsini N, Bellocco R, Bottai M, Pagano M, Andersson SO, Johansson JE, Giovannucci E & Wolk A. (2009). A prospective study of lifetime physical activity and prostate cancer incidence and mortality. British Journal of Cancer, 101(11): 1932-1938.

Pan SY, Johnson KC, Ugnat AM, Wen SW, Mao Y, Canadian Cancer Registries Epidemiology Research Group. (2004). Association of obesity and cancer risk in Canada. American Journal of Epidemiology, 159(3): 259-268.

Papantoniou K, Castano-Vinyals G, Espinosa A, Aragones N, Perez-Gomez B, Burgos J, Gomez-Acebo I, Llorca J, Peiro R, Jimenez-Moleon JJ, Arredondo F, Tardon A, Pollan M & Kogevinas M. (2015a). Night shift work, chronotype and prostate cancer risk in the MCC-Spain case-control study. International Journal of Cancer, 137(5): 1147-1157.

Papantoniou K, Pozo OJ, Espinosa A, Marcos J, Castano-Vinyals G, Basagana X, Juanola Pages E, Mirabent J, Martin J, Such Faro P, Gasco Aparici A, Middleton B, Skene DJ & Kogevinas M. (2015b). Increased and mistimed sex hormone production in night shift workers. Cancer Epidemiology, Biomarkers & Prevention, 24(5): 854-863.

Parent ME & Siemiatycki J. (2001). Occupation and prostate cancer. Epidemiologic Reviews, 23(1): 138-143.

Parent ME, Desy M & Siemiatycki J. (2009). Does exposure to agricultural chemicals increase the risk of prostate cancer among farmers? McGill Journal of Medicine, 12(1):70-77.

Parent ME, El-Zein M, Rousseau MC, Pintos J & Siemiatycki J. (2012). Night work and the risk of cancer among men. American Journal of Epidemiology, 176(9): 751-759.

Parent MÉ, Goldberg MS, Crouse DL, Ross NA, Chen H, Valois MF & Liautaud A. (2013). Traffic-related air pollution and prostate cancer risk in Montreal, Canada. Occupational & Environmental Medicine, 70: 511–518.

Parent ME, Rousseau MC, El-Zein M, Latreille B, Desy M & Siemiatycki J. (2011). Occupational and recreational physical activity during adult life and the risk of cancer among men. Cancer Epidemiology, 35: 151-159.

Parikesit D, Mochtar CA, Umbas R & Hamid ARAH. (2016). The impact of obesity towards prostate diseases. Prostate International, 4(1): 1-6.

Park SY, Murphy SP, Wilkens LR, Henderson BE & Kolonel LN. (2007). Fat and meat intake and prostate cancer risk: the multiethnic cohort study. International Journal of Cancer, 121(6): 1339-1345.

Pearce N, Checkoway H & Kreibel D. (2007). Bias in occupational epidemiology studies. Occupational and Environmental Medicine, 64(8): 562-568.

Perdana NR, Mochtar CA, Umbas R & Maid ARAH. The risk factors of prostate cancer and its prevention: a literature review. Acta Med Indones 2016, 48(3): 228-238.

Peters CE, Demers PA, Kalia S, Hystad P, Villeneuve PJ, Nicol A, Kreiger N & Koehoorn MW. (2016). Occupational exposure to solar ultraviolet radiation and the risk of prostate cancer. Occupational and Environmental Medicine, 73; 743-748.

Peters PA, Tjepkema M, Wilkins R, Fines P, Crouse DL, Chan PCW & Burnett RT. (2013). Data resource profile: 1991 Canadian census cohort. International Journal of Epidemiology, 42: 1319-1326.

Peters S, Reid A, Fritschi L, Musk AW & de Klerk N. (2013). Cancer incidence and mortality among underground and surface goldminers in Western Australia. British Journal of Cancer, 108(9):1879-1882.

Peters C, Villeneuve P, Ladak S & Parent M. (2016). P193 occupation as a predictor of prostate cancer screening behaviour. Occupational and Environmental Medicine, 73 (Issue Suppl 1).

Plata BA & Concepcion MT. (2014). Prostate cancer epidemiology. Archivos Espanoles De Urologia, 67(5):373-82.

Platz, E. A., & Giovannucci, E. (2010). Cancer epidemiology and prevention – prostate cancer, 3rd edition. New York, USA: Oxford University Press. Pages 1128-1150.

Potosky AL, Feuer EJ & Levin DL. (2001). Impact of screening on incidence and mortality of prostate cancer in the United States. Epidemiologic Reviews, 23(1): 181-186.

Prins GS. (2008). Endocrine disruptors and prostate cancer risk. Endocrine Related Cancer, 15(3): 649.

Pronk A, Coble J & Stewart P. (2009). Occupational exposure to diesel engine exhaust: a literature review. Journal of Exposure Science and Environmental Epidemiology, 19(5): 443-457.

