Determining the Natural History of Men with Initially Negative Prostate Biopsies

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science

Institute of Medical Sciences University of Toronto

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Abstract

Prostate biopsies have significant false negative rates. Thus, men with negative results may undergo continued evaluation for prostate cancer. Long-term prostate cancer diagnosis, mortality, and treatment rates are currently unknown in North American men with a negative prostate biopsy. We thus aimed to determine the long-term rates and predictors of these outcomes.

Using linked health administrative data, we identified 95,655 men with a single negative prostate biopsy. The outcomes cumulative rates were determined under a competing risk setting and regression analysis was used to assess potential predictors.

The 20-year prostate cancer diagnosis and mortality cumulative rates were 23.7% and 1.8%, respectively. Older patients had higher cancer diagnosis and mortality risks; whereas men of higher socioeconomic status and urban residence had increased cancer diagnosis, yet lower cancer mortality risks. These results will allow physicians to inform patients of their cancer-specific outcomes and identify men at higher risk of adverse long-term outcomes.

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Statement of Contributions

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List of Abbreviations

ADT: Androgen deprivation therapy AMACR: α-methyl-CoA racemase AS: Active surveillance AUA: American Urological Association BCL2: B-cell lymphoma 2 BRCA1: Breast cancer 1 BRCA2: Breast cancer 2 CAPB: Cancer of the Prostate and Brain CCI: Canadian Classification of Health Interventions CCO: Cancer Care Ontario CIF: Cumulative incidence function CIHI DAD: Canadian Institute for Health Information- Discharge Abstract Database CRPC: Castrate-resistant prostate cancer DRE: Digital rectal examination EAU: European Association of Urology EBRT: External beam radiotherapy ED: Erectile dysfunction EphB2: Ephrin type-B receptor 2 ERSPC: European Randomized Study of Screening for Prostate Cancer FN: False negative GnRH: Gonadotropin-releasing hormone **GS:** Gleason Score HBOC: Hereditary Breast and Ovarian Cancer HGPIN: High-grade prostatic intraepithelial neoplasia HPC-1: Hereditary prostate cancer 1 HR. Hazard ratio ICD: International Statistical Classification of Diseases and Related Health Problems ICES: Institute of Clinical and Evaluative Sciences IGF-1: Insulin-like Growth Factor 1

IKN: ICES Key Number

IQR: Interquartile range

LHRH: Luteinizing hormone-releasing hormone

MAST: Metformin Active Surveillance

MOHLTC: Ministry of Health and Long Term Care

MRI: Magnetic resonance imaging

NCCN: National Comprehensive Cancer Network

OCR: Ontario Cancer Registry

ODB: Ontario Drug Benefit

OHIP: Ontario Health Insurance Plan

OR: Odds ratio

ORGD: Office of the Registrar General – Deaths

PCa: Prostate cancer

PCAP: Predisposing for Prostate Cancer

PEATS: Prostate evasive anterior tumors

PHIPA: Personal Health Information Protection Act

PIVOT: Prostate Cancer Intervention versus Observation Trial

PLCO: Prostate, Lung, Colorectal, and Ovarian

PSA: Prostate-specific antigen

RCT: Randomized controlled trial

RP: Radical prostatectomy

RPDB: Registered Persons Database

RR: Relative risk

SELECT: Selenium and Vitamin E Cancer Prevention Trial

SPCG-4: Scandinavian Prostate Cancer Group Study Number 4

TNM: Tumor-node-metastasis

TRUS: Transrectal ultrasound

TRUS-Bx: Transrectal ultrasound-guided prostate biopsy

TURP: Trans-urethral resection of the prostate

USPSTF: United States Preventive Services Task Force

WW: Watchful waiting

XRT: Radiotherapy

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Chapter One Literature Review

1 Literature Review

1.1 Epidemiology of Prostate Cancer

Prostate cancer (PCa) is the second most commonly diagnosed cancer among men, second only to non-melanoma skin cancer ("Prostate cancer statistics", 2017), and accounted for 14% (903,500) of all new cancer cases in 2008 (Ferlay, 2010). It is estimated that the lifetime risk of diagnosis with PCa among Canadian men is one in eight ("Prostate cancer statistics", 2017).

With regards to mortality risk, it is estimated that one in 27 Canadian men will actually die from PCa (~3.7% lifetime risk) ("Prostate cancer statistics", 2017), accounting for 6% of total cancer deaths (Ferlay, 2010). It is estimated that about 4,000 Canadian men die yearly from PCa ("Prostate cancer statistics", 2017).

Incidence rates of PCa differ worldwide, with the highest rates recorded in Europe, North America and Australia and the lowest rates in various Asian countries ("American Cancer Society", 2017). This higher rate is partly explained by the common use of the prostate-specific antigen (PSA), an enzyme specifically secreted by prostate epithelial cells, screening test in these countries. However, it is important to note that such differences in incidence rates existed prior to widespread use of PSA testing, emphasizing the importance of other geographic, environmental and genetic factors in PCa pathogenesis ("American Cancer Society", 2017). With respect to cancer mortality, it is recognized that males of African descent in the Caribbean region have the highest PCa mortality rates, which is potentially due to specific genetic mutations in this population (Bock et al., 2009; Miller et al., 2003).

Interestingly, despite the lifetime risk of being diagnosed with PCa being one in eight, it seems that the corresponding risk of developing or harboring PCa is much higher. In an autopsy study of Russian and Japanese men who died from causes other than PCa, 37% of Caucasian men and 35% of Asian men harbored PCa, with nearly 60% of those aged greater than 80 having PCa (Zlotta et al., 2013). These results provide additional impetus to the argument that a significant proportion of PCa is clinically insignificant and has an indolent course. The clinical challenge herein remains to discern which cancers are significant and mandate active intervention.

1.2 Risk Factors for Prostate Cancer

PCa pathogenesis is a multifactorial process that is dependent on the interplay between various risk factors. It is well established that the risk of PCa is elevated in men of African ethnicity, older men, and in those with a positive family history. Behavioral risk factors such as diet, smoking, and excessive alcohol consumption have also been shown to be associated with an increased risk of PCa (Hamid, 2016). There also seems to be roles for both genetic predispositions among certain ethnic groups (Hamid, 2016) and availability of healthcare as risk factors for diagnosis/development of PCa ("American Cancer Society", 2017).

1.2.1 Age

The risk of PCa increases considerably with age. PCa is rarely diagnosed in men under the age of 40, whereas this risk increases to about 12.5% (i.e. one in eight) in men over 70 years of age (Siegel R et al., 2011). Autopsy studies have also shown that the prevalence of PCa is considerably higher in men who died at an older age. Interestingly, 10% of men aged 20 had evidence of cancer in their prostate, with this risk increasing to nearly 80% by 80 years old (Sakr et al., 1994). These results highlight two important biologic characteristics of PCa: the long natural history of prostate cancer and that the majority of cancers are indolent and clinically insignificant.

1.2.2 Family History

A positive family history is another important risk factor. A history of PCa in a firstdegree relative increases a man's lifetime risk by two- to three-fold compared to a person with a negative family history (Bratt, 2002). This risk rises as the number of affected family members increases and as the age of diagnosis in the family members decreases (Gronberg, 2003). Twin studies have shown high concordance rate between monozygotic twins, highlighting the importance of genetic factors in PCa pathogenesis (Page et al., 1997). Hereditary prostate cancer 1 (HPC-1), breast cancer 1 (BRCA1), and breast cancer 2 (BRCA2) are three important genes that have been shown to be strongly associated with an increased risk of PCa (Mitra et al., 2010; Narod et al., 2008; Tryggvadottir et al., 2007).

1.2.3 Ethnicity

Numerous studies have shown that ethnicity is an important risk factor for PCa. Specifically, African American men, Caribbean men with West African ancestry, and South American men have a higher PCa incidence (and mortality), compared to Caucasian men (Jayadevappa et al., 2011). Data from the National Cancer Institute has revealed that men of African American ethnicity have a two-fold increased risk of PCa diagnosis (54.2/100,000 vs. 24.7/100,000), compared to men of all other ethnicities (Bechis et al., 2010). Moreover, PCa diagnosed in such men is biologically and genetically more aggressive compared to those in men of other ethnic profiles (Wu et al., 2012). Possible genetic explanations for this increased risk among African American men include higher likelihood of having chromosome 8q24 variant mutations, which have been shown to be associated with an increased PCa risk. Higher rates of variation in B- cell lymphoma 2 (BCL2), a cell apoptosis gene, and Ephrin type-B receptor 2, (EphB2), a tumor suppressor gene, are also present in African American men (Whitmann et al., 2010, Wu et al., 2012;). However, it seems that genetic factors are not solely responsible for the differences in PCa risk among different ethnicities. Studies of migrant populations have demonstrated that individuals who move from low-incidence regions to higher-incidence ones have an elevated lifetime risk of PCa diagnosis, similar to that seen in the higher-incidence region. Men from Asian countries, such as China and Japan, who immigrated to the USA, had a higher risk of diagnosis with PCa compared to men living in China and Japan (Gronberg, 2003). These results suggest that disparities in PCa risk among different ethnicities are likely due to a combination of environmental, behavioral, as well as genetic differences between these groups.

1.2.4 Diet

Numerous studies have linked a westernized diet, which is typically rich in animal fat, red meat and dairy products, with an increased risk of PCa (Harvei et al., 1997; Luo et al., 2002). Increased animal saturated fat consumption has consistently been shown to be positively associated with both the incidence and mortality of PCa (Pauwels, 2011). This increased risk may be mediated via α -methyl-CoA racemase (AMACR), an enzyme involved in the oxidation of branched chain fatty acids, which is up regulated in PCa cells (Luo et al., 2002). Fatty acid oxidation leads to generation of reactive oxygen species, which are carcinogenic by nature (Shirai et al., 2002). Increased animal fat consumption, and consequently high-energy intake levels, may also increase basal metabolism and levels of insulin growth factors, leading to increased cellular proliferation and may also promote prostate carcinogenesis via increased androgen levels (Arab et al., 2013; Schultz et al., 2011). Results from the Physicians' Health Study, a cohort of male U.S. physicians, showed that those who consumed more than 600 mg of calcium daily had a 30% increased risk of PCa compared to those who consumed 150 mg or less (Chan et al., 2001). This may be due to increased calcium levels down-regulating the production of

1,25-dihydroxyvitamin D3, which is a protective agent against PCa (Giovannucci et al., 2002).

The lower risk of PCa in Asian men may be due to the regional differences in dietary habits. Traditional Asian diets contain less meat and saturated animal fats, compared to Westernized diets, and conversely contain higher amounts of soybeans and other dietary phytoestrogens (Gibson et al., 2010). These agents have been shown to decrease tumor size, increase apoptosis, and decrease secretion of PSA (Daley et al., 2010). Foods containing lycopene, including tomatoes, have been shown to be associated with decreased risk of PCa (Giovannucci et al., 2002), probably by decreasing oxidative stress in the prostate gland (Klein, 2004). A number of studies have shown that Selenium and Vitamin E use may be associated with lower incidence rates of PCa (Duffield-Lillico et al., 2003; Heinonen et al., 1998), although the Selenium and Vitamin E Cancer Prevention Trial (SELECT), a randomized controlled trial (RCT) evaluating whether these agents had protective effects against PCa, demonstrated no protective benefits for these agents (Lippman et al., 2009).

1.2.5 Obesity

Results from different studies have been conflicting as to whether obesity is a risk factor for PCa. Many have demonstrated that there is a positive association between obesity and PCa incidence (Andersson et al., 1997; Aziz et al., 2000; Gronberg et al., 1996; Putnam et al., 2000; Severson et al., 1989; Sung et al., 1999; Veierod et al., 1997), and that obesity may also be a risk factor for more aggressive forms of cancer (Mcbride, 2012). This may be due to elevated levels of leptin, which is an adipocyte-derived hormone that regulates satiety and energy levels (Cioffi et al., 1996). Leptin receptors are highly expressed in prostate cells (Somasundar et al., 2004), and elevated levels have been shown to increase angiogenesis and proliferation of PCa cells (Nazian et al., 1999). Another causal factor may be increased levels of Insulin-like Growth Factor 1 (IGF-1). Obese patients typically have some degree of insulin resistance. This leads to chronically elevated blood levels of IGF-1, which is a growth-enhancing hormone that causes increased cellular proliferation and tumorigenesis (Kaaks et al., 2010). Conversely, data from a prospective study of more than 50,000 male USA-based health professionals showed that an increased BMI is associated with a decreased risk of PCa (Giovannucci et al., 2003). A plausible explanation for this may be the altered hormonal profile in obese men, who typically have lower levels of testosterone and higher levels of estrogen due to increased peripheral conversion of androgens into estrogens in fat cells (O'Malley et al., 2006).

1.2.6 Smoking

As is the case with many other cancers, smoking has been shown to be a risk factor for PCa. A meta-analysis of 24 cohort studies, comprising a total of 21,579 patients, demonstrated that overall smoking status does not increase risk of PCa. However, when stratified by the amount smoked, it was shown that heavier smokers had progressively increasing risks of PCa (number of cigarettes per day: Relative Risk [RR]: 1.22, pack years of smoking: RR: 1.11). Former smokers had increased risk of diagnosis (RR: 1.09), whereas current smokers also had an increased risk of fatal PCa (RR: 1.14). This is likely due to the myriad of carcinogenic chemicals found in tobacco and cigarette smoke (Huncharek et al., 2010).

1.2.7 Alcohol

Similar to obesity and risk of PCa, data on a possible association between alcohol consumption and risk of PCa has been inconsistent. One study showed that men who consumed more than eight drinks/day (i.e. heavy users) had a significantly increased risk of PCa when compared to nondrinkers or those with moderate levels of consumption (Giovannucci et al., 1993). Conflictingly, a different study suggested that moderate red wine consumption might be linked with a lower risk of PCa (Schoonen et al., 2005).

1.2.8 Vitamin D Deficiency

Recent studies have suggested that Vitamin D deficiency may be a cause of PCa. This is supported by data showing that men with stage IV PCa receiving Vitamin D supplementation had a 50% reduction in PSA levels after almost two years of treatment (Woo et al., 2005) and that Vitamin D supplementation in PCa patients increases intraprostatic calcitriol levels, which is associated with decreased cellular proliferation (Wagner et al., 2013). Notably, ecologic studies assessing the geographic distribution of UV radiation and risk of PCa revealed that the geographic regions with the highest sun exposure (i.e. regions with increased endogenous production of Vitamin D) had lower rates of PCa (Hanchette et al., 1992).

1.2.9 Sexually Transmitted Infections

A history of sexually transmitted infections increases risk of prostate cancer. A metaanalysis demonstrated that history of any sexually transmitted infection (Odds Ratio [OR]: 1.48, 95% Confidence Interval [CI]: 1.26-1.73), gonorrhea (OR: 1.35, 95% CI: 1.05-1.83), and human papillomavirus (OR: 1.39, 95% CI: 1.12-2.06) are associated with an increased risk of PCa (Taylor et al., 2013).

1.2.10 Genetics

Genetics play a significant role in PCa pathogenesis. It is now recognized that five to ten percent of PCa cases are due to high-risk inherited genetic factors or cancer susceptibility genes (Bratt, 2002). None of the implicated genes is a definitive cause of PCa, however mutations in these genes increase the risk of PCa. Hereditary Prostate Cancer has been shown to be associated with seven potential genes: HPC1, Predisposing for Prostate Cancer (PCAP) and Cancer of the Prostate and Brain (CAPB) (located on chromosome

1), HPC2 (chromosome 17), HPC20 (chromosome 20), HPCX (X Chromosome), and cmyc gene (chromosome 8) (Cooney et al., 1997; Gronberg et al., 1997; Sato et al., 1999). Genetic syndromes, such as the Hereditary Breast and Ovarian Cancer (HBOC) syndromes, are also associated with increased risks of PCa. As the name suggests, this syndrome is classically associated with a markedly increased risk of breast and ovarian cancer in females; however, via its BRCA1 and/or BRCA2 gene mutations, it is also associated with increased risks of both breast and PCa in men (Bratt, 2002).

From this available data, we can conclude that PCa pathogenesis is a complex, multifactorial process that is dependent on the interplay between many different variables. It appears that increasing age, African American ethnicity, and a positive family history/genetics are the strongest contributors to this risk. It is important to note that these studies assessed risk factors for diagnosis of PCa (as opposed to true prevalence of PCa), the risk of which is dependent on a large number of subjective factors, including decision to undergo screening/testing for PCa or not, temporal changes in patterns of screening, and physician/patient decision to go for a diagnostic prostate biopsy after a positive PSA test result. It is hard to account for such confounders in retrospective studies, and thus all results must be interpreted in light of these limitations. Issues regarding screening and diagnosis of PCa will be discussed further in later chapters.

1.3 Grading, Staging, and Risk Group Classification of Prostate Cancer

1.3.1 Grading of Prostate Cancer

In general, the goal of assigning a grade and stage to any cancer is to determine its likely extent and aggressiveness. Grade is an inherent histologic characteristic of the tumor, independent of its location or extent. PCa grade, which is predominantly assigned using the Gleason Scoring System (Gleason et al., 1974), is the most important prognostic

factor for PCa and is a major determinant of a patient's risk of PCa-specific mortality (Albertsen et al., 1998). Thus, it is the assigned Gleason Score (GS) that often drives the choice of management, contrary to other tumors where the management is classically stage-driven.

Described by Dr. Donald Gleason in 1944, the Gleason Scoring System assesses the histologic architecture of PCa cells and subsequently assigns a grade from 1 to 5, with 5 being the worst, based on the degree of loss of normal tissue glandular architecture (Gleason et al., 1974). In a specimen obtained from a diagnostic biopsy, the GS or sum is calculated by adding both the predominant and most aggressive patterns. For example, if the predominant pattern is a Gleason 3 and the most aggressive pattern is a Gleason 4, then the GS is 3+4. On the other hand, in a specimen obtained surgically after a radical prostatectomy (RP), the GS is obtained by adding the two most predominant patterns (Albertsen et al., 1998; Stephenson et al., 2005). The Gleason Scoring System has undergone a number of modifications, with the last being in 2005 (Epstein et al., 2005). Based upon the GS, physicians commonly classify PCa into one of the following categories:

- 1. GS 6 or less: Low grade
- 2. GS 7: Intermediate grade
- 3. GS greater than or equal to 8: High grade

The more complex National Comprehensive Cancer Network (NCCN)-recommended risk-group classification will be discussed in a later section.

1.3.2 Staging of Prostate Cancer

PCa is typically staged using the tumor-node-metastasis (TNM) staging system (Epstein et al., 2005). This system depends on the findings from a digital rectal examination (DRE), imaging (e.g. transrectal ultrasound [TRUS] or magnetic resonance imaging [MRI]), prostate biopsy, and/or a trans-urethral resection of the prostate [TURP]. T1 and

T2 tumors are localized cancers, whereas T3 and T4 tumors are those with local extension. A clinical T1 stage is assigned to a tumor that is neither palpable nor visible by imaging (i.e. clinically inapparent), with T1a, T1b and T1c referring to tumors that are incidentally found in \leq 5% of TURP-resected tissue, in >5% of TURP-resected tissue and those identified by a prostate needle biopsy, respectively. T2 tumors, which are those detected by DRE or imaging, are confined to the prostate gland. T2a, T2b, and T2c tumors refer to those that involve one half or less of a lobe, more than one half of a lobe but not both, and those that involve both lobes, respectively. T3a refers to cancers with extracapsular extension, T3b to those that invade the seminal vesicles, and T4 to those that invade the bladder, are fixed to pelvic sidewall, and/or invade other adjacent structures. N1 refers to positive regional lymph nodes and M1 to presence of distant metastasis (Sobin et al., 2009). Interestingly, despite tumor stage usually being a strong prognostic indicator for most cancers (May et al., 2004; Soerjomataram et al., 2008), clinical stage in PCa does not seem to be a strong determinant of prognosis (Reese et al., 2010).

1.3.3 Risk Group Classification for Prostate Cancer

Despite the presence of a large number of prognostic classification tools that help predict PCa outcomes (Kattan et al., 1998; Sayyid et al., 2016), the classification proposed by D'Amico et al in 1998 remains the most frequently used. This classification system assigns PCa to one of three groups (low, intermediate, and high risk) based on risk for biochemical recurrence (i.e. rising tumor marker levels) following definitive therapy. This classification system is based on preoperative PSA level, biopsy GS, and DRE-determined clinical stage, tools that are widely available to urologists in varying clinical settings (D'Amico et al., 1998). This classification system is also valid for predicting risk of disease progression and survival following RP (Boorjian et al., 2008; D'Amico et al., 2002). In 2012, an additional risk group was added: very-low risk, which refers to clinically insignificant PCa (Mohler et al., 2012). The NCCN currently recommends the adoption of this risk group classification standard in clinical practice:

1. Very-low risk:

- PSA < 10 ng/mL
- Non-palpable tumor
- Biopsy GS ≤ 6
- <3 cores involved
- $\leq 50\%$ of any core involved
- PSA density <0.15 ng/mL/g

2. Low risk:

- PSA <10ng/ml
- cT1c-T2a
- Biopsy GS ≤ 6
- 3. Intermediate risk:
 - PSA 10-20 ng/mL
 - cT2b
 - Biopsy GS 7
- 4. High risk:
 - PSA > 20 ng/mL
 - cT2c or worse
 - Biopsy GS 8-10

1.4 Treatment Options for Prostate Cancer

Prior to discussing the screening and diagnostic options for PCa, and the relevant issues of debate, the various treatment options for PCa will be discussed.

1.4.1 Expectant management

The rationale behind expectant management is supported by results from a number of studies. As discussed previously, the lifetime risk of PCa diagnosis is about 1 in 8 ("Prostate cancer statistics", 2017), the prevalence of PCa in autopsy specimens from men who did not die from PCa is as high as 80% in those older than 80 years (Sakr et al., 1994), whereas the lifetime risk of PCa mortality is only about 3.7% ("Prostate cancer statistics", 2017). This suggests that a large proportion of cancers are not clinically significant and do not cause mortality, and hence one of the challenges is to be able to differentiate those that are potentially significant from others which are not. The D'Amico risk group classification and others help with this distinction. Furthermore, studies have demonstrated that men with low-risk PCa (i.e. those who are potential candidates for expectant management) have excellent prognoses, with the 10-year cancerspecific mortality estimated to be around 3% (Albertsen et al., 2005).

Significantly, definitive therapeutic options for PCa (i.e. surgery and radiotherapy [XRT]) are associated with significant side effects, including erectile dysfunction (ED) and urinary incontinence (Hugosson et al., 2011), which negatively impact quality of life and may cause post-treatment regret in patients with localized cancers (Christie et al., 2015). Thus, expectant management is a suitable choice in appropriately selected patients who have low-risk disease features and are unlikely to die from their disease (Chen et al., 2016).

1.4.1.1 Watchful Waiting

Compared to other management options, watchful waiting (WW) is unique in that its ultimate goal is palliative, not curative. WW entails following up a patient until he develops cancer-related symptoms and subsequently managing those symptoms (e.g. TURP for obstructive voiding symptoms or palliative XRT for bony metastases) (Schröder et al., 2003). Currently the European Association of Urology (EAU)

recommends that WW may be offered to patients not eligible for local curative treatment and those with a short life expectancy (i.e. less than 10 years), and that decision to start non-curative treatment should be based on symptoms and disease progression ("EAU-ESTRO-SIOG Guidelines on Prostate Cancer", 2016).

1.4.1.2 Active Surveillance

Contrary to WW, the intent of active surveillance (AS) is curative. The basic principle of this management option is to observe patients with low-risk PCa and curatively intervene at the first sign of disease progression. The goal is to reduce overtreatment by intervening only in those patients with worrisome disease features, while observing those who consistently retain low-risk features. By eschewing likely unnecessary intervention, AS avoids, or sometimes only delays, the aforementioned side effects associated with surgery or XRT (Hugosson et al., 2011), and allows men to maintain a good quality of life (Bellardita et al., 2015).

AS protocols entail serial serum PSA (PCa tumor marker) measurements, DREs, and prostate biopsies. It is currently recommended that patients with low-risk (i.e. GS \leq 6) localized prostate cancer should be offered AS, with patients having low-volume, intermediate risk (GS 3+4=7) PCa also being potential candidates (Chen et al., 2016).

Despite these obvious benefits for AS, some concerns remain with this management technique. Patients with initially low-risk features may have either local or metastatic progression before definitive therapy is implemented (Klotz et al., 2015). Treatment of cancers that have progressed to more aggressive and/or extensive forms may be more difficult and associated with higher risk of morbidity (Bastian et al., 2012). Importantly, AS may cause anxiety in some patients (Rittenmeyer et al., 2016) and necessitates long-term, repeated follow up. To date, there is no consensus on the appropriate candidates for AS and ideal follow up/management regimen.

1.4.2 Definitive Therapy

1.4.2.1 Radical Prostatectomy

RP is the surgical removal of the entire prostate gland between the urethra and bladder and accompanying seminal vesicles, along with sufficient surrounding tissue to ensure negative surgical margins ("EAU-ESTRO-SIOG Guidelines on Prostate Cancer", 2016). This procedure may be performed via an open or laparoscopic/robotic technique. Studies have shown that patients with organ-confined disease treated with radical prostatectomy have excellent 12-year cancer-specific survival rates (Wilt et al., 2012). Long-term side effects of this procedure include: urinary incontinence (0-87%) (Alivizatos et al., 2005; Foote et al., 1991; Grise et al., 2001; Krane, 2000; Nandipati et al., 2006), impotence (13-89%) (Alivizatos et al., 2005), and stricture of the vesico-urethral anastomosis (2-9%) (Heidenreich et al., 2010). EAU currently recommends that RP be offered to patients with low- and intermediate-risk PCa and a life expectancy greater than ten years, as well as in a multimodality setting to patients with high-risk localized or locally advanced PCa (T3a) and a life expectancy greater than ten years ("EAU-ESTRO-SIOG Guidelines on Prostate Cancer", 2016).

1.4.2.2 Definitive Radiotherapy

External beam radiotherapy (EBRT) and brachytherapy are also considered definitive treatment options for PCa. Despite the absence of a randomized controlled trial comparing RP and XRT, it is well accepted, based on data from observational studies, that these two modalities are similar in terms of long-term survival rates and quality of life outcomes ("EAU-ESTRO-SIOG Guidelines on Prostate Cancer", 2016; Mohler et al., 2012).

The goal of EBRT is to administer maximum radiation dosage to the prostate while minimizing adjacent tissue damage. Similarly, brachytherapy aims to achieve high

precision, targeted XRT using different imaging modalities to maximize organ radiation while minimizing surrounding tissue damage. Two different techniques exist to treat PCa: low-dose rate brachytherapy, which involves permanently implanting seeds into prostate tissue and high-dose rate brachytherapy, which entails temporarily placing radioactive sources into the gland via implanted needles (Chao et al., 2015).

Retrospective studies have shown that EBRT, brachytherapy, and RP lead to similar cancer control and long-term survival rates (Boorjian et al., 2011; Grimm et al., 2012). XRT may be associated with fewer long-term side effects compared to RP (Ferrer et al., 2008; Sylvester et al., 2011). These include: impotence, urinary incontinence, diarrhea, and proctitis. EAU guidelines state that XRT is a suitable option for patients with low-, intermediate- or high-risk PCa, albeit with different corresponding radiation doses ("EAU-ESTRO-SIOG Guidelines on Prostate Cancer", 2016).

1.4.3 Androgen Deprivation Therapy

In 1941, Huggins and Hodges demonstrated that PCa cells are androgen dependent (i.e. testosterone stimulates cellular growth and proliferation) (Huggins et al., 1941). Consequently, androgen deprivation therapy (ADT), medically via luteinizing hormone-releasing hormone (LHRH) agonists, antiandrogens, and/or gonadotropin-releasing hormone (GnRH) antagonists or surgically via bilateral orchiectomy, has become standard therapy for advanced disease (Heidenreich et al., 2014; Nishiyama, 2014). The objective of ADT is to achieve castrate levels of testosterone, classically defined as less than 1.7 nmol/L (50 ng/dL) (Wilke et al., 1987), thereby inhibiting growth of tumor cells and allowing for improved disease control (Heidenreich et al., 2014; Nishiyama, 2014). Current guidelines recommend that ADT be used for men with distant metastases (i.e. M1), symptomatic men with advanced disease (T3, T4, or N1), in patients with biochemical recurrence, and in combination with XRT ("EAU-ESTRO-SIOG Guidelines on Prostate Cancer", 2016). Occasionally, patients who present with considerably elevated PSA levels and signs and symptoms extremely suggestive of PCa are assumed to

have metastatic PCa and are automatically started on ADT, without any histologic diagnosis from a biopsy.

Medical and surgical castrations, which have comparable effectiveness (Hedlund et al., 2008; Seidenfeld et al., 2000), are both associated with significant side effects, which include: hot flashes, decreased sexual desire, impotence, osteoporosis, fatigue, increased risk of diabetes and cardiovascular events, weight gain, decreased muscle mass, anemia, and loss of memory. Some of these effects are at least partially reversible once the ADT is discontinued (e.g. patients on intermittent ADT), whereas the effects of bilateral orchiectomy are permanent (Nguyen et al., 2015). Despite ADT ensuring remission in about 90% of patients, as evidenced by lower PSA levels, disease progression eventually ensues within an average period of two to three years, despite continued ADT use. This is known as castrate-resistant prostate cancer (CRPC) (Harris et al., 2009). This likely occurs because of intratumoral production of androgens that activate androgen receptor signaling (Karantanos et al., 2013). Patients with metastatic CRPC have a poor prognosis, with a mean survival time of less than three years (Ryan et al., 2015). Due to this inevitable disease progression, it is generally accepted that patients on ADT have poor cancer prognoses. Recent advances in pharmacologic therapies, however, have allowed for improved survival outcomes in patients who have advanced to a castrate-resistant state (Ritch et al., 2016).