Prostate Cancer Canada. (2016). The PSA test. Toronto, Canada: Prostate Cancer Canada. http://prostatecancer.ca/Prostate-Cancer/Testing-and-Diagnosis/The-PSA-Test (accessed November 7, 2016)

Prostate Cancer Canada. (2016). Young men & prostate cancer. Toronto, Canada: Prostate Cancer Canada. http://prostatecancer.ca/Prostate-Cancer/Care-and-Support-Post-Treatment/Young-Men-Prostate-Cancer (accessed October 17, 2016)

Prostate Cancer Canada. (2017). Transurethral resection of the prostate (TURP). Toronto Canada: Prostate Cancer Canada. http://prostatecancer.ca/Prostate-Cancer/Treatment/TURP (accessed May 25, 2017)

Prostate Cancer Foundation. (2017). Prevention. Santa Monica, USA. https://www.pcf.org/c/prevention/ (accessed August 24, 2017)

Pukkala E, Aspholm R, Auvinen A, Eliasch H, Gundestrup M, Haldorsen T, Hammar N, Hrafnkelsson J, Kyyronen P, Linnersjo A, Rafnsson V, Storm H & Tveten U. (2003). Cancer incidence among 10, 211 airline pilots: a nordic study. Aviation, Space, and Environmental Medicine, 74(7): 699-706.

Pukkala E, Martinsen JI, Lynge E, Gunnarsdottir HK, Sparen P, Tryggvadottir L, Weiderpass E & Kjaerheim K. (2009). Occupation and cancer – follow-up of 15 million people in five Nordic countries. Acta Oncologica, 48(5): 646-790.

Pukkala E, Martinsen JI, Weiderpass E, Kjaerheim K, Lynge E, Tryggvadottir L, Sparen P & Demers PA. (2014). Cancer incidence among firefighters: 45 years of follow-up in five Nordic countries. Occupational and Environmental Medicine, 71: 398-404.

Rafnsson V. (2007). Farming and prostate cancer. Occupational and Environmental Medicine, 64(3): 143.

Ragin C, Davis-Reyes B, Tadesse H, Daniels D, Bunker CH, Jackson M, Ferguson TS, Patrick AL, Tulloch-Reid MK & Taioli E. (2013). Farming, reported pesticide use, and prostate cancer. American Journal of Men's Health, 7(2): 102-109.

Rao D, Yu H, Bai Y, Zheng X & Xie L. (2015). Does night-shift work increase the risk of prostate cancer? A systematic review and meta-analysis. OncoTargets & Therapy, 8:2817-26.

Richardson H, Aronson KJ, James A, McGregor ES & Bryant H. (2007). Factors related to use of prostate cancer screening: the Alberta tomorrow project. Open Medicine, 1(1): e3-e12.

Richter CA, Birnbaum LS, Farabollini F, Newbold RR, Rubin BS, Talsness CE, Vandenbergh JG, Walser-Kuntz DR & vom Saal FS. (2007). In vivo effects of bisphenol A in laboratory rodent studies. Reproductive Toxicology, 24(2): 199-224.

Ritter L, Blair A, Kerkvliet NI, Sigal EA & Stellman JM. (2014). Report of the independent fact-finding panel on herbicide 2, 4, 5-T: final report. Government of Ontario. http://www.ontario.ca/page/contact-herbicide-245-t (accessed 25 November 2015)

Robinson CF, Petersen M & Palu S. (1999). Mortality patterns among electrical workers employed in the US construction industry, 1982-1987. American Journal of Industrial Medicine, 36(6): 630-637.

fRoddam AW, Allen NE, Appleby P, and Endogenous Hormones and Prostate Cancer Collaborative Group. (2008). Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. Journal of National Cancer Institute, 100(3): 170-183.

Rogers D, Boyd DD, Fox EE, Cooper S, Goldhagen M, Shen Y, del Junco DJ. (2011). Prostate cancer incidence in air force aviators compared with non-aviators. Aviation, Space, and Environmental Medicine, 82(11): 1067-1070.

Ronco G, Costa G & Lynge E. (1992). Cancer risk among Danish and Italian farmers. British International Journal of Medicine, 49(4): 220-225.

Rooney C, Beral V, Maconochie N, Fraser P & Davies G. (1993). Case-control study of prostatic cancer in employees of the United Kingdom atomic energy authority. BMJ, 307(6916): 1391-1397.

Ross L, Dark T, Orom H, Underwood W, Anderson-Lewis C, Johnson J & Erwin DO. (2011). Patterns of information behaviour and prostate cancer knowledge among African-American men. Journal of Cancer Education, 26(4): 708-716.

Ruder AM, Hein MJ, Hopf NB & Waters MA. (2014). Mortality among 24,865 workers exposed to polychlorinated biphenyls (PCBs) in three electrical capacitor manufacturing plants: a ten-year update. International Journal of Hygiene and Environmental Health, 217(0): 176-187

Rundle A, Neckerman KM, Sheehan D, Jankowski M, Kryvenko ON, Tang D & Rybicki BA. (2014). A prospective study of socioeconomic status, prostate cancer screening and incidence among men at high risk for prostate cancer. Cancer Causes Control, 24(2): 297-303.

Sahmoun AE, Case LD, Jackson SA & Schwartz GG. (2005). Cadmium and prostate cancer: a critical epidemiologic analysis. Cancer Investigation, 23(3):256-263.

Sanderson M, Coker AL, Logan P, Zheng W & Fadden MK. (2004). Lifestyle and prostate cancer among older African-American and Caucasian men in South Carolina. Cancer Causes and Control, 15: 647-655.