1.6 Screening for Prostate Cancer

Screening for PCa is a topic that has generated a lot of discussion. Currently, DRE and serum PSA levels are the two most commonly used screening tools for PCa

1.6.1 Prostate-Specific Antigen Biology and History

PSA is an androgen-regulated serine protease produced by both prostate epithelial and PCa cells (Balk et al., 2003). It is a member of the tissue kallikrein family, located on chromosome 19q13.4 (Yousef et al., 2001). Prostate epithelial cells secrete PSA into the semen, where it is responsible for semen liquefaction and enhanced spermal motility (Balk et al., 2003). Originally identified in prostatic tissue in 1970 (Ablin et al., 1970) and later on in blood in 1980 (Rao et al., 2008), Stamey et al. in 1987 were the first to assess the utility of PSA as a serum tumor marker. The authors analysed 2,200 serum samples from 699 patients, 378 of whom had PCa. They demonstrated that serum PSA levels correlated with both the advancing stage of PCa and estimated tumor volume, and that it was a superior tumor marker to prostatic acid phosphatase. They also showed that serum PSA levels became undetectable after RP (half-life of about two days), suggesting that PSA could be used as a surveillance marker for residual or recurrent disease (Stamey et al., 1987). Consequently, PSA gained popularity in clinical practice as a screening/testing tool for PCa, as well as a marker for tumor recurrence and residual disease post treatment, despite the lack of a comprehensive evaluation of its utility and potential benefits and/or harms as a screening test (Potosky et al., 1995).

1.6.2 Stage-Shift Due to Introduction of Prostate-Specific Antigen as Screening Tool

The introduction of PSA testing in the early 1990s coincided with a temporal increase in the incidence of PCa (Baade et al., 2009; Kvale et al., 2007). Significantly, this was associated with a stage-shift among diagnosed cancers, from cancers that were mostly detected at later stages, as either locally advanced or metastatic, to those that are now detected at earlier, pre-clinical stages (Pashayan et al., 2009). This increased detection/incidence of earlier stage cancers has necessitated adoption of novel management techniques, such as AS. Since most PCa cases nowadays are detected

following an elevated serum PSA test, the question remains whether this novel screening/testing modality leads to improved survival outcomes.

This stage-shift has raised concerns about the possibility of the emergence of two biases: lead-time bias and length-time bias (Albertsen, 2005; Gann et al., 1995; Hugosson et al., 2000). Lead-time bias occurs when a condition such as cancer is detected at an earlier, asymptomatic stage, leading to an apparent increase in survival due to longer disease duration. Thus, regardless of therapy, people whose PCa is detected at an earlier stage by screening will appear to have improved survival compared to people who did not undergo screening and were diagnosed at a later stage. Length-time bias refers to a perceived improvement in survival due to screening detecting a disproportionately large number of slowly progressing cases. Since more aggressive cancers are asymptomatic for shorter periods of time, screening is expected to detect a larger proportion of indolent, slow-growing cancers, which have more favorable survival outcomes.

1.6.3 Impact of Prostate-Specific Antigen-Based Screening Programs on Survival

Multiple studies have documented an improvement in cancer-specific survival in the post-PSA era (Mettlin et al., 1998; Meyer et al., 1999; Roberts et al., 1999; Smart, 1997); however, some ambiguity remained as to the certainty of these results (Kramer et al., 1993; Labrie et al., 1999). Consequently, two RCTs were conducted to assess the utility of PSA-based screening programs in reducing PCa-specific death rates.

1.6.3.1 The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial randomly assigned 76,693 men from 10 U.S. study centers from 1993 to 2001 to undergo either

annual screening with PSA and DRE (38,343 subjects), as the intervention arm, versus usual care (38,350 subjects), as the control arm. After seven years of follow-up, there was no significant difference in death incidence rate between the two arms, despite a higher incidence rate of PCa diagnosis in the screening arm (116 diagnoses per 10,000 personyears in the screened group versus 95 in the control group, p<0.05) (Andriole et al., 2009, 2012; Ciatto et al., 2003). These results were similar after 10 and 13 years of follow-up (Andriole et al., 2012). The authors concluded that despite a 22% increase in the PCa diagnosis rate with PSA-based screening programs, there is no evidence that these programs offer any survival advantage compared to usual levels of care. This RCT was criticized due to a number of issues. The PSA cutoff level (>4 ng/mL) used as a trigger for biopsy was outdated. Furthermore, greater than 40% of enrolled men had undergone screening for PCa within the prior three years. Notably, 15% of participants in the screening arm were never screened during the study period, and crucially, rates of screening in the control arm ranged from 40% in the first year to 62% in the sixth year (Andriole et al., 2009). This suggests that any potential benefits for PSA-based screening may have been substantially diluted, leading to the insignificant differences between the two study groups.

1.6.3.2 The European Randomized Study of Screening for Prostate Cancer

The European Randomized Study of Screening for Prostate Cancer (ERSPC) similarly aimed to assess the impact of PSA screening on PCa mortality rates. Beginning in the early 1990's, the study enrolled 182,000 men between the ages of 50 and 74 from seven European countries. These men were randomized to receive either PSA screening once every four years (intervention arm) or to receive no such screening (control arm). PSA cutoff was defined as 3.0 ng/ml. The authors identified a priori the group of men between the ages of 55 and 69 as the core group for analysis (162,243 men). After a median follow-up of nine years, the cumulative incidence rate for PCa diagnosis was 8.2% in the screened group, compared to 4.8% in the control group. Significantly, men in the

screened group were 20% less likely to die of PCa at nine years (Rate Ratio: 0.80, p<0.05). The absolute risk difference of 0.71 deaths per 1000 men meant that the number needed to be screened and the number needed to be treated to prevent one death from PCa were 1410 and 48, respectively. Sensitivity analysis restricted to men in the intervention arm who actually received PSA testing (82% of men in the screening arm) revealed that PSA screening reduces the risk of death by 27% (Rate Ratio: 0.73, p<0.05). The authors concluded that PSA-based screening programs reduce cancer mortality rates, at the expense of a risk of overdiagnosis (Schröder et al., 2009). Updated analyses with longer follow-up periods of 11 and 13 years showed that the difference in cancer-specific death rates between the two groups continued to increase (Schröder, 2012, 2014), with a considerably lower number needed to be treated of only 12 (Hugosson et al., 2010). Contrary to the PLCO trial, which had a contamination rate of up to 62% in the control arm, it is estimated that the equivalent rate was only about 20% in the ERSPC trial (Ciatto et al., 2003), which provides a possible explanation as to why the ERSPC trial showed a mortality benefit from PSA screening, whereas the PLCO trial did not.

1.6.4 PSA Screening Recommendations

Since these two prospective trials showed inconsistent survival benefits for PSA-based screening programs and screening has a definite risk of overdiagnosis, the United States Preventive Services Task Force (USPSTF) and Canadian Task Force on Preventive Health Care currently both recommend against PSA-based screening for PCa ("U.S. Preventive Services Task Force", 2012; "Canadian Task Force on Preventive Health Care", 2014). These recommendations have coincided with a temporal decrease in both the rates of PSA testing and incidence of early-stage PCa (Barocas et al., 2015; Fleshner et al., 2017; Jemal et al., 2015), with a concurrent shift towards detection of higher grade and stage tumors (Fleshner et al., 2017).

On the other hand, the American Urological Association (AUA) and EAU have not adopted such absolute anti-PSA stances. While the AUA does not recommend PSA screening in men under age 40, those between ages 40 and 54 at average risk, those older than 70 years, or those with a life expectancy of less than 10 to 15 years, it does recommend discussing the pros and cons of screening with men ages 55 to 69 years, with any decision ultimately a shared one between both patient and physician ("AUA Early Detection of Prostate Cancer", 2017). The EAU similarly recommends adopting an "individualized risk-adapted strategy" to screening in well-informed men with life expectancy of at least 10 years and in men at elevated risk for PCa ("EAU-ESTRO-SIOG Guidelines on Prostate Cancer", 2016). These two organizations recognize that a major reason for improvement in PCa outcomes is early disease detection, with subsequent adoption of appropriate treatment regimens. Urologists recognize the morbidity associated with aggressive treatment modalities, and management strategies such as AS have been appropriately adopted in order to avoid unnecessary therapy in patients with low-risk disease. Given the ageing nature of the world's population ("World Population Ageing", 2013), combined with PCa being a disease of the elderly, it is probable that PCa will become an even bigger public health issue in the future. Future studies will be needed to assess the impact of the USPSTF recommendations on rates of advanced, metastatic disease as well as PCa-specific mortality.

1.7 Diagnosis of Prostate Cancer

Following a positive test (PSA and/or DRE), a patient typically undergoes a prostate biopsy to histologically confirm or exclude a possible diagnosis of PCa. Prostate biopsies are frequently performed in clinical practice, with almost one million biopsies undergone annually in the United States (Welch et al., 2007).

1.7.1 Prostate Biopsy Technique

1.7.1.1 Transrectal versus Transperineal Approach

Prostate biopsies can be performed via a transrectal or transperineal approach. These two approaches differ with regards to the puncture site and route, as well as type of TRUS. In the transperineal approach, the biopsy needle punctures the skin of the perineum under the guidance of a bi-planar transducer, whereas in the transrectal approach, the needle is directed through the anterior rectal wall with the aid of an end-fire transducer. An RCT comparing the two techniques in a random sample of 339 Chinese men found the two methods to be equivalent in terms of cancer detection rate, with the transrectal approach having a higher major complication rate and the transperineal technique being more time-consuming, twice as painful and associated with higher rates of repeated biopsy and additional anesthesia (Guo et al., 2015). Presently, the vast majority of urologists in the United States utilize a transrectal approach, with the transperineal method utilized by some centers in Asian and European Countries (Kawakami et al., 2004; Kojima et al., 2001; Takenaka et al., 2006).

1.7.1.2 Finger- versus Transrectal Ultrasound-Guided Needle Biopsy

First carried out in 1937, and later gaining popularity in the mid 1950s, the finger-guided needle biopsy was a commonly used technique for biopsying patients. This method involved palpating the prostate for areas of abnormalities, and then directing the needle through the rectal mucosa toward these areas and obtaining tissue specimens (Astraldi, 1937). The development of TRUS to visually evaluate the prostate gland ushered the modern era of prostate biopsying. In 1989, Hodge et al. described the sextant method of biopsying. They compared TRUS-guided prostate biopsies (TRUS-Bx) of palpable or visually detected abnormalities to those taken in a random systematic manner. This latter technique involved sampling from six locations: apex, middle and base of each prostate lobe, parasagitally, plus any hypoechoic lesion seen on TRUS. This systematic sampling
detected nine percent more cancers compared to the targeted technique (Hodge et al., 1989). Consequently, this systematic approach, with TRUS guidance to accurately direct needle placement, was adopted in clinical practice. It is noteworthy to mention that the finger-guided technique was still commonly practiced in a number of centers in Ontario up until the mid to late 1990's (based on input from experienced, Ontario-based practicing urologists).

1.7.1.3 Number of Biopsy Cores

After the introduction of the TRUS-guided sextant method into clinical practice, numerous attempts were made to optimize the ideal number and location of biopsy cores to be taken. In 1995, Stamey modified this technique by taking sextant biopsies lateral to the mid-sagittal plane, in the peripheral zone, where PCa is usually located (Stamey, 1995).

The next logical step was to assess whether increasing the number of cores taken would enhance the yield of this procedure. However, increasing number of cores was associated with a proportional increase in discomfort level (Nash et al., 1996). This issue was resolved with the finding that effective pain relief could be attained with an infiltrating local anesthetic (Nash et al., 1996).

In 1997, Eskew et al. presented the systematic extended biopsy technique that involved taking five additional cores (two from the far lateral portions of each side and three centralized ones). Using this technique, 35% of patients diagnosed with PCa had disease detected exclusively in one of these five additional cores (Eskew et al., 1997). A few years later, Levine et al. evaluated the utility of performing two independent, consecutive sets of sextant biopsies at the same visit. This 12-core biopsy had a 31% cancer detection rate compared to 21% with the sextant method (Levine et al., 1998). Ten core and 11 core biopsy protocols were subsequently described (Babaian et al., 2000; Presti et al., 2000). Bauer et al. compared the sextant technique to a 10- or 12-core biopsy protocol using

whole mount radical prostatectomy specimens with three dimensional computer simulation and found that this extended biopsy protocol detected 99% of cancers, compared to only 73% with the sextant technique (Bauer et al., 1999). Since one of the previous issues with increasing the number of cores taken was increased pain levels (prior to utilization of infiltrating local anesthetic), Naughton et al. conducted an RCT comparing pain and morbidity associated with six compared to 12 biopsies and found that there was no significant difference in discomfort levels experienced and rates of moderate or major complications (Naughton et al., 2000). Currently, the extended-pattern 12-core biopsy, which includes the standard sextant along with targeted biopsies of palpable nodules and suspicious images, is most commonly performed in clinical practice and is recommended by the NCCN panel ("NCCN Clinical Practice Guidelines", 2012), although other techniques such as saturation biopsies (20+ cores taken) and magnetic resonance imaging/ultrasound fusion biopsies are occasionally performed, especially in the setting of previous negative biopsies. Multiparametric magnetic resonance imaging (mp-MRI) in particular has gained popularity over the past few years as a risk-stratifying tool for patients with previous negative biopsies who remain at high risk for PCa, with the goal being to avoid unnecessary repeat biopsies. mp-MRI has been shown to be effective at both detecting and ruling out clinically significant PCa following a negative prostate biopsy (Abd-Alazeez et al., 2014). In summary, there has been a considerable evolution in prostate biopsy technique, with changing methods over the years having different PCa detection rates.

1.7.2 False Negative Rate of Prostate Biopsies

Despite the collective efforts of the aforementioned investigators to optimize the biopsy technique, the reality is that this procedure still has a significant false negative (FN) rate. A recent study evaluated the accuracy of a 12-core biopsy in 90 PCa patients who were diagnosed via a 12-core TRUS-Bx and underwent an RP. A 12-core biopsy was repeated on the surgical specimens ex-vivo, and cancer was detected in only 68% of patients, meaning that the FN rate of this procedure was 32% (Serefoglu et al., 2013). Other

studies have estimated that this FN rate is around 20% (Babaian et al., 2000; Eskew et al., 1997). This has naturally led to the argument of re-biopsying patients with negative TRUS-Bx who, despite a negative result, retain a high risk for PCa.

Despite repeat biopsies offering the obvious advantage of detecting cancers missed on previous attempts, there are a number of issues to consider when weighing whether a patient should undergo another TRUS-Bx. TRUS-Bx are not benign and have a number of associated complications, including bleeding, infections, pain, anxiety, urinary retention, and erectile dysfunction (see Section 1.7.3).

1.7.3 Complications of Prostate Biopsy

1.7.3.1 Hemorrhagic Complications

Bleeding, in the form of hematuria, hematochezia, and hematospermia, is a frequent, bothersome complication of TRUS-Bx. Hematuria, or blood in the urine, has been reported to occur 66% of the time (Rosario et al., 2012), and in severe cases may necessitate hospital admission and/or catheter insertion (Nam et al., 2013). The reported rate of hematochezia, or rectal bleeding, ranges between 1.3% and 45% ("AUA/SUNA White Paper", 2012; Lee et al., 2008). Hematospermia, or blood in the ejaculate, has been reported to occur in up to 93% of post-biopsy patients (Lee et al., 2009). Unlike hematuria and hematochezia, hematospermia is quite distressing for patients and may be perceived as concerning/alarming (Rosario et al., 2012)

1.7.3.2 Infectious Complications

Infectious complications post-TRUS-Bx remains common, despite the widespread use of antibiotic prophylaxis. The Global Prevalence Study of Infections in Urology reported that 3.5% of patients had a febrile urinary tract infection and 3.1% required

hospitalization post biopsy (Wagenlehner et al., 2013). Worryingly, the routine use of antibiotic prophylaxis seems to be causing antimicrobial, in particular fluoroquinolone, resistance (Feliciano et al., 2008). This has corresponded with an increase in post-biopsy infectious complications over this period, with studies of Canadian men suggesting that the 30-day post-biopsy hospitalization rate has risen from 1% in 1996 to 4.1% in 2005 (Nam et al., 2013) and rate of infections has more than quadrupled from 0.52 per 100 biopsies in 2002-2009 to 2.15 per 100 biopsies in 2010-2011 (Raheem et al., 2012). Significantly, the risk of infection increases with each subsequent biopsy (Ehdaie et al., 2014).

1.7.3.3 Pain and Anxiety

Despite the routine use of pre-operative anesthetic modalities, TRUS-Bx remains a cause of pain, discomfort and anxiety in a subset of men (Peyromaure et al., 2002), who subsequently are less likely to accept a repeat biopsy procedure (Rosario et al., 2012). Anxiety seems to be amplified in patients who experience problematic post-biopsy symptoms such as pain, shivers, hematuria, or hematochezia (Wade et al., 2013).

1.7.3.4 Lower Urinary Tract Symptoms and Urinary Retention

Acute urinary retention post-biopsy has been reported in up to 2.1% of cases (Chiang et al., 2007). This event is usually transient and does not necessitate a surgical intervention in the majority of patients (Ganeswaran et al., 2012). Short-term exacerbation of urinary symptoms occurs in a subset of men (Glaser et al., 2012). Reported rates of post-biopsy dysuria have been in the range of 6% to 25% (Ecke et al., 2008; Fujita et al., 2009)

1.7.3.5 Erectile Dysfunction

Studies assessing the impact of TRUS-Bx on erectile function have concluded that this procedure may cause a transient worsening of EF. A prospective study evaluating EF, using the International Index of Erectile Function-5 questionnaire, in 88 men undergoing TRUS-Bx revealed that 12% of previously potent patients reported mild to moderate ED after 1 month, with none reporting ED at 6 months follow up (Akbal et al., 2008). ED rates may be higher in patients who receive periprostatic local anesthetic nerve blocks (Klein et al., 2010). Biopsy-associated ED is likely due to a combination of temporary inflammation and neurovascular damage, in addition to the increased anxiety present at time of screening/testing, biopsy, and immediately following the procedure (Dale et al., 2005), which is particularly heightened in patients who receive a positive diagnosis of PCa (Helfand et al., 2013).

1.7.3.6 Other Consequences of Prostate Biopsy

In addition to the above-mentioned medical complications of TRUS-Bx, there are other implications to consider. Screening for PCa in general is expensive and carries a significant cost burden for the health care system. The PSA test itself is inexpensive, however the downstream procedures such as biopsy, pathological analysis and possible hospitalization due to biopsy complications are the main drivers of cost, accounting for 72% of screening costs (Ma et al., 2014). Based on information from The Ontario Ministry of Health and Long-Term Care (MOHLTC), the estimated average charge for a prostate biopsy is \$91.45 ("Male Genital Surgical Procedure", 2015), The financial implications on the healthcare system become obvious, especially in the context of the Canadian healthcare system where health services are provincially funded. This procedure also requires the concerted efforts of a number of healthcare professionals: the urologist or radiologist performing the TRUS-Bx, the pathologist who analyzes the specimens, the paramedical staff assisting with the procedure, and additional staff who may be needed if major complications arise. Thus, unnecessary repeated biopsy attempts may lead to inefficient utilization of the healthcare workforce. From a patient perspective,

this procedure, in addition to causing pain and anxiety, is quite time consuming and may even necessitate missing work days. Thus, when considering a repeat biopsy in patients with previously negative biopsies, the physician must weigh the potential advantages of detecting previously missed cancers against these possible complications. These complications are summarized in Table 1.1.

Table 1.1 Summary of prostate biopsy complications			
Complication	Incidence	Reference	
Hematuria	66.0%	Rosario et al., 2012	
Hematochezia	1.3 ^a -45.0% ^b	^a Lee et al., 2009	
		^b "AUA/SUNA White	
		Paper", 2012	
Hematospermia	93%	Lee et al., 2009	
Febrile urinary tract	3.5%	Wagenlehner et al., 2013	
infection			
Hospitalization due to	4.1%	Nam et al., 2013	
infectious complication			
Pain	47.6%	Peyromaure et al., 2002	
Anxiety	48.0%	Peyromaure et al., 2002	
Urinary Retention	2.1%	Chiang et al., 2007	
Dysuria	6 ^a -25% ^b	^a Ecke et al., 2008	
		^b Fujita et al., 2009	
Transient Erectile	12%	Akbal et al., 2008	
Dysfunction			

1.8 Outcome Studies of Patients with a Negative Prostate Biopsy

Patients with a single negative prostate biopsy are a very interesting group to study. Since such patients have undergone a biopsy, they must have had a positive screen/test (i.e. elevated PSA and/or positive DRE) at some point prior to the biopsy, and as such are presumed to be at higher risk of adverse disease outcomes compared to those with a negative screen or the general population. Thus, studies that evaluate PCa-related outcomes in such men are particularly significant.

1.8.1 Prostate Cancer Diagnosis on Repeat Biopsies

A number of studies have attempted to quantify the utility of a repeat biopsy with regards to detecting cancers missed on previous biopsy attempts. An early study by Fleshner et al. attempted to determine the prevalence of and risk factors for PCa in 130 patients with a single negative sextant TRUS-Bx. A TRUS-Bx was repeated in each of these men and potential predictors of cancer detection/diagnosis such as age, pathological result on first biopsy, time interval between biopsies, PSA level, PSA density, PSA velocity, abnormal TRUS, and a family history of PCa were evaluated. Of these 130 patients, 39 (30%) had cancer detected on repeat biopsy. On univariate analysis, a PSA level of greater than 20 ng/ml and abnormal findings on TRUS were found to be predictive of PCa detection on repeat biopsy. On multivariate analysis, however, only a PSA level of greater than 20 ng/ml remained a significant predictor (OR: 4.48, p<0.05). Significantly, the authors identified the subset of patients with the lowest-risk features: PSA less than 10 ng/ml. PSA density less than 0.15mg/ml/cm³, PSA velocity less than 0.75 ng/ml/year, no prostatic intraepithelial neoplasia, and negative TRUS, DRE and family history. They reported that five out of these 21 patients (24%) were diagnosed with PCa on repeat biopsy. This significant finding led the authors to recommend that repeat TRUS-Bx

should be considered in all patients with a negative biopsy for whom a high clinical suspicion for PCa remains (Fleshner et al., 1997).

A similar study by Eggener et al. evaluated the risk of PCa detection on repeat biopsy in men with PSA of 2.6 to 4.0 ng/ml and an initially negative prostate biopsy. Using data on 24,893 men from a community-based PCa screening study, this group identified 1,011 men meeting the study inclusion criteria and having adequate follow-up and similarly attempted to identify predictors of PCa detection on repeat biopsy. Of these 1,011 men, 136 (13.5%) subsequently received a diagnosis of PCa. Thirty-five percent of men with high-grade prostatic intraepithelial neoplasia (HGPIN) on initial biopsy (p<0.01), 18% of those with abnormal or suspicious DRE (p=0.02), and 16% of men with an annual PSA velocity of 0 ng/ml (p=0.002) were subsequently diagnosed with PCa. On multivariate analysis, presence of HGPIN, initial PSA between 3.6 and 4.0 ng/ml, positive DRE, family history of PCa, and an annual PSA velocity of 0 ng/ml significantly predicted PCa diagnosis on repeat biopsy. These results prompted the authors to recommend that men with a negative biopsy and PSA levels between 2.6 and 4.0 ng/ml should be considered for repeat biopsy if they have a history of any of the aforementioned predictors (Eggener et al., 2005).

Ploussard et al. prospectively followed over ten years a group of 1,995 French patients with an initially negative prostate biopsy to determine the predictors of both re-biopsy attempts and PCa detection among such patients. Re-biopsy attempts were performed at the discretion of the treating physician. Of these 1,995 men, 617 (31%) were subjected to at least one further biopsy attempt over a mean follow-up of 19 months. Thirty-four percent of patients underwent a repeat biopsy attempt within five years of follow-up. PCa was diagnosed in seven percent of patients. The PCa detection rates were 16.7%, 16.9%, and 12.5% at the second, third, and fourth biopsy attempts, respectively. The five-year cancer-free survival rate was 92.5%. Indicators/predictors of repeat biopsy attempts were elevated PSA levels (p<0.01), high PSA density (p<0.01), and younger age (p<0.01). The risk of PCa detection on repeat biopsies was found to be significantly increased in

patients with PSA levels >6 ng/ml, PSA density >0.15 ng/ml/g, free-to-total PSA ratio <15, and a prostate volume <50 cc (Ploussard et al., 2013).

The next issue to address is whether cancers detected on later biopsy attempts are similar in nature to those detected on earlier ones. A study of 2,411 consecutive patients undergoing RP at a single center was performed, whereby patients were grouped by the biopsy attempt on which their PCa was detected, and a potential correlation between biopsy number and risk of clinically insignificant disease and/or adverse pathology at RP was evaluated. The number of patients who underwent one, two, and three or more biopsies prior to RP was 1867 (77.4%), 281 (11.9%) and 175 (7.3%), respectively. Patients who underwent a greater number of biopsies prior to surgery were more likely to have larger prostate volumes (p<0.01), elevated PSA levels (p<0.01), presence of HGPIN on biopsy (p<0.01), and had a higher probability of clinical GS 6 or less cancer (p<0.01). Patients who were subjected to a higher number of biopsies were also more likely to have low-volume (p < 0.01), organ-confined (p < 0.01) disease on the final surgical specimen. As for clinically insignificant disease, defined as pathologic GS ≤ 6 , estimated tumor volume of <10%, absence of extracapsular extension, negative lymph nodes, no seminal vesicle invasion, and negative surgical margins, the risk of such disease was determined to be 31%, 44%, and 47% in patients who underwent one, two, and three or more prostate biopsies, respectively. On the other hand, the risk of adverse pathology (i.e. clinically significant disease) was determined to be present in 65%, 53% and 52% of patients who underwent one, two, and three or more prostate biopsies, respectively. Despite the risk of insignificant disease rising as the number of biopsy attempts needed increases, the risk of adverse pathology, even in patients who are diagnosed after three or more biopsies, remains prohibitively high and must be taken into consideration when considering repeat biopsies in patients who have already undergone multiple previous attempts (Resnick et al., 2011).

Despite the chances of detecting less aggressive disease increasing as the number of biopsy attempts increases, there remains a chance that aggressive, anteriorly-located tumors, commonly referred to as prostate evasive anterior tumors (PEATS) have been

missed on these initial biopsies. Developing imaging modalities, such as MRI, have assisted with the identification of PEATS, typically following a negative biopsy, and have allowed for the targeting of such lesions during subsequent biopsy attempts. The Princess Margaret Cancer Centre experience with PEATS was published in 2015. Edwan et al. identified 189 patients between January 2006 and December 2012 who met the criteria for PEATS. Of the 189 men who had MRI-detected PEATS, 148 had subsequent biopsy-proven cancer in the anterior zone, with almost 60% of these tumors given a grade of GS 7 or worse. Of the 68 patients who elected to undergo surgery, 82% had GS 7 disease or worse, 60% had pathological stage T3 or worse, margins were positive in 46% of patients, and 20% had biochemical recurrence (i.e. rising PSA levels after definitive therapy) within 20 months of surgery (Edwan et al., 2015). These results highlight the aggressive nature of these cancers, and underline the importance of considering the possibility of missed PEATS tumors in patients with negative prostate biopsies.

These studies highlight the myriad of issues physicians must take into account when considering referring a patient for a repeat biopsy. Despite the majority of patients with initially negative biopsies having further negative results on repeat attempts (Eggener et al., 2005; Fleshner et al., 1997; Ploussard et al., 2013) and cancers detected on later biopsy attempts being more likely to be clinically insignificant (Resnick et al., 2011), the fact remains that the cancer detection rate may be as high as 30% (Fleshner et al., 1997) and the risk of adverse pathology after three or more biopsy attempts may be as high as 52% (Resnick et al., 2011). Despite the identification of risk factors for subsequent PCa detection, such as elevated PSA levels, positive family history, and abnormal DRE, deciding which and when patients should undergo repeat biopsy, and how many if continually negative, remains a challenging clinical question that needs further evaluation.

Overall, these studies have several important limitations. The sample sizes and follow up durations were modest (sample sizes as small as 130 patients and median follow up times as short as 19 months, respectively). Also, these studies were strictly from urban, academic, tertiary centers. Patients recruited from these centers are inherently a source of

selection bias as they typically have different demographics than the rest of the population and are treated and followed up differently at these centers than they would be at rural, secondary centers. In addition, it is likely that a subset of patients may have been lost to follow-up because they sought care/second opinion in a different center, which is also a source of selection bias. In short, it is difficult to extrapolate data from these patients to the rest of the population. Population-based studies based on data from health administrative sources could potentially resolve some of these issues by providing much larger sample sizes, with longer follow-up periods, and including patients from all different types of centers in a certain geographical region.

1.8.2 Prostate Cancer-Specific Mortality

As mentioned previously, the prevalence of PCa in men in the general population is high and one of the challenges is differentiating those that are clinically significant from those that are not. As there is a disparity between PCa prevalence in autopsy specimens (up to 80% at 80 years) (Sakr et al., 1994) and lifetime risk of death due to PCa (3.7%) ("Prostate cancer statistics", 2017), we can conclude that the majority of patients do not die from their disease. Thus, after determining what proportion of men with initially negative biopsies gets diagnosed on repeat biopsy attempts, the next step is to determine the PCa-specific mortality rates of such men.