SAS Institute Inc. (2015). SAS 9.4. Cary, USA: SAS. http://www.sas.com/en_ca/home.html (accessed October 2015).

Sass Kortsak AM, Purdham JT, Kreiger N, Darlington G & Lightfoot NE. (2007). Occupational risk factors for prostate cancer. American Journal of Industrial Medicine, 50(8): 568-576.

Sauve JF, Lavoue J & Parent ME. (2016). Occupation, industry and the risk of prostate cancer: a case-control in Montreal, Canada. Environmental Health, 15:100.

Savovic J & Martin RM. (2008). Height and prostate cancer risk. Cancer Epidemiology, Biomarkers & Prevention, 17(9): 2325-2336.

Schroder FH, Hugosson J, Roobol MJ, Tammela TLJ, Ciatto S, Nelen V, et al. (2009). Screening and prostate-cancer mortality in a randomized European study. The New England Journal of Medicine, 360: 1320-1328.

Schroder FH, Hugosson J, Roobol MJ, Tammela TLJ, Zappa M, Nelen V et al. (2014). The European randomized study of screening for prostate cancer – prostate cancer mortality at 13 years of follow-up. Lancet, 384(9959): 2027-2035.

Schuurman AG, Goldbohm RA, Dorant E & van den Brandt PA. (1998). Vegetable and fruit consumption and prostate cancer risk: a cohort study in the Netherlands. Cancer Epidemiology Biomarkers and Prevention, 7(8): 673–680.

Schwartzbaum J, Ahlbom A & Feychting M. (2007). Cohort study of cancer risk among male and female shift workers. Scandinavian Journal of Work, Environment & Health, 33(5): 336-343.

Seidler A, Heiskel H, Bickeboller R & Elsner G. (1998). Association between diesel exposure at work and prostate cancer. Scandinavian Journal of Work, Environmental & Health, 24(6): 486-494.

Shah D. (2009). Healthy worker effect phenomenon. Indian Journal of Occupational and Environmental Medicine, 13(2): 77-79.

Shang Y, Han G, Li J, Zhao J, Cui D, Liu C & Yi S. (2015). Vasectomy and prostate cancer risk: a meta-analysis of cohort studies. Scientific Reports, 5: 9920.

Sharlip ID, Belker AM, Honig S, Labrecque M, Marmar JL, Ross LS, Sandlow JI & Sokal DC. (2012). Vasectomy: AUA guideline. Maryland: USA, American Urological Association. Accessed on October 13, 2016 from https://www.auanet.org/common/pdf/education/clinical-guidance/Vasectomy.pdf

Sharma M, Lawson JA, Kanthan R, Karunanayake C, Hagel L, Rennie D, Dosman JA, Pahwa P & the Saskatchewan Rural Cohort Study Group. (2016). The Journal of Rural Health, 32: 125-135.

Sharma-Wagner S, Chokkalingam AP, Malker HS, Stone BJ, McLaughlin JK & Hsing AW. (2000). Occupation and prostate cancer risk in Sweden. Journal of Occupational and Environmental Medicine, 42(5): 517-525.

Shelke AR & Mohile SG. (2011). Treating prostate cancer in elderly men: how does aging affect the outcome? Geriatric Oncology, 12: 263-275.

Shephard RJ. (2017). Physical activity and prostate cancer: an updated review. Sports Medicine, 47(6): 1055-1073.

Siddiqui MK, Srivastava S & Mehrotra PK. (2002). Environmental exposure to lead as a risk for prostate cancer. Biomedical and Environmental Sciences, 15, 298-305.

Siemiatycki J, Richardson L, Straif K, Benoit L, Lakhani R, Campbell S, Rousseau MC & Boffetta P. (2005). Listing occupational carcinogens. Environmental Health Perspectives, 112(15): 1447-1459.

Sigurdardottir LG, Valdimarsdottir UA, Fall K, Rider JR, Lockley SW, Schernhammer E & Mucci LA. (2012). Circadian disruption, sleep loss, and prostate cancer risk: a systematic risk of epidemiologic studies. Cancer Epidemiology, Biomarkers & Prevention, 21(7): 1002-1011.

Silva JFS, Mattos IE, Luz LL, Carmo CN & Aydos RD. (2016). Exposure to pesticides and prostate cancer: systematic review of the literature. Reviews on Environmental Health, doi: 10.1515/reveh-2016-0001.

Silva M, Santana VS & Loomis D. (2000). Cancer mortality among Brazilian navy personnel. Revista de Saude Publica, 34(4): 373-379.

Sim MR, Del Monaco A, Hoving JL, Macfarlane E, McKenzie D, Benke G, de Klerk N & Fritsch L. (2009). Mortality and cancer incidence in workers in two Australian prebake aluminum smelters. Occupational and Environmental Medicine, 66(7): 464-470.

Singh GK & Jemal A. (2017). Socioeconomic and racial/ethnic disparities in cancer mortality, incidence, and survival in the United States, 1950-2014: over six decades of changing patterns and widening inequalities. Journal of Environmental and Public Health, 2017: 2819372.