Lewicki et al. used data from the PLCO trial to determine the cancer-specific mortality rates among men with a negative prostate biopsy. The screening/intervention arm of the PLCO trial included 36,525 men, of whom 4,064 had a positive first screen, and 1,233 underwent a related biopsy. Of these 1,233 men, 473 had a positive biopsy, whereas 760 had a negative biopsy. The 36,560 patients in the non-screened arm were included as the control subjects, with their mortality risk assumed to be similar to that of the general population (although as discussed in section 1.6.3.1, up to 60% of men in the non-screened arm still underwent off-study PSA screening). Median follow up for the three groups (positive biopsy, negative biopsy, and control subjects) was approximately 13

years in each group. By the end of follow-up, 34 of 473 (7.2%) men with a positive biopsy, 8 of 760 (1.1%) men with a negative biopsy, and 132 of 36,560 (0.4%) men in the control arm had died of PCa. Using competing risk analysis accounting for other-cause mortality, it was determined that men with a negative biopsy had a mortality rate 2.93fold higher than that of men in the general population (p < 0.05), while men with a positive biopsy having an 18.77 fold higher risk (p<0.05). The authors also used this opportunity to compare the PCa incidence rates between the negative biopsy and control groups. Patients with a negative biopsy had a 2.6 fold higher chance of PCa diagnosis (p < 0.01), with corresponding rates of 25.2 and 9.6 diagnoses per 1000-person years in the negative biopsy and control groups, respectively. Interestingly, patients in the negative biopsy group also had a 1.8 fold higher risk of being diagnosed with clinically significant disease (i.e. GS \geq 7) (p<0.01), but not with high-risk disease (i.e. GS \geq 8). Despite these patients having a higher PCa-specific mortality rate than the general population, the absolute risk is still quite low (1.1%). These results led the authors to suggest that it might be quite difficult in the future to use newer markers and biopsy techniques to improve survival in this group. The necessary next step is to determine these long-term mortality rates in a large population-based cohort (Lewicki et al., 2016).

Klemann et al. assessed the risk of PCa-specific mortality in two groups of Danish men: those with a negative result on their initial TRUS-Bx and those with PCa detected on that initial biopsy. Using data from the Danish Prostate Cancer Registry, a population-based registry including all men who have undergone tissue assessment of the prostate in Denmark, 64,430 men referred for an initial TRUS-Bx between January 1, 1995 and December 31, 2011 were identified. Of the 62,340 men eligible for inclusion in the study, 35,159 (56.4%) had a malignant biopsy, whereas 27,181 (43.6%) had a negative biopsy. After a median follow-up time of 5.9 years (interquartile range [IQR]: 3.8-8.5 years), 10,407 (30%) of men with a positive biopsy had died of PCa, compared to 541 (2%) of men with a negative initial biopsy. Using a competing-risk analysis model, the 20-year overall mortality rate at 25.6% and other-cause mortality at 50.5%. In men who had a positive biopsy, the 20-year overall mortality rate was 85.7%, with the PCa-specific mortality rate at 43.6%. Men with a negative biopsy had a 65.1% 20-year overall mortality rate, and significantly, a 5.2% cancer-specific mortality rate (Klemann et al., 2017).

Serum PSA levels were available for 13,895 (22%) of the patients. These measurements were taken up to two years before and three months after the TRUS-Bx. PSA levels were used to risk-stratify patients with regards to cancer diagnosis and mortality outcomes. In men who had a benign initial biopsy and PSA level of 10 ug/L or less, the 15-year cumulative incidence of PCa-specific mortality was only 0.7%. The corresponding cumulative incidences in men with PSA levels between 10 and 20 ug/L and greater than 20 ug/L were 3.6% and 17.6%, respectively. On univariate regression analysis, PSA level (logarithmically transformed on a base 2 scale) was a significant predictor of PCa-specific mortality (Hazard Ratio [HR]: 2.20, p<0.01). Interestingly, stratification by PSA level also seemed to correlate with the cumulative incidence of other-cause mortality, with the value rising from 26.1% to 39.8% to 56.2% in patients with PSA levels of 10 ug/L or less, 10-20 ug/L, and 20 ug/L or higher, respectively (Klemann et al., 2017).

Among the 27,181 men who had a negative initial biopsy, 8,526 (31.4%) underwent reevaluation using either another TRUS-Bx or TURP within a median follow-up period of 11 months. The number of men who were subsequently diagnosed with PCa was 2,845 (10%). Of these 2,845 men, 44% were diagnosed with low risk disease (i.e. GS \leq 6). Significantly, 191 of 18,655 (1%) of patients who did not undergo histopathological reassessment still died of PCa (Klemann et al., 2017).

The cumulative incidence of PCa diagnosis after an initially negative biopsy was 11.1% at 20 years. PSA level at time of initial referral (i.e. up to two years prior to or three months after initial biopsy) was used to stratify this diagnosis risk. In patients who initially had a PSA level of 10 ug/L or less, the 15-year cumulative incidence of cancer detection was 7.6%. In patients with PSA levels of 10-20 ug/L and greater than 20 ug/L, the corresponding cumulative incidences were 12.1% and 25.2%, respectively (Klemann et al., 2017).

The authors concluded by emphasizing the prognostic significance of the first TRUS-Bx, both with regards to cancer-specific and overall mortality rates. Since the long-term cumulative incidence of PCa-specific mortality in men with an initially negative biopsy and low PSA levels were exceedingly low (0.7% at 15 years) and the other-cause mortality cumulative incidences were much higher (26.1% at 15 years), the authors questioned whether such men should undergo further diagnostic assessment after the first negative biopsy (Klemann et al., 2017).

The importance of this landmark study cannot be overstated. It is the first to evaluate long-term PCa-specific mortality rates in men with a single negative TRUS-Bx using data from large population-based registries. However, there are several issues that need to be considered. Results from a Scandinavian cohort may not be applicable to a North American population. As previously discussed, the introduction of PSA testing has introduced major changes with respect to PCa incidence and caused a stage/risk-category shift. The historical uptake of PSA testing is likely to have had significant geographical variations. Whereas North American urologists, led by Catalona in 1991 (Catalona et al., 1991), were quick to employ PSA as a screening tool in clinical practice, data suggests that PSA uptake patterns were different amongst their Scandinavian counterparts. This is best exemplified by comparing the patient cohorts from the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) and Prostate Cancer Intervention versus Observation Trial (PIVOT), two RCTs that compared mortality outcomes in patients with clinically localized PCa treated with RP versus watchful waiting/observation in the 1990's (i.e. early PSA period) (Bill-Axelson et al., 2014; Wilt et al., 2012). In the Scandinavian study, only five percent of the patients had cancers detected via a PSA test (i.e. the others were detected by DRE or due to local symptoms), and this was reflected in the proportion of patients who had clinical stage \leq T1c (i.e. non-palpable disease): only 12% of patients in the Scandinavian study (Bill-Axelson et al., 2014) compared to 50% of the patients in the U.S-based PIVOT study (Wilt et al., 2012). Despite all patients having clinically localized disease, this stage discrepancy suggests that the U.S. patients were diagnosed at an earlier point in their disease process compared to their Scandinavian counterparts,

likely due to significant differences in frequency of utilization of the PSA test. This stage discrepancy was reflected in the results of these two trials whereby the SPCG-4 trial showed a survival benefit for RP compared to observation (Bill-Axelson et al., 2014), whereas results from PIVOT showed no benefit for treatment (Wilt et al., 2012). This is possibly due to patients in the Scandinavian group having more advanced disease, which is likely a reflection of differences in screening approaches between the geographical regions. In addition, the proportion of Danish patients who had a malignant first biopsy (35,159/64,430 or 54.6%) was considerably higher than the corresponding values that are currently reported in the literature, which are typically in the 25-30% range (Brawer et al., 1992; Catalona et al., 1994; Schroder et al., 2000). This difference likely reflects, once again, the implications of geographic variations in PCa screening/diagnostic approaches.

Importantly, this study by Klemann et al. did not assess the proportion of patients with an initially negative biopsy who eventually received treatment. As previously discussed, some of the issues with PSA testing and management of PCa are over-detection and over-treatment, respectively. Optimizing management of PCa is not only an issue of minimizing mortality, but also limiting investigation- and treatment-related morbidities and side effects. Thus, in addition to determining cancer-specific mortality rates in these patients, it is important to have an appreciation of the extent of health services utilization and resource allocation. For example, determining what proportion of such patients receive definitive treatment, such as RP and XRT, castration for presumed advanced disease, and further TRUS-Bx would help quantify the extent of health services utilization by these patients. This will also give us an appreciation of disease-related morbidity, as these procedures are not without significant side effects.

Given the relevance and importance of these issues, it becomes clear that a populationbased, North American study that evaluates the long-term rates of PCa diagnosis, PCaspecific and overall mortality, and health services utilization in patients with a single negative TRUS-Bx is necessary.

Chapter Two Research Aims and Hypotheses

2 Research Aims and Hypotheses

2.1 Study Objectives

The overall purpose of this study was to determine the PCa-specific health outcomes of Ontario-based men with a history of a single negative TRUS-Bx, using population-based health administrative data from January 1, 1994 to December 31, 2015.

The primary objective of this study was to determine the PCa-specific mortality rates in men with a single negative TRUS-Bx.

The secondary objectives were to determine in men with a single negative TRUS-Bx:

- i. Other-cause and overall mortality rates
- ii. PCa diagnosis rates
- iii. Repeat biopsy frequency distributions
- iv. Rates of treatment with RP
- v. Rates of treatment with definitive XRT
- vi. Rates of treatment with ADT
- vii. Predictors of PCa diagnosis and mortality

2.2. Study Hypotheses

We predicted that the cumulative incidence of PCa-specific mortality at 20 years would be 3%. The corresponding mortality rate in the Danish study was about 5% (Klemann et

al., 2017), and given that the use of PSA testing is more widespread in North America and patients are followed up/treated more intensively, we predicted that this would be favorably reflected in superior cancer-specific mortality rates.

We predicted that the overall mortality rates would be similar to those in the Danish study, with about 66% of patients dying by 20 years follow-up. PCa is a disease of the elderly and patients undergoing PSA/biopsy investigations are likely to be older, thus explaining the high 20-year mortality rates.

We predicted that the PCa diagnosis rate at 20 years would be about 20%. The corresponding diagnosis rate in Danish patients was 11% (Klemann et al., 2017). However, due to geographic differences in management approaches, we expected the more intensive follow-up to lead to a much higher diagnostic rate than 11%.

We hypothesized that 50% of men would undergo a repeat prostate biopsy. These men had positive screens that prompted the initial biopsy, and we expected that this heightened pre-test risk would prompt further biopsy attempts in half of these patients. Although only 31% of patients underwent a repeat biopsy in the study by Ploussard et al., we expected that our cohort's median follow up duration would be significantly longer than only 18 months and that this would reflect in a higher number of patients undergoing a repeat biopsy.

Since we expected the PCa diagnosis rate at 20 years to be around 20%, we hypothesized that the combined rate of receiving either RP or definitive XRT will be around 15%. We predicted a rate of 15%, and not 20%, because the introduction of AS has led to many patients with low-risk PCa avoiding RP/XRT, and population-based analysis has shown that the uptake of AS in Ontario has increased from 24.1% in 2002 to 34.1% in 2010 (Richard et al., 2016). Based on those results, we estimated that a quarter of patients in our cohort would avoid definitive therapy. We predicted that the 20-year rate of receiving ADT would be about 10%, as ADT is a treatment for patients with advanced disease, and

we anticipated that the majority of patients diagnosed would have low to intermediate risk disease.

We predicted that increasing age at index biopsy, increasing neighborhood income quintile, residing in an urban area, and lower combined Aggregated Diagnosis Groups (cADG) score (i.e. fewer co-morbid medical conditions) would be associated with increased risk of PCa diagnosis. Risk of PCa is known to increase with age (Siegel et al., 2011). We suspected that patients with higher income quintiles and those residing in an urban area would be more likely to follow-up with their physicians, undergo testing for PCa, and thus be at higher risk of PCa detection. Similarly, we anticipated that patients with less co-morbid medical conditions (i.e. healthier patients) would be more likely to be offered/undergo testing for PCa following a negative TRUS-Bx, leading to increased PCa detection.

We hypothesized that increasing age at index biopsy, lower income quintiles, and residing in a rural area would increase risk of PCa mortality, with cADG score (i.e. co-morbidity status) not associated with PCa mortality risk. Older men are known to have more aggressive disease (Borek et al., 1990), and thus higher disease mortality. Since we expected patients with higher income quintiles and those living in an urban area to follow up more closely with their physicians, we hypothesized that this will reflect favorably with respect to PCa mortality outcomes, with patients of lower income quintiles and those residing in rural areas having higher PCa-specific mortality rates.

Chapter Three Methods

3 Methods

3.1 Study Design

This was a retrospective, observational, population-based cohort study using linked data from health administrative databases housed at the Institute of Clinical and Evaluative Sciences (ICES). ICES is an independent, not-for-profit organization that utilizes provincial health information from residents of the Province of Ontario in order to conduct health services and health outcomes research. The collection of health information from Ontario residents is facilitated by the nature of Ontario's publicly funded health care system. ICES houses patient-level, coded, and linkable medical records from universal health coverage-eligible Ontario patients since 1986 ("ICES Homepage", 2017).

3.2 Ethics and Confidentiality

ICES is accepted as a "prescribed entity" under the Personal Health Information Protection Act (PHIPA). Under this act, ICES is legally allowed to collect and utilize health administrative information for the goal of monitoring and assessing the provincial health system ("Law Document English View", 2014). The Information and Privacy Commissioner of Ontario is responsible for reviewing and approving all ICES policies, practices, and procedures every three years ("Institute of Clinical Evaluative Sciences Letter", 2005). The ICES Key Number (IKN) is an anonymous, unique patient identifier that is used to link patient-level health data from different databases. All linkages are securely performed by an ICES analyst prior to making the data available for analysis. ICES ethics approval is insured via completion of a Privacy Impact Assessment form. Ethics approval was also obtained from the University Health Network (Appendix A) and The University of Toronto research ethics board (Appendix B).

3.3 Study Participants, Setting, and Timeline

3.3.1 Eligibility Criteria

Our patient cohort included men 40 years of age and older residing in Ontario and having a single negative TRUS-Bx, accrued between January 1, 1994 and October 1, 2014.