Sinha R, Park Y, Graubard BI, Leitzmann MF, Hollenback A, Schatzkin A & Cross AJ. (2009). Meat and meat-related compounds and risk of prostate cancer in a large prospective cohort study in the United States. American Journal of Epidemiology, 170(9): 1165-1177.

Song JW & Chung KC. (2010). Observational studies: cohort and case-control studies. Plastic and Reconstruction Surgery, 126(6): 2234-2242.

Sorahan T & Esmen N. (2004). Lung cancer mortality in UK nickel-cadmium battery workers, 1947–2000. Occupational and Environmental Medicine, 61: 108–116.

Sorahan T, Lister A, Gilthorpe MS & Harrington JM. (1995). Mortality of copper cadmium alloy workers with special reference to lung cancer and non-malignant diseases of the respiratory system, 1946–92. Occupational and Environmental Medicine, 52: 804–812.

Southcott C. (2008). The changing industrial structure of Northern Ontario. Ontario; Canada: Local Boards of Northern Ontario, 1-39. http://awic.ca/documents/assets/uploads/files/en/6_the_changing_industrial_structure_of_northern_ontario.pdf (accessed September 20, 2017)

Sritharan J, Demers PA, Harris SA, Cole DC, Kreiger N, Sass-Korstak A & Lightfoot N. (2016). Natural resource-based industries and prostate cancer risk in Northeastern Ontario: a case-control study. Occupational and Environmental Medicine, 73: 506-511.

Sritharan J, Demers PA, Harris SA, Cole DC, Peters CE, the Canadian Cancer Registries Epidemiology Research Group & Villeneuve PJ. (2017a). Occupation and risk of prostate cancer in Canadian men: a case-control study across eight Canadian provinces. Cancer Epidemiology, 48: 96-103.

Sritharan J, MacLeod J, Harris S, Cole DC, Harris A, Tjepkema M, Peters PA & Demers PA. (2018). Prostate cancer surveillance by occupation and industry: the Canadian census health and environment cohort (CanCHEC). Manuscript submitted to Cancer Medicine (currently under review).

Sritharan J, Pahwa M, Demers PA, Harris S, Cole DC & Parent ME. (2017b). Prostate cancer in firefighting and police work: a systematic review and meta-analysis of epidemiologic studies. Manuscript submitted to Environmental Health, 16: 124.

Stangelberger A, Waldert M & Djavan B. (2008). Prostate cancer in elderly men. Reviews in Urology, 10(2): 111-119.

Statistics Canada. (1980). Standard industrial classification. Ottawa: Minister of Supply and Services. http://www23.statcan.gc.ca/imdb/p3VD.pl?Function=getVD&TVD=53446 (accessed August 2015)

Statistics Canada. (1993). Standard occupational classification. Ottawa: Minister of Industry, Science and Technology. http://www23.statcan.gc.ca/imdb/p3VD.pl?Function=getVD&TVD=143375 (accessed August 2015)

Statistics Canada. (2009). Visible minority population, by province and territory (2006 census). Ottawa, Canada; Statistics Canada. http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/demo52a-eng.htm (accessed July 9, 2017)

Statistics Canada. (2010). ARCHIVED – chronic diseases in Canada. Ottawa: Public Health Agency of Canada. http://www.phac-aspc.gc.ca/publicat/hpcdp-pspmc/30-4/preface-eng.php (accessed September 2015)

Statistics Canada. (2011). Canadian forces cancer and mortality study: causes of death. Ottawa, ON: Statistics Canada and Health Canada. http://www.statcan.gc.ca/pub/82-584-x/82-584-x2011001-eng.pdf (accessed October 7, 2016)

Statistics Canada. (2015). Labour force survey: Average hours usually worked. Ottawa, CA: Statistics Canada. http://www.statcan.gc.ca/pub/71-222-x/2008001/sectionh/h-hours-heures-eng.htm (accessed July 10, 2017)

Statistics Canada. (2016). Portrait of Canada's labour force. Statistics Canada; Ottawa, Canada. https://www12.statcan.gc.ca/nhs-enm/2011/as-sa/99-012-x/99-012-x2011002-eng.cfm (accessed December 1, 2016).

Stellman SD, Demers PA, Colin D, & Boffetta P. (1998). Cancer mortality and wood dust exposure among participants in the American cancer society cancer prevention study-II (CPS-II). American Journal of Industrial Medicine, 34: 229-237.

Stewart RE, Dennis LK, Dawson Dv, Resnick MI. (1999). A meta-analysis of risk estimates for prostate cancer related to tire and rubber manufacturing operations. Journal of Occupational and Environmental Medicine, 41: 1079-1084.

Storm HH, Jorgensen HO, Kejs AMT & Engholm G. (2006). Depleted uranium and cancer in Danish Balkan veterans deployed 1992-2001. European Journal of Cancer, 42: 2355-2358.

Strand LA, Martinsen JI & Borud EK. (2015). Cancer incidence and all-cause mortality in a cohort of 21 582 Norwegian military peacekeepers deployed to Lebanon during 1978-1998. Cancer Epidemiology, 39: 571-577.