A patient was considered to have undergone a TRUS-Bx if <u>both</u> of the following conditions were met:

- Ontario Health Insurance Plan (OHIP) billing code for a prostate needle biopsy (Z712, Z713, S644, E780)
- OHIP billing code for a pelvic/abdominal ultrasound (J128, J135, J138, J149, J162, J180) within two days of the prostate needle biopsy

Subsequently, a patient was considered to have had a negative TRUS-Bx if he had undergone a TRUS-Bx and had:

- No record of PCa diagnosis (International Statistical Classification of Diseases and Related Health Problems [ICD]-10: C61, ICD-O: C61.9) in the Ontario Cancer Registry (OCR)
- No record of receiving ADT (implantation of hormone pellets, defined by OHIP billing code: G342, was used as a surrogate for receiving ADT injections)
- No record of bilateral orchiectomy (defined using the Canadian Classification of Health Interventions [CCI] code 1QM89 with location code as bilateral) in the Canadian Institute for Health Information- Discharge Abstract Database (CIHI DAD)

within 90 days after the date of the TRUS-Bx. These three criteria combined were used as our definition for PCa, since occasionally in practice, patients may present with very high levels of PSA and symptoms very suggestive of PCa metastasis and receive treatment with ADT/bilateral orchiectomy for their advanced disease without undergoing a confirmatory diagnostic biopsy. Hence, these patients' presumptive diagnoses would not have been captured in OCR, leading to underestimation of the true incidence/prevalence of PCa. For that reason we added treatment with ADT/bilateral orchiectomy to capture those patients who received therapy with no OCR diagnosis of PCa. These definitions were arrived at after lengthy discussions with an expert urologist, two health services researchers, an ICES statistician, and two ICES data analysts. A time window of two days and 90 days were used to define a TRUS-Bx and negative TRUS-Bx, respectively, to account for inaccuracies characteristic of health administrative databases and increase the accuracy of our results. Patients were required to have had valid, unexpired OHIP medical coverage to be included in the cohort. Forty years was chosen as the age limit as patients of younger age rarely undergo screening for PCa.

We wanted to ensure that all patients included in our study had a <u>single</u> negative TRUS-Bx at time of entry into the cohort. In order to ascertain this, we excluded patients who had a billing code for a prostate biopsy prior to cohort entry. The look-back window was from the date of cohort entry till January 1, 1991. For example, patients enrolled on January 1, 1994 had a look-back window of three years, whereas those enrolled on January 1, 1997 had a look-back window of six years. Patients were also excluded if they had a record of PCa diagnosis in OCR, implementation of hormone pellets OHIP billing code, or bilateral orchiectomy in CIHI DAD prior to cohort entry. Men with invalid IKNs at time of TRUS-Bx or date of death were also excluded. The study inclusion and exclusion criteria are summarized in Table 3.1.

Table 3.1 Study inclusion and exclusion criteria as defined in the ICESDataset Creation Plan

Inclusion Criteria	Exclusion Criteria (same order as that	
	used to create our cohort)	
1. Prostate needle biopsy (OHIP billing	1. Invalid IKN	
codes Z712, Z713, S644, E780)	2. Female sex	
2. Pelvic/abdominal ultrasound (OHIP	3. Death prior to/on biopsy date	
billing codes J128, J135, J138, J149, J162,	4. Prostate needle biopsy (OHIP billing codes	
J180 within two days of prostate needle	Z712, Z713, S644, E780) prior to January 1,	
biopsy)	1994	
	5. PCa diagnosis (ICD-10: C61, ICD-O:	
	C61.9) in OCR prior to January 1, 1994	
	6. Implantation of hormone pellets (OHIP	
	billing code G342) prior to January 1, 1994	
	7. Bilateral orchiectomy (CCI code: 1QM89	
	with location code as bilateral only) record in	
	CIHI DAD prior to January 1, 1994	
	8. PCa diagnosis (ICD-10: C61, ICD-O:	
	C61.9) in OCR within 90 days after prostate	
	biopsy	
	9. Implantation of hormone pellets (OHIP	
	billing code G342) within 90 days after	
	prostate biopsy	
	10. Bilateral orchiectomy (CCI code: 1QM89	
	with location code as bilateral only) record in	
	CIHI DAD within 90 days after prostate	
	biopsy	
	11. Age under 40 at time of prostate biopsy	
	12. OHIP ineligible at the date of biopsy	
	13. Censored in the first 90 days post index	
	biopsy	

3.3.2 Study Time Frame Definitions

The study time frame definitions are illustrated in Figure 3.1. Patients were accrued between January 1, 1994 and October 1, 2014. The first cutoff was chosen because OHIP billing information was available from January 1, 1991 and we wanted to implement a look-back window of at least three years duration, prior to patient accrual, to ascertain that patients did not have a previous biopsy or PCa diagnosis prior to cohort entry. The second cutoff was chosen because data in OCR was complete up to that time point only at time of cohort creation. The follow-up period ended December 31, 2015, as OHIP and OCR data were not available after this time point. Patients were followed forward from the index date (date of biopsy) up until any of the following censoring events occurred: death, one year following end of OHIP eligibility, or December 31, 2015 (Max follow-up date).

Figure 3.1 Study Timeline



3.4 Data Sources

3.4.1 Data Linkage

Patient-level health information is recorded in a number of different administrative databases, all housed at ICES, as previously mentioned. Linking this data at the individual level is possible via the IKN. The IKN is an anonymous, unique identifier assigned to each individual with valid OHIP coverage and is derived from the person's Ontario health card number. Since Canada employs a publicly funded health care system, more than 95% of Ontario residents are under the care of OHIP, and thus have their health information available in ICES databases. Individuals residing near provincial borders may theoretically decide to seek care in centers located across these borders; however, this seems to be of little significance as only one percent of OHIP claims are billed from outside Ontario (Clarke et al., 1991).

3.4.2 Ontario Health Insurance Plan Database

This database contains records of all the billing claims from health care providers for insured health services provided to Ontario residents with valid health coverage. As mentioned above, more than 95% of Ontario residents are publicly insured and thus it is assumed that about 95% of all billing claims for insured health services are included in this database. The OHIP covers the vast majority of health services provided by health care providers, including those located outside of province, except those considered to be medically unnecessary, such as cosmetic procedures ("Ontario Health Insurance Plan", 2017). Each billing claim, recorded as a single event, represents a single administration of the health service to a unique person at a given time (e.g. if a patient undergoes the same procedure twice on the same day, two billing claims will be recorded). Relevant information for each billing claim is available in this database and includes: description of service provided (OHIP fee code), date service was provided, diagnosis

codes/information, center where service was provided, and physician who billed for the service.

In our study we used billing claims from the OHIP database to identify patients who underwent a TRUS-Bx, using a billing claim for a prostate needle biopsy and a separate one for concurrent pelvic/abdominal ultrasound. The OHIP database has several strengths that are worth highlighting. About 95% percent of practicing physicians in Ontario are compensated in a "fee-for-service" fashion ("Institute for Clinical Evaluative Sciences. Data holdings: Ontario Health Insurance Plan", 2017). In other words, if these physicians do not submit billing claims for the various services provided, they will not be compensated accordingly. This creates a strong incentive for these physicians to always submit claims in a timely manner, thus increasing the reliability and validity of OHIP data. Importantly, OHIP captures billing claims for services provided at various medical centers besides hospitals, such as medical laboratories. This is relevant to our study as prostate biopsies, for example, may be performed in such centers. OHIP insures that data for such procedures is captured. Results from ICES investigative reports have been reassuring that these various procedures are accurately captured in OHIP (Chan et al., 2005). A validation study assessing the accuracy of both physician claims and hospital discharge abstracts compared to chart records for women with node negative breast cancer, from April 1991 to December 1991, was conducted. The results were reassuring, as agreement between surgeon billing claims and chart records was 95.4% for most definitive procedures, whereas that between hospital discharge abstracts and chart records was 86.2% (Pinfold et al., 2000). Another study comparing the accuracy of OHIP billing claims for prostate, breast, lung, and colorectal cancer procedures in the OHIP database to information in CIHI DAD revealed these billing procedures to be accurate 93% to 97% of the time (Simunovic et al., 2005). Interestingly, another study validating billing claims of XRT sessions for PCa showed that the agreement rates for these treatments were lower than those for surgical billing claims (about 80%) (Alibhai, 2001). This highlights the importance of physicians being compensated in a "fee-for-service" manner with regards to data completion in administrative databases. Whereas 95% of physicians are compensated in this manner, a significant proportion of Ontario-based radiation

oncologists (who bill for these procedures) are paid a fixed salary, and thus have a lower incentive to accurately bill for these procedures, which is reflected in the study results.

We used OHIP billing claims in our study to identify/define the following events: undergoing TRUS-Bx, undergoing XRT, healthcare contact with an urologist, and implantation of hormone pellets (validated surrogate for ADT drug use). The specific OHIP billing claims used are listed in Appendix C.

As mentioned above, we used the OHIP billing code for implantation of hormone pellets (G342) as a surrogate for ADT drug use. The Ontario Drug Benefit (ODB) claims database, which contains records of all drug prescription claims for eligible recipients, is complete only for individuals over 65 years of age and those younger with special conditions, such as social assistance or long-term disability ("ICES Homepage", 2017). Thus, data on prescription claims for ADT drugs, such as LHRH agonists and GnRH antagonists, is only accurately available for those older than 65 years. As our cohort eligibility extended to patients as young as 40 years old, this makes the use of ODB for this purpose impractical. Fortunately, the OHIP G342 billing code, which is routinely used when injectable, but not oral, ADT drugs are administered, has been validated as a reliable surrogate for ADT drug administration using two different reference standards: (1) prescription of at least one LHRH agonist or antagonist drug and (2) prescription of any ADT drug. Despite the sensitivity of this code being less than ideal (71% and 66%) for the first and second reference standards, respectively), the overall percent agreement and specificity were reassuring (90% and 99%, respectively, for first reference standard and 85% and 99%, respectively, for the second reference standard) (Bhindi, 2014). In order to ensure consistency over all age groups, we exclusively used the OHIP billing code G342 to identify patients who received ADT drugs.

3.4.3 Ontario Cancer Registry

The OCR is a population-based tumor registry that contains records on all new cancer cases in Ontario, except non-melanoma skin cancers, since 1964. It is the most complete cancer registry in the Province of Ontario. OCR is operated by Cancer Care Ontario (CCO), which coordinates and provides comprehensive cancer treatments for the residents of Ontario (Hall et al., 2006).

The OCR is a passive registry, which obtains its data from four key sources (Hall et al., 2006). The first source of data is CIHI DAD, which sends hospital discharge information to the MOHLTC. All hospitals are obligated to send discharge diagnosis data to the MOHLTC. In every hospital, trained data-abstracters are responsible for abstracting the following data from medical charts: hospital admission and discharge dates, primary, secondary, and all major diagnoses, any therapeutic interventions, any complications during hospital stay, and patient demographics. The MOHLTC reviews the abstracts for completion and returns them to the hospital, if incomplete, for re-editing. The MOHLTC in turn forwards a copy of the discharge abstract for every patient with cancer, except non-melanoma skin cancers, to CCO, which in turn is recorded in the OCR (Clarke et al., 1991). The second data source is all Ontario Regional Cancer Centers, including Princess Margaret Cancer Centre. These centers forward diagnosis and management information for all cancer patients to CCO/OCR on a monthly basis. The third source is all Ontario labs that are licensed to process tumor specimens. These labs send all pathology reports of cancer patients to CCO/OCR. The fourth data source is the Registrar General's Office in the Ontario Ministry of Consumer and Commercial Relations, which submits death certificate records for all Ontarians to CCO/OCR every three months, with a total of almost 400,000 records forwarded per year (Nishri, 2011).

Unfortunately, the OCR does not contain comprehensive grading and staging information for PCa, as data from manually archived pathology reports have not been regularly recorded in this registry over the years. As the predominant source of OCR is CIHI DAD, the accuracy, reliability, and validity of most fields in OCR are similar to those in CIHI DAD.

We used OCR in our study to identify patients who were histologically diagnosed, via a TRUS-Bx or TURP, with PCa (ICD-10: C61, ICD-0: C61.9). However, as previously discussed, our definition of PCa included those without histological diagnosis, but had received treatment for presumptive diagnosis, in order to ensure all cases are captured. Two studies have demonstrated that the OCR contains a record of at least one confirmatory histological report for more than 93% of patients with a diagnosis of PCa (Holowaty et al., 1996; Robles et al., 1988).

3.4.4 Canadian Institute for Health Information Discharge Abstract Database

The CIHI DAD, initiated in 1963, records administrative, clinical, and demographic data on hospital discharges, with some provinces and territories also recording day surgery data. As opposed to OHIP and OCR, which house provincial data only, CIHI DAD contains national data. The data sources for CIHI DAD are acute care facilities, health/regional authorities, or ministry/departments of health. All facilities in all provinces and territories are required to report, with the exception being the Province of Quebec which forwards data directly to CIHI via the ministère de la Santé et des Services Sociaux du Québec. CIHI DAD receives more than 3.2 million abstracts each year, which represents about three-quarters of all acute inpatient discharges in Canada ("Data Quality Documentation, Discharge Abstract Database", 2012).

Each record in CIHI DAD is a codified summary of a patient's hospital stay. Once a patient is discharged, the hospital's health information management specialists (i.e. coders) review patient health charts and code the documented information, according to CIHI standards. Each record contains up to 25 diagnoses and 20 interventions, in addition to patients demographics and administrative information. Prior to April 2001, diagnostic

data was coded according to the ICD-9 and ICD-9-Clinical Modification, while intervention data was coded using both the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures and the procedure section of the ICD-9-Clinical Modification ("CIHI: ICD-9/CCP and ICD-9-CM", 2017). Currently, diagnostic data is coded according to the ICD, 10th Revision, Canada, while interventions are coded according to CCI ("Canadian Coding Standards", 2015).

CIHI DAD employs a Data Quality Program, which performs a number of measures, such as reabstraction studies, to ensure data completeness and accuracy. Reabstraction studies specifically assess quality of abstract coding, detect systematic issues, and evaluate the impact of any coding concerns on CIHI products ("Data Quality Study of the 2015-2016 Discharge Abstract Database", 2016). Using chart abstraction as the reference standard, such studies found patient demographics to be both complete and accurate for more than 93% of all patients (Juurlink et al., 2006; Williams et al., 1996). As for the "most responsible diagnosis", there was at least partial agreement between original coders and reabstractors in more than 85% of the cases. This figure was higher for surgical interventions (Hawker et al., 1997; "Ontario Hospital Association", 1991; Ugnat, 1995; Williams et al., 1996).

For the purposes of our study, the CIHI DAD was used to identify patients that underwent radical prostatectomy and bilateral orchiectomy. The specific codes used to identify these procedures are presented in Appendix C.

3.4.5 Registered Persons Database

The Registered Persons Database (RPDB), a population-based registry directed by the MOHLTC, houses demographic data for all people who have ever had an Ontario health card number for OHIP coverage. It contains data on patient's birth date, sex, address postal code, date of death, and any changes in eligibility status for health insurance coverage (Clarke et al., 1991).

The RPDB was our data source for age at index biopsy (time of cohort entry), postal code address (used to derive urban versus rural residence status and neighborhood income quintile, a surrogate for socioeconomic status), death date (if applicable) and date of last health care system contact (used to censor patients). The death date is derived from various sources, including the MOHLTC, CIHI DAD, and OCR (Clarke et al., 1991).

3.4.6 Office of the Registrar General - Deaths

The Office of the Registrar General – Deaths (ORGD) contains death records/certificates for all Ontarians. Data from the ORGD was used to ascertain cause of death (PCa-specific versus other-cause mortality). For the purposes of our study, PCa was considered the cause of death if it was documented as the primary (i.e. underlying) cause of death on the patient's death record.

3.4.7 The Johns Hopkins Adjusted Clinical Groups and Aggregated Diagnosis Groups Score

The Johns Hopkins Adjusted Clinical Groups (ACG) System is a valid, diagnosis-based, case-mix technique that was developed to predict individuals' previous and future healthcare resources utilization and expenses ("The Johns Hopkins ACG Case-Mix Adjustment System", 2017). Aggregated Diagnosis Groups (ADGs) are diagnosis clusters to which the ACG system assigns an ICD-9 code. Specific medical conditions are allocated into one of the 32 ADG clusters depending on their underlying cause, duration, severity, diagnostic certainty, and involvement of specialty care. ("The Johns Hopkins ACG Case-Mix Adjustment System", 2017; Starfield et al., 1991; Weiner et al., 1991). Individuals in the same ADG category are expected to similarly utilize healthcare resources. The ACG system's external validity and ability to predict patient mortality has

been previously demonstrated in a number of studies (Austin et al., 2011b; Petersen et al., 2005; Pietz et al., 2007; Reid et al., 2001; Reid et al., 2002). A point-based scoring system that summarizes the individual's comorbidity risk score into a single summary score was subsequently derived from the ACG system (Austin et al., 2011a). This score is calculated as a weighted sum of the individual's various comorbidities. It has been shown to reliably predict one-year mortality (Austin et al., 2011a).

3.5 Statistical Methods and Analysis

3.5.1 Statistical software and significance level

All statistical analyses were performed using R version 3.3.1 (Copyright © 2016 The R Foundation for Statistical Computing). Statistical significance was set at a two-sided p-value of 0.05.

3.5.2 Descriptive Statistics

Univariate statistics were used to describe our cohort's baseline characteristics. Continuous variables were described using medians and interquartile ranges, whereas categorical variables were characterized using proportions. Continuous variables were compared using the student's t-test, whereas categorical variables were compared using the Chi-square test.

3.5.3 Competing risk analysis

3.5.3.1 Cumulative Incidence Functions

Cumulative incidence functions (CIF) were used to estimate the short- and long-term rates of PCa and other-cause mortality, PCa diagnosis, undergoing RP and XRT, and receiving ADT. CIFs account for the risk of competing events (i.e. events that preclude the occurrence of the event of interest). In our analysis, death due to any cause was the competing event that we accounted for. Since PCa is a disease of the elderly, men undergoing evaluation for PCa are typically of older age. Thus, when attempting to determine 20-year event rates, we suspect that a significant proportion of such patients will die, thus obliging us to account for this competing event in our analysis. Usually, this analysis is incorrectly performed using a 1-Kaplan Meier curve, with patients experiencing competing events censored at the time of their occurrence. However, this is incorrect because after death (competing event), having the event of interest is no longer possible, whereas censoring implies that the event might have occurred later on had a longer follow-up period been possible (Scrucca et al., 2007). As a result of this, at any specific time, the overall 1-Kaplan Meier curve is equivalent to the summation of the CIFs for each type of event (Klein et al., 2001; Satagopan et al., 2004). CIFs were calculated using the 'cuminc' function found in the 'cmprsk' package (version 2.2-7) ("Package 'cmprsk", 2014).

3.5.3.2 Regression Analyses

In order to assess whether age, neighborhood income quintile (surrogate for socioeconomic status), and urban versus rural residence were independent predictors of risk of PCa diagnosis and PCa-specific mortality, we performed both univariate and multivariate regression analyses, accounting for the competing risk of death. Only those variables that were significant on univariate regression analyses were included in the multivariate model. We used the semiparametric proportional hazards model proposed by

Fine and Gray to estimate the subdistribution HR of the various covariates for each outcome of interest (Fine et al., 1999). These regression analyses were performed using the 'crr' function found in the 'cmprsk' package (version 2.2-7) ("Package 'cmprsk'", 2014). The overall significance (p-value) for categorical variables with three or more levels was calculated using the Wald test (Scrucca et al., 2010). The Wald test was performed using the 'wald.test' function found in the 'aod' package (version 1.3) ("Package 'aod'", 2012). We did not use the Cox proportional hazards model for our time-to-event regression analysis since this model improperly censors patients who had the competing risk of interest (Scrucca et al., 2010). Description of the covariates used in our regression analyses is shown in Table 3.2.

Table 3.2 Description of variables used in regression analyses			
Variable	Туре	Levels	
Age at index (years)	Continuous	N/A	
Age at index (years)	Categorical	40-49	
		50-59	
		60-69	
		70-79	
		80+	
Neighborhood Income	Categorical	1 to 5 (lowest to highest)	
Quintile			
Residence Location	Categorical	Urban or Rural	
Combined Aggregated	Continuous	0-100 (higher scores	
Diagnosis Groups Score		indicate greater	
		comorbidity)	

3.5.4 Sensitivity Analyses

We used sensitivity analysis to compare outcomes in patients who specifically had a negative TRUS-Bx to those who had a negative prostate biopsy of any type (TRUS- or finger-guided). Health administrative databases at ICES do not automatically identify patients who underwent TRUS-Bx. Our definition of a TRUS-Bx was patients who underwent a prostate biopsy and had a billing code for a concurrent pelvic/abdominal ultrasound within two days of the biopsy. We are assuming that this definition will identify patients who underwent a TRUS-Bx, whereas those who had no billing code for a pelvic/abdominal ultrasound within this time window were presumed to have had a finger-guided biopsy, which is currently no longer performed in clinical practice.

We wanted to assess whether our decision to restrict cohort entry to those who had a pelvic/abdominal ultrasound within two days of the index biopsy had any impact on our results. In order to assess that, we evaluated whether men with a negative prostate biopsy of any type, at time of cohort entry, had significantly different outcomes compared to those who specifically had a negative TRUS-Bx. We determined the following in all patients who had a single negative prostate biopsy (TRUS- or finger-guided):

- PCa-specific mortality rates
- Other-cause mortality rates (i.e. all cause mortality minus PCa-specific mortality)
- PCa diagnosis rates
- Frequency distribution of repeat biopsies
- RP rates
- XRT rates
- ADT rates

The event incidence rates of these patients were statistically compared to those of patients with a single negative TRUS-Bx by examining whether there is an overlap between the corresponding 95% CIs. If no overlap was present, differences were deemed to be

statistically significant. Clinical significance was evaluated by calculating the absolute differences.

3.5.5 Power and Sample Size Calculations

We did not perform any sample size calculations, as our primary objective was to determine both short- and long-term outcomes rates in <u>all</u> patients who had a single negative TRUS-Bx in Ontario. Including the largest number of patients possible in this study allowed for the most truthful, valid determination of these rates. Even though our secondary objectives included performing regression analyses to determine if a number of covariates predicted for PCa diagnosis or mortality and including very large sample sizes may lead to over-powering of a model (i.e. clinically insignificant variables may reach statistical significance on regression analyses, leading to erroneous conclusions), we were more concerned with the clinical significance, and not the statistical significance, of our results (i.e. we were more concerned with the value of the subdistribution HR rather than that of the p-value). For these reasons, we included all patients who met our definition for a single negative TRUS-Bx.

Chapter Four Results

4 Results

4.1 Study Cohort Characteristics

Our cohort consisted of 95,675 men with a single negative TRUS-Bx at time of cohort entry. Initially, 400,871 prostate biopsies underwent by Ontario residents between January 1, 1994 and March 31, 2015 were identified. Of these biopsies, 125,232 were excluded because these were not the first biopsies underwent by patients. A further 15,841 records were excluded as patients had a PCa diagnosis prior to these events, while an additional 102,912 (42.2%) were excluded as these biopsies were followed by a diagnosis of PCa in OCR within 90 days. In total, 123,700 patients with a negative prostate biopsy were identified. Of these 123,700 patients, 95,675 (77.3%) were identified to have had a TRUS-Bx, constituting our final cohort. A flow diagram illustrating all the administrative steps used to derive our cohort is displayed in Figure 4.1. Our cohort's characteristics at baseline are displayed in Table 4.1. Median patient age was 63.0 years, with 73.3% of patients falling in the 50-69 years age category. Men were relatively evenly distributed across the various neighborhood income quintiles, and the majority (92.2%) resided in an urban area. Median follow-up was 8.09 years (IQR: 4.53-12.34 years), with a total follow up period of 831,057 person-years.


Figure 4.1 Flow chart of all steps used to identify our final patient cohort

Table 4.1 Study cohort baseline characteristics (n=95,675)					
Median age, years (IQR)	63.0 (57.0-69.0)				
Age groups					
40-49	5131 (5.4%)				
50-59	28835 (30.1%)				
60-69	41310 (43.2%)				
70-79	18417 (19.2%)				
80+	1982 (2.1%)				
Median Combined Aggregated Diagnosis	16.0 (7.0-22.0)				
Groups Score (IQR)					
Neighborhood income quintile					
1	13873 (14.5%)				
2	17126 (17.9%)				
3	18657 (19.5%)				
4	20857 (21.8%)				
5	25162 (26.3%)				
Area of residence					
Urban	88212 (92.2%)				
Rural	7463 (7.8%)				

4.2 Rates of study outcomes

4.2.1 Prostate Cancer-Specific Mortality

The total number of PCa-specific deaths was 629, accounting for 0.66% of the total cohort. The PCa-specific mortality rates at 5, 10, 15, and 20 years of follow up were 0.0016 (95% CI: 0.0014-0.0019), 0.0057 (95% CI: 0.0051-0.0063), 0.0128 (95% CI: 0.0122-0.0135), and 0.0182 (95% CI: 0.0160-0.0201), respectively. The CIF for PCa-specific mortality is displayed in Figure 4.2.

Figure 4.2 Cumulative incidence functions for prostate cancer-specific and other-cause mortality for men after a single negative TRUS biopsy



Time from first negative biopsy (Years)

The impact of age on PCa-specific mortality was graphically assessed in two ways. Separate CIFs were generated for each age category. The total numbers of PCa-specific deaths for patients in the 40-49, 50-59, 60-69, 70-79, and 80+ age groups were 4, 51, 238, 266, and 70, respectively, accounting for 0.08%, 0.18%, 0.58%, 1.44%, and 3.53% of patients in each age category, respectively. The CIFs for PCa-specific mortality by age groups are shown in Figure 4.3. The 5, 10, 15, and 20-year rates of PCa-specific mortality are displayed in Table 4.2. **Figure 4.3** Cumulative incidence functions for prostate cancer-specific mortality by age groups for men after a single negative TRUS biopsy



Time from first negative biopsy (Years)

Table 4.2 Prostate cancer-specific mortality rates (with 95% CI) by				
age group				
Age Category	5 years	10 years	15 years	20 years
40-49	0	0.0014	0.0022	0.0022 (0.0020-
		(0.0012-	(0.0020-	0.0024)
		0.0016)	0.0024)	
50-59	0.0005	0.0017	0.0045	0.0069 (0.0067-
	(0.0003-	(0.0015-	(0.0043-	0.0071)
	0.0007)	0.0019)	0.0047)	
60-69	0.0012	0.0042	0.0112	0.0166 (0.0164-
	(0.0010-	(0.0040-	(0.0110-	0.0167)
	0.0014)	0.0043)	0.0114)	
70-79	0.0033	0.0113	0.0242	0.0318 (0.0316-
	(0.0032-	(0.0111-	(0.0241-	0.0321)
	0.0035)	0.0114)	0.0244)	
80+	0.0149	0.0407	0.0460	0.0685 (0.0683-
	(0.0147-	(0.0405-	(0.0458-	0.0687)
	0.0151)	0.0410)	0.0462)	

The relationship between age and PCa-specific mortality was also assessed by constructing a CIF with age in years, as opposed to duration of follow-up, as the time component. This is illustrated in Figure 4.4. The number of deaths due to PCa by ages 50, 60, 70, 80, 90, and 100 were 0, 7, 87, 312, 591, and 629, respectively. The risks of PCa-specific mortality at 50, 60, 70, 80, 90, and 100 years were 0, 0.0001 (95% CI: 0-0.0001), 0.0013 (95% CI: 0.0010-0.0015), 0.0075 (95% CI: 0.0066-0.0083), 0.0291 (95% CI: 0.0263-0.0319), and 0.0419 (95% CI: 0.0361-0.0048), respectively.

Figure 4.4 Cumulative incidence function for PCa-specific mortality as a function of patient age for men after a single negative TRUS biopsy



Cumulative incidence function for prostate cancer-specific mortality for men after a single negative TRUS-guided prostate biopsy

4.2.1.1 Predictors of Prostate Cancer-Specific Mortality

On univariate regression analysis, age, as a categorical variable, was a significant predictor of PCa-specific mortality. Using the 40-49 years age group as the reference category, increasing age was significantly associated with increased risk of PCa-specific mortality. The subdistribution HRs for age groups 50-59, 60-69, 70-79, and 80+ were 2.18 (95% CI: 0.79-6.04, p=0.13), 6.36 (95% CI: 2.37-17.08, p<0.01), 14.67 (95% CI: 5.46-39.38, p<0.01), and 37.52 (95% CI: 13.68-102.90, p<0.01), respectively. The overall significance of age as a categorical variable, assessed using the Wald test, was p<0.01.

Similarly, neighborhood income was a significant predictor of PCa-specific mortality on univariate regression analysis. With the lowest income quintile group as the baseline reference, the subdistribution HRs for increasing income quintile groups were 0.85 (95% CI: 0.66-1.10, p=0.22), 0.69 (95% CI: 0.53-0.99, p<0.01), 0.77 (95% CI: 0.60-0.99, p=0.04), and 0.70 (95% CI: 0.55-0.89, p<0.01), respectively. The overall significance of neighborhood income quintile, assessed using the Wald test, was p=0.02.

Residence location (urban versus rural) was also a significant predictor of PCa-specific mortality. When compared to urban residence, the subdistribution HR for rural residence was 1.54 (95% CI: 1.20-1.98, p<0.01). In other words, patients living in a rural residence had a 54% higher risk of PCa-specific mortality compared to urban dwellers.

cADG score was a significant predictor of PCa-specific mortality on univariate regression analysis. The subdistribution HR for each one-unit increase in cADG score was 1.01 (95% CI: 1.01-1.02, p<0.01).

On multivariate regression analysis, age, neighborhood income quintile, and residence location remained significant predictors of PCa-specific mortality. Using the 40-49 years age group as the reference category, the subdistribution HRs for age groups 50-59, 60-69, 70-79, and 80+ were 2.10 (95% CI: 0.76-5.81, p=0.15), 6.28 (95% CI: 2.34-16.86, p<0.01), 14.48 (95% CI: 5.40-38.88 p<0.01), and 37.18 (95% CI: 13.56-101.92, p<0.01), respectively. The overall significance of age as a categorical variable, assessed using the Wald test, was p<0.01.