Strand LA, Martinsen JI, Koefoed VF, Sommerfelt-Pettersen J & Grimsrud TK. (2011). Cause-specific mortality and cancer incidence among 28 300 royal Norwegian navy servicemen followed for more than 50 years. Scandinavian Journal of Work, Environment & Health, 37(4): 307-315.

Sun Y, Taeger D, Weiland SK, Keil U & Straif K. (2003). Job titles and work areas as surrogate indicators of occupational exposure. Epidemiology, 14(3): 361-367.

Svensson B-G, Nilsson A, Jonsson E, Schutz A, Akesson B & Hagmar L. (1995). Fish consumption and exposure to persistent organochlorine compounds, mercury, selenium, methylamines among Swedish fishermen. Scandinavian Journal of Work, Environment & Health, 21(2): 96-105.

Szymanski KM, Wheeler DC & Mucci LA. (2010). Fish consumption and prostate cancer risk: a review and meta-analysis. The American Journal of Clinical Nutrition, 92(5): 1223-1233.

Tangen CM, Goodman PJ, Till C, Schenk JM, Scott Lucia M & Thompson IM. (2016). Biases in recommendations for and acceptance of prostate biopsy significantly affect assessment of prostate cancer risk factors: results from two large randomized clinical trials. Urologic Oncology, 34(36): 4338-4344.

Tornling G, Gustavsson P & Hogstedt C. (1994). Mortality and cancer incidence in Stockholm fire fighters. American Journal of Industrial Medicine, 25: 219-228.

Tsai RJ, Luckhaupt SE, Schumacher P, Cress RD, Deapen DM & Calvert GM. (2015). Risk of cancer among firefighters in California, 1988-2007. American Journal of Industrial Medicine, 58(7): 715-729.

Tseng M, Breslow RA, Graubard BI & Ziegler RG. (2005). Dairy, calcium, and vitamin D intakes and prostate cancer risk in the national health and nutrition examination epidemiologic follow-up study cohort. American Journal of Clinical Nutrition, 81(5), 1147–1154.

Tshiswaka DI, Donley T, Okafor A, Memiah P & Mbizo J. (2016). Prostate and colorectal cancer screening uptake among US and foreign-born males: evidence from the 2015 NHIS survey. Journal of Community Health, 10.1007/s10900-016-0296-1.

Tyson MD, Andrews PE, Etzioni DA, Ferrigni RG, Humphreys MR Swanson SK & Castle EK. (2013). Marital status and prostate cancer outcomes. The Canadian Journal of Urology, 20(2): 6702-6706.

US Department of Veterans Affairs. (2016). Military exposures. Washington, DC: US Department of Veterans Affairs. http://www.publichealth.va.gov/exposures/ (accessed October 7, 2016)

Vallieres E, Pintos J, Parent ME & Siemiatycki J (2015). Occupational exposure to wood dust and risk of lung cancer in two population-based case-control studies in Montreal, Canada. Environmental Health, 14:1.

Van der Gulden JWJ. (1996). Farmers at risk for prostate cancer. British Journal of Urology, 77(1): 6-14.

Van der Gulden JWJ. (1997). Metal workers and repairmen at risk for prostate cancer: a review. The Prostate, 30(2): 107-116.

Van der Gulden JWJ, Kolk JJ & Verbeek ALM. (1992). Prostate cancer and work environment. Journal of Occupational Medicine, 34(4): 402-409.

Van Maele-Fabry G & Willems JL. (2003). Occupation related pesticide exposure and cancer of the prostate: a meta-analysis. Occupational and Environmental Medicine, 60(9):634-42.

Van Maele-Fabry G, Libotte V, Willems J & Lison D. (2006). Review and meta-analysis of risk estimates for prostate cancer in pesticide manufacturing workers. Cancer Causes Control, 17(4):353-373.

Vena JE & Fiedler RC. (1987). Mortality of a municipal-worker cohort: IV. Fire fighters. American Journal of Industrial Medicine, 11: 671-684.

Vena JE, Charles LE, Gu JK, Burchfiel CM, Andrew ME, Fekedulegn D & Violanti JM. (2014). Mortality of a police cohort: 1950-2005. Journal of Law Enforcement Leadership and Ethics, 1(1): 7-20.

Verougstraete V, Lison D & Hotz P (2003). Cadmium, lung and prostate cancer: a systematic review of recent epidemiological data. Journal of Toxicology Environmental Health, Part B: Critical Reviews, 6, 227-55.

Veugelers PJ & Yip AM. (2003). Socioeconomic disparities in health care use: does universal coverage reduce inequalities in health? Journal of Epidemiology and Community Health, 57: 424-428.

Villeneuve PJ, Johnson KC, Kreiger N, Mao Y & the Canadian Cancer Registries Epidemiology Research Group. (1999). Risk factors for prostate cancer: results from the Canadian National Enhanced Cancer Surveillance System. Cancer Causes and Control, 10(5): 355-367.

Villeneuve S, Cry D, Lynge E, Orsi L, Sabroe S, Merletti F, Gorini G, Morales-Suarez-Varela M, Ahrens W, Baumgardt-Elms C, Kaerlev L, Eriksson M, Hardell L, Fevotte J & Guenel P. (2010). Occupation and occupational exposure to endocrine disrupting chemicals in male breast cancer: a case-control study in Europe. Occupational and Environmental Medicine, 67(12): 837-844.

Violanti JM, Vena JE & Petralia S. (1998). Mortality of a police cohort: 1950-1990. American Journal of Industrial Medicine, 33: 366-373.

von Hippel PT. (2015). The heterogeneity statistic I2 can be biased in small meta-analyses. BMC Medical Research Methodology, 15: 35.

Wallner LP, Sarma AV, Lieber MM, St Sauver JL, Jacobson DJ, McGree ME, Gowan ME & Jacobsen SJ. (2008). Psychosocial factors associated with an increased frequency of prostate cancer screening in men ages 40 to 79 years: the Olmsted County study. Cancer Epidemiology, Biomarkers, and Prevention, 17(12): 3588-3592.

Wallstrom P, Bjartell A, Gullberg B, Olsson H & Wirfalt E. (2007). A prospective study on dietary fat and incidence of prostate cancer (Malmo, Sweden). Cancer Causes & Control, 18(10): 1107-1121.

Watanabe KK & Kang HK. (1996). Mortality patterns among Vietnam veterans. Journal of Occupational and Environmental Medicine, 38(3): 272-278.

Weichenthal S, Lavigne E, Valois MF, Hatzopoulou M, Van Ryswyk K, Shekarrizfard M, Villeneuve P, Goldberg M & Parent MÉ. (2017). Spatial variations in ambient ultrafine particle concentrations and the risk of incident prostate cancer: a case-control study. Environmental Research, 156: 374-380.

Wells TS, Bukowinski AT, Smith TC, Smith B, Dennis LK, Chu LK, Gray GC & Ryan MAK. (2010). Racial differences in prostate cancer risk remain among US servicemen with equal access to care. The Prostate, 70: 727-734.

Wilkins R, Tjepkema M, Mustard C & Choiniere R. (2008). The Canadian census mortality follow-up study, 1991 through 2001. Health Reports, 19:25-43.

Wingren G & Axelson O. (2007). Cancer incidence and mortality in a Swedish rubber tire manufacturing plant. American Journal of Industrial Medicine, 50:901-909.

Wirth M, Burch J, Violanti J, Burchfiel C, Fekedulegn D, Andrew M, Zhang H, Miller DB, Hebert JR & Vena JE. (2011). Shiftwork duration and the awakening cortisol response among police officers. Chronobiology International, 28(5): 446-457.

Wirth M, Vena JE, Smith EK, Bauer SE, Violanti J & Burch J. (2013). The epidemiology of cancer among police officers. American Journal of Industrial Medicine, 56(4): 439-453.
Wong O & Raabe GK. (2000). A critical review of cancer epidemiology in the petroleum industry, with a meta-analysis of a combined database of more than 350,000 workers. Regulatory Toxicology & Pharmacology, 32, 78-98.

Workplace Safety and Insurance Board (WSIB). (2017). Cancers in firefighters and fire investigators. Ontario, Canada: WSIB. http://www.wsib.on.ca/WSIBPortal/faces/WSIBManualPage?cGUID=23-02-01&fGUID=835502100635000537&_afrLoop=759728824674000&_afrWindowMode=0&_afrWindowId=null#%40%3FcGUID%3D23-02-01%26_afrWindowId%3Dnull%26_afrLoop%3D759728824674000%26_afrWindowMode%3D0%26fGUID%3D835502100635000537%26_adf.ctrl-state%3D4nca5nbd7_4 (accessed March 2, 2018).

World Cancer Research Fund International. (2014). Diet, nutrition, physical activity, and prostate cancer. London, UK: WCRF. http://www.wcrf.org/sites/default/files/Prostate-Cancer-2014-Report.pdf (accessed July 19, 2016)

World Health Organization. (1994). Global strategy on occupational health for all: the way to health at work. www.who.int/occupational_health/publications/globstrategy/en/index2.html

Wu I. (2012). Disparities in prostate cancer in African American men: what primary care physicians can do. Cleveland Clinic Journal of Medicine, 79(5): 313-320.

Xu C, Han FF, Zeng XT, Liu TZ, Li S & Gao ZY. (2015). Fat intake is not linked to prostate cancer: a systematic review and dose-response meta-analysis. PloS One, 10(7): e0131747.

Yamane GK. (2006). Cancer incidence in the U.S. air force: 1989-2002. Aviation, Space, and Environmental Medicine, 77: 7789-7794.

Yi SW. (2013). Cancer incidence in Korean Vietnam Veterans during 1992-2003: the Korean Veterans health study. Journal of Preventative Medicine and Public Health, 46: 309-318.

Yong M, Blettner M, Emrich K, Nasterlack M, Oberlinner C & Hammer GP. (2014). A retrospective cohort study of shift work and risk of incident cancer among German male chemical workers. Scandinavian Journal of Work, Environment & Health, 40(5): 502-510.

Young HA, Maillard JD, Levine PH, Simmens SJ, Mahan CL & Kang HK. (2010). Investigating the risk of cancer in 1990-1991 US gulf war veterans with the use of state cancer registry data. Annals of Epidemiology, 20(4): 265-272.

Young, E., Kreiger, N., Purdham, J., & Sass-Kortsak, A. (2009). Prostate cancer and driving occupations: could whole body vibrations play a role? International Archives of Occupational and Environmental Health, 82(5): 551-556.

Young-McCaughan S. (2012). Potential for prostate cancer prevention through physical activity. World Journal of Urology, 30(2): 167-179.

Zeegers MP, Friesema IH, Goldbohm RA & van den Brandt PA. (2004). A prospective study of occupation and prostate cancer risk. Journal of Occupational & Environmental Medicine, 46(3): 271-279.

Zhao J, Stockwell T, Roemer A & Chikritzhs T. (2016). Is alcohol consumption a risk factor for prostate cancer? A systematic review and meta-analysis. BMC Cancer, 16: 845.

Zhu K, Devesa SS, Wu H, Zahm SH, Jatoi I, Anderson WF, Peoples G, Maxwell LG, Granger E, Potter JF, & McGlynn KA. (2009). Cancer incidence in the U.S. military population: comparison with rates from the SEER program. Cancer Epidemiology, Biomarkers, and Prevention, 18(6): 1740-1745.

Zuccolo L, Harris R, Gunnell D, Oliver S, Lane JA, Davis M, Donovan J, Neal D, Hamdy F, Beynon R, Savovic J, Martin RM. (2008). Height and prostate cancer risk: a large nested case-control study (ProtecT) and meta-analysis. Cancer Epidemiology, Biomarkers, and Prevention, 17(9): 2325-36.

Appendix 1.

Contributions

I, Jeavana Sritharan, was the primary contributor to this thesis. I was involved in all aspects of this thesis including planning and preparation, analysis and interpretation, and writing of all research and publications.

Dr. Paul A. Demers (Primary Supervisor): Mentorship, guidance with planning and preparation, interpretation of analysis, and manuscript and thesis preparation

Dr. Shelley A. Harris (Committee Member): Mentorship, guidance, interpretation of analysis, manuscript and thesis preparation

Dr. Donald C. Cole (Committee Member): Mentorship, guidance, interpretation of analysis, manuscript and thesis preparation

Dr. John R. McLaughlin (Additional Faculty at the Final PhD Committee Meeting): assistance with preparation of final thesis and defense

Study 1: Northeastern Ontario Prostate Cancer Study
Dr. Nancy Lightfoot, Dr. Nancy Kreiger, and Dr. Andrea Sass-Kortsak: assistance in obtaining data, interpretation of results, and manuscript preparation

Study 2: National Enhanced Cancer Surveillance System
Dr. Paul J. Villeneuve, Dr. Cheryl E. Peters, and the Canadian Cancer Registries Epidemiology Research Group: assistance in obtaining data, interpretation of results, and manuscript preparation

Study 3: Canadian Census Health & Environment Cohort
Jill MacLeod, Michael Tjepkema, Dr. Paul A. Peters, and Dr. Anne Harris: assistance in obtaining data, analysis and interpretation of results, and manuscript preparation

Study 4: Prostate Cancer in Firefighting and Police Work: Systematic Review & Meta-analysis

Dr. Marie-Elise Parent and Manisha Pahwa: assistance in obtaining data, analysis and interpretation of results, and manuscript preparation

Appendix 2.

Supplementary Table 1. Industry and occupation categories based on standard industrial and occupational classification systems for the Northeastern Ontario Prostate Cancer Study

Industry Categories	Standard Industrial Classification (SIC80)
Agriculture and Farm Work, Services Incidental to Agriculture	0111 Dairy Farms
	0112 Cattle Farms
	0113 Hog Farms
	0114 Poultry and Egg Farms
	0115 Sheep and Goat Farms
	0119 Livestock Combination Farms
	0121 Honey and Other Apiary Product Farms
	0122 Horse and Other Equine Farms
	0123 Furs and Skins, Ranch
	0129 Other Animal Specialty Farms n.e.c.
	0131 Wheat Farms
	0132 Small-Grain Farms (Except Wheat)
	0133 Oilseed Farms (Except Corn)
	0134 Grain Corn Farms
	0135 Forage, Seed and Hay Farms
	0136 Dry Field Pea and Bean Farms
	0137 Tobacco Farms
	0138 Potato Farms
	0139 Other Field Crop Farms
	0141 Field Crop Combination Farms
	0151 Fruit Farms
	0152 Other Vegetable Farms
	0159 Fruit and Vegetable Combination Farms
	0161 Mushrooms
	0162 Greenhouse Products
	0163 Nursery Products
	0169 Other Horticultural Specialties
	0171 Livestock, Field Crop and Horticultural Combination Farms
	0211 Veterinary Services
	0212 Farm Animal Breeding Services (Except Poultry)
	0213 Poultry Services
Fishing and Trapping	0311 Salt Water Fishing Industry
	0312 Inland Fishing Industry
	0321 Services Incidental to Fishing
	0331 Furs and Skins, Wild
	0339 Other Trapping

Forestry and Logging	0411 Logging Industry (Except Contract Logging) 0412 Contract Logging Industry 0511 Forestry Services Industry
Metal Mining	0611 Gold Mines 0612 Copper and Copper-Zinc Mines 0613 Nickel-Copper Mines 0614 Silver-Lead-Zinc Mines 0615 Molybdenum Mines 0616 Uranium Mines 0617 Iron Mines 0619 Other Metal Mines
Non Metal Mining	0621 Asbestos Mines 0622 Peat Industry 0623 Gypsum Mines 0624 Potash Mines 0625 Salt Mines 0629 Other Non-Metal Mines (Except Coal) 0631 Bituminous Coal Mines 0632 Subbituminous Coal Mines 0633 Lignite Mines 3592 Asbestos Products Industry 3593 Gypsum Products Industry
Other Services Incidental to Mining	0921 Contract Drilling Industry (Except Oil and Gas) 0929 Other Service Industries Incidental to Mining
Paper and Allied Products	2711 Pulp Industry 2712 Newsprint Industry 2713 Paperboard Industry 2714 Building Board Industry 2719 Other Paper Industries 2721 Asphalt Roofing Industry 2731 Folding Carton and Set-Up Box Industry 2732 Corrugated Box Industry 2733 Paper Bag Industry 2791 Coated and Treated Paper Industry 2792 Stationery Paper Products Industry 2793 Paper Consumer Products Industry 2799 Other Converted Paper Products Industries n.e.c.
Petroleum and Coal	0711 Conventional Crude Oil and Natural Gas Industry 0712 Non-Conventional Crude Oil Industry 0911 Contract Drilling, Oil and Gas Industry 0919 Other Service Industries Incidental to Crude Petroleum and Natural Gas 3611 Refined Petroleum Products Industry (Except Lubricating Oil and Grease)

	3612 Lubricating Oil and Grease Industry 3699 Other Petroleum and Coal Products Industries 4112 Gas, Oil and Other Energy Related Structures (Except Pipelines) 4113 Gas and Oil Pipelines
Quarrying	0811 Granite Quarries 0812 Limestone Quarries 0813 Marble Quarries 0814 Sandstone Quarries 0815 Shale Quarries 0821 Sand and Gravel Pits
Wood Products	2511 Shingle and Shake Industry 2512 Sawmill and Planing Mill Products Industry (Except Shingles and Shakes) 2521 Hardwood Veneer and Plywood Industry 2522 Softwood Veneer and Plywood Industry 2541 Prefabricated Wooden Buildings Industry 2542 Wooden Kitchen Cabinet and Bathroom Vanity Industry 2543 Wooden Door and Window Industry 2549 Other Millwork Industries 2561 Wooden Box and Pallet Industry 2581 Coffin and Casket Industry 2591 Wood Preservation Industry 2592 Particle Board Industry 2593 Wafer Board Industry 2599 Other Wood Industries n.e.c.
Occupation Categories	**Standard Occupational Classification (SOC91)**
Farmers, Farm and Agriculture Managers	I011 Farmers and Farm Managers I012 Agricultural and Related Service Contractors and Managers I013 Farm Supervisors and Specialized Livestock Workers I014 Nursery and Greenhouse Operators and Managers I017 Aquaculture Operators and Managers
Agriculturists and Related Specialists	C023 Agricultural Representatives Consultants and Specialists C122 Agricultural and Fish Products Inspectors C124 Conservation and Fishery Officers C125 Landscape and Horticultural Technicians and Specialists G134 Grain Elevator Operators
General Farm Workers and Labourers	I021 General Farm Workers I022 Nursery and Greenhouse Workers I211 Harvesting Labourers

Fishing, Trapping, and Hunting	I171 Fishing Masters and Officers I172 Fishing Vessel Skippers and Fishermen-women I181 Fishing Vessel Deckhands I182 Trappers and Hunters I213 Aquaculture and Marine Harvest Labourers
Forestry and Logging	C022 Forestry Professionals C123 Forestry Technologists and Technicians I111 Supervisors Logging and Forestry I151 Logging Machinery Operators I161 Chain-saw and Skidder Operators I162 Silviculture and Forestry Workers I216 Logging and Forestry Labourers
Mining, Quarrying, Oil, and Gas	C043 Mining Engineers H622 Drillers and Blasters - Surface Mining Quarrying and Construction I121 Supervisors Mining and Quarrying I122 Supervisors Oil and Gas Drilling and Service I131 Underground Production and Development Miners I132 Oil and Gas Well Drillers Servicers Testers and Related Workers I141 Underground Mine Service and Support Workers I142 Oil and Gas Well Drilling Workers and Services Operators I214 Mine Labourers I215 Oil and Gas Drilling Servicing and Related Labourers
Primary Production and Manufacturing Managers	A373 Transportation Managers A381 Primary Production Managers - except Agriculture A391 Manufacturing Managers
Pulp and Papermaking	J113 Pulping Control Operators J114 Papermaking and Coating Control Operators J142 Pulp Mill Machine Operators J143 Papermaking and Finishing Machine Operators J145 Paper Converting Machine Operators J314 Labourers in Wood Pulp and Paper Processing
Wood Processing and Making	H015 Contractors and Supervisors Carpentry Trades H121 Carpenters H122 Cabinetmakers J015 Supervisors Forest Products Processing J141 Sawmill Machine Operators J144 Other Wood Processing Machine Operators J146 Lumber Graders and Other Wood Processing Inspectors and Graders J193 Woodworking Machine Operators J223 Other Wood Products Assemblers and Inspectors