As for neighborhood income quintile, with the lowest income quintile group as the baseline reference, the subdistribution HRs for increasing income quintile groups were 0.85 (95% CI: 0.66-1.10, p=0.22), 0.73 (95% CI: 0.56-0.95, p=0.02), 0.86 (95% CI: 0.67-1.10, p=0.23), and 0.80 (95% CI: 0.62-1.02, p=0.07), respectively. The overall significance of neighborhood income quintile, assessed using the Wald test, was p=0.04.

With regards to residence location, with urban residence as the reference, the subdistribution HR for rural residence was 1.46 (95% CI: 1.20-1.88, p<0.01).

cADG score was no longer predictive of PCa-specific mortality on multivariate regression analysis. The subdistribution HR was 1.00 (95% CI: 0.99-1.01, p=0.89).

4.2.2 Other-Cause Mortality

The total number of deaths in the cohort was 16,153 (629 due to PCa and 15,524 due to all other causes), accounting for 16.9% of the cohort. The other-cause mortality rates at 5, 10, 15, and 20 years of follow up were 0.0591 (95% CI: 0.0576-0.0607), 0.1559 (95% CI: 0.1544-0.1574), 0.2968 (95% CI: 0.2922-0.3014), and 0.4587 (95% CI: 0.4496-0.4678), respectively. The CIF for other-cause mortality is displayed in Figure 4.2. CIF for all-cause mortality is the sum of CIFs for PCa-specific mortality and other-cause mortality.

4.2.3 Prostate Cancer Diagnosis

The total number of PCa diagnoses was 15,690, accounting for 16.4% of the total cohort. The PCa diagnosis rates at 5, 10, 15, and 20 years of follow up were 0.1268 (95% CI: 0.1245-0.1290), 0.1835 (95% CI: 0.1807-0.1863), 0.2165 (95% CI: 0.2131-0.2199), and 0.2373 (95% CI: 0.2328-0.2418), respectively. The CIF for PCa diagnosis is shown in Figure 4.5. **Figure 4.5** Cumulative incidence function for prostate cancer diagnosis for men after a single negative TRUS biopsy



The impact of age on PCa diagnosis rates was graphically assessed in two ways. Separate CIFs were generated for each age category. The total numbers of PCa diagnoses for patients in the 40-49, 50-59, 60-69, 70-79, and 80+ age groups were 472, 4,216, 7,288, 3,369, and 345, respectively, accounting for 9.2%, 14.6%, 17.6%, 18.3%, and 17.4% of patients in each age category, respectively. The CIFs for PCa diagnosis by age group are shown in Figure 4.6. The 5, 10, 15, and 20-year rates of PCa diagnosis are displayed in Table 4.3.

Cumulative incidence function for prostate cancer diagnosis for men after a single negative TRUS-guided prostate biopsy

Figure 4.6 Cumulative incidence functions for prostate cancer diagnosis by age group for men after a single negative TRUS biopsy



Time from first negative biopsy (Years)

Table 4.3 Pro	ostate cancer d	iagnosis rates	(with 95% CI)) by age group
Age Category	5 years	10 years	15 years	20 years
40-49	0.0655	0.1014	0.1360	0.1640 (0.1608-
	(0.0635-	(0.0988-	(0.1338-	0.1670)
	0.0675)	0.1040)	0.1382)	
50-59	0.1074	0.1669	0.2096	0.2406 (0.2376-
	(0.1055-	(0.1648-	(0.2071-	0.2436)
	0.1093)	0.1690)	0.2121)	
60-69	0.1191	0.1976	0.2310	0.2406 (0.2379-
	(0.1174-	(0.1957-	(0.2288-	0.2433)
	0.1208)	0.1995)	0.2332)	
70-79	0.1470	0.1987	0.2208	0.2325 (0.2295-
	(0.1450-	(0.1965-	(0.2183-	0.2355)
	0.1490)	0.2009)	0.2233)	
80+	0.1510	0.1916	0.1967	0.2003 (0.1973-
	(0.1490-	(0.1894-	(0.1942-	0.2033)
	0.1530)	0.1938)	0.1992)	

The relationship between age and PCa diagnosis was also assessed by constructing a CIF with age in years, as opposed to duration of follow-up, as the time component. This is illustrated in Figure 4.7. The number of PCa diagnoses by ages 50, 60, 70, 80, 90, and 100 were 237, 2,922, 9,604, 14,556, 15,647, and 15,690, respectively. The risks of PCa diagnosis at 50, 60, 70, 80, 90, and 100 years were 0.0025 (95% CI: 0.0022-0.0028), 0.0324 (95% CI: 0.0313-0.0336), 0.1265 (95% CI: 0.1261-0.1310), 0.2432 (95% CI: 0.2547-0.2629), 0.3082 (95% CI: 0.3575-0.3736), and 0.3188 (95% CI: 0.3896-0.4457).

Figure 4.7 Cumulative incidence function for prostate cancer diagnosis as a function of patient age for men after a single negative TRUS biopsy



4.2.3.1 Predictors of Prostate Cancer Diagnosis

On univariate regression analysis, age, as a categorical variable, was a significant predictor of PCa diagnosis. With the 40-49 years age group as the reference category, increasing age was significantly associated with increased risk of PCa diagnosis. The subdistribution HRs for age groups 50-59, 60-69, 70-79, and 80+ were 1.85 (95% CI: 1.71-1.99, p<0.01), 2.26 (95% CI: 2.14-2.38, p<0.01), 2.12 (95% CI: 2.01-2.23, p<0.01), and 2.08 (95% CI: 1.95-2.21, p<0.01), respectively. The overall significance of age as a categorical variable, assessed using the Wald test, was p<0.01.

Similarly, neighborhood income was a significant predictor of PCa diagnosis on univariate regression analysis. With the lowest income quintile group as the reference baseline, the subdistribution HRs for increasing income quintile groups were 1.09 (95% CI: 0.98-1.20, p=0.12), 1.13 (95% CI: 1.03-1.25 p=0.03), 1.07 (95% CI: 0.97-1.18, p=0.09), and 1.15 (95% CI: 1.05-1.27, p=0.02), respectively. The overall significance of neighborhood income quintile, assessed using the Wald test, was p=0.03.

Area of residence (urban versus rural) was a significant predictor of PCa diagnosis. When compared to rural residence, the subdistribution HR for urban residence was 1.07 (95% CI: 1.01-1.13 p=0.03).

cADG score was not predictive of PCa-specific mortality on univariate regression analysis. The subdistribution HR for each one-unit increase in cADG score was 1.00 (95% CI: 0.98-1.02, p=0.88).

On multivariate regression analysis, age, neighborhood income quintile, and residence location remained significant predictors of PCa diagnosis. Using the 40-49 years age group as the reference category, the subdistribution HRs for age groups 50-59, 60-69, 70-79, and 80+ were 1.72 (95% CI: 1.48-1.99, p<0.01), 2.05 (95% CI: 1.77-2.38, p<0.01), 1.96 (95% CI: 1.69-2.28 p<0.01), and 2.00 (95% CI: 1.60-2.49, p<0.01), respectively. The overall significance of age as a categorical variable, assessed using the Wald test, was p<0.01.

As for neighborhood income quintile, with the lowest income quintile group as the baseline reference, the subdistribution HRs for increasing income quintile groups were 1.02 (95% CI: 0.94-1.12, p=0.61), 1.09 (95% CI: 1.00-1.19, p=0.04), 1.04 (95% CI: 0.95-1.13, p=0.39), and 1.10 (95% CI: 1.01-1.19, p=0.02), respectively. The overall significance of neighborhood income quintile, assessed using the Wald test, was p=0.03.

With regards to location of residence, with rural residence as the reference, the subdistribution HR for urban residence was 1.11 (95% CI: 1.01-1.22, p<0.01). In other

words, patients living in an urban residence had an eleven percent higher risk of being diagnosed with PCa compared to those living in a rural residence.

4.2.4 Repeat Prostate Biopsies

The total number of repeat prostate biopsies was 49,402, with a corresponding incidence rate of 0.07 biopsies per person-year. The frequency distribution of repeat biopsies underwent among all patients with an initially negative TRUS-Bx is shown in Table 4.4, whereas that specific to men subsequently diagnosed with PCa is shown in Table 4.5

Table 4.4 Frequency distribution of repeat prostate biopsies in all							
men with an initially negative TRUS-guided prostate biopsy							
(n=95,675)							
0	1	2	3	4	5		
62,115	23,137	7,003	2,206	756	278		
(64.9%)	(24.2%)	(7.3%)	(2.3%)	(0.8%)	(0.3%)		
6	7	8	9	10+			
99	47	13	12	9			
(0.1%)	(0.05%)	(0.01%)	(0.01%)	(0.01%)			

Table 4.5 Frequency distribution of repeat prostate biopsies in men diagnosed with prostate cancer after an initially negative TRUSguided prostate biopsy (n=15,690) 0 1 2 3 4 5+ 3,175 8,928 2,429 748 256 154 (20.2%)(56.9%) (4.8%) (1.6%) (15.5%) (1.0%)

4.2.5 Radical Prostatectomy

The total number of RPs in the cohort was 5,783, accounting for 6.0% of the cohort and 36.9% of patients diagnosed with PCa. The rates of undergoing RP at 5, 10, 15, and 20 years of follow up were 0.0516 (95% CI: 0.0501-0.0531), 0.0681 (95% CI: 0.0663-0.0698), 0.0739 (95% CI: 0.0720-0.0759), and 0.0761 (95% CI: 0.0739-0.0782), respectively. The CIF for undergoing RP is displayed in Figure 4.8. The proportion of patients who died within 30 days of RP was 13/5,783 (0.22%).

Figure 4.8 Cumulative incidence function for undergoing radical prostatectomy for men after a single negative TRUS biopsy



Time from first negative biopsy (Years)

4.2.5.1 Salvage Radiotherapy after Radical Prostatectomy

Among the 5,783 patients who underwent RP, 869 (15.0%) subsequently received salvage XRT. After undergoing RP, the rates of receiving salvage XRT within 1, 2, 5, 10, 15, and 20 years of RP were 0.0670 (95% CI: 0.0605-0.0735), 0.0921 (95% CI: 0.0844-0.0996), 0.1420 (95% CI: 0.1229-0.1410), 0.164 (95% CI: 0.1540-0.1749), 0.183 (95% CI: 0.1709-0.1958), and 0.1898 (95% CI: 0.1759-0.2037), respectively.

4.2.5.2 Adjuvant Androgen Deprivation Therapy after Radical Prostatectomy

Among the 5,783 patients who underwent RP, 436 (7.5%) subsequently received adjuvant ADT. After undergoing RP, the rates of receiving adjuvant ADT within 1, 2, 5, 10, 15, and 20 years of RP were 0.0280 (95% CI: 0.0236-0.0324), 0.0408 (95% CI: 0.0355-0.0461), 0.0611 (95% CI: 0.0545-0.0677), 0.0877 (95% CI: 0.0792-0.0961), 0.1045 (95% CI: 0.0934-0.1157), and 0.1394 (95% CI: 0.1124-0.1665), respectively.

4.2.6 Definitive Radiotherapy

The total number of patients who received definitive XRT was 3,325, accounting for 3.5% of the cohort and 21.2% of patients diagnosed with PCa. The rates of receiving definitive XRT at 5, 10, 15, and 20 years of follow up were 0.0213 (95% CI: 0.0203-0.0223), 0.0386 (95% CI: 0.0370-0.0402), 0.0521 (95% CI: 0.0499-0.0542), and 0.0611 (95% CI: 0.0580-0.0642), respectively. The CIF for undergoing definitive XRT is displayed in Figure 4.9. The proportion of patients who died within 30 days of definitive XRT was 15/3,325 (0.45%).

Figure 4.9 Cumulative incidence function for receiving definitive radiotherapy for men after a single negative TRUS biopsy



4.2.6.1 Androgen Deprivation Therapy after Definitive Radiotherapy

Among the 3,325 patients who underwent definitive XRT, 336 (10.1%) subsequently received ADT. After undergoing definitive XRT, the rates of receiving ADT within 1, 2, 5, 10, and 15 years of definitive XRT were 0.0829 (95% CI: 0.0735-0.0923), 0.0924 (95% CI: 0.0844-0.0104), 0.1181 (95% CI: 0.1066-0.1295), 0.1508 (95% CI: 0.1363-0.1654), and 0.1866 (95% CI: 0.1534-0.2198), respectively.

4.2.7 Androgen Deprivation Therapy

The total number of patients who received ADT (medical or surgical castration) was 3,786, accounting for 4.0% of the cohort and 24.1% of patients diagnosed with PCa. The rates of receiving ADT at 5, 10, 15, and 20 years of follow up were 0.0231 (95% CI: 0.0221-0.0241), 0.0434 (95% CI 0.0419-0.0449), 0.0596 (0.0575-0.0617), and 0.0723 (0.0691-0.0756), respectively. The CIF for receiving ADT is displayed in Figure 4.10.

Figure 4.10 Cumulative incidence function for receiving androgen deprivation therapy for men after a single negative TRUS biopsy





Time from first negative biopsy (Years)

4.3 Sensitivity Analyses

4.3.1 Baseline Characteristics

The total number of patients with a single negative prostate biopsy was 123,700. Median follow-up for such patients was 8.60 years (IQR: 4.83-13.13). The total follow up duration was 1,134,044 person-years. These patients' baseline characteristics are displayed in Table 4.6.

4.3.2 Rates of Study Outcomes

4.3.2.1 Prostate Cancer-Specific Mortality

The total number of PCa-specific deaths was 1,092, accounting for 0.88% of the total cohort. The PCa-specific mortality rates at 5, 10, 15, and 20 years of follow up were 0.0022 (95% CI: 0.0020-0.0024), 0.0071 (95% CI: 0.0069-0.0074), 0.0149 (95% CI: 0.0146-0.0152), and 0.0199 (95% CI: 0.0195-0.0203), respectively. The CIF for PCa-specific mortality is displayed in Figure 4.11. Compared to patients with a single negative TRUS-Bx, the PCa-specific mortality rates were statistically significantly higher at 5, 10, and 15 years by 0.0006, 0.0014, and 0.0021, respectively.

Table 4.6 Baseline characteristics	for	all	patients	with	a	single	nega	tive
prostate bionsy (n=123.700)								

Patient	Value for all	Value for patients	P-value
Characteristic	patients	undergoing TRUS	(Compared to
		biopsy	patients with a
			negative TRUS
			biopsy)
Median age (IQR)	64.0 (57.0-70.0)	63.0 (57.0-69.0)	<0.01 ^a
Age categories			
40-49	6494 (5.2%)	5131 (5.4%)	
50-59	34328 (27.8%)	28835 (30.1%)	
60-69	51794 (41.9%)	41310 (43.2%)	
70-79	26955 (21.8%)	18417 (19.2%)	
80+	4129 (3.3%)	1982 (2.1%)	
Median Combined	16.0 (7.0-22.0)	16.0 (7.0-22.0)	.57
Aggregated Diagnosis			
Groups Score (IQR)			
Neighborhood			
income quintile			
1	18679 (15.1%)	13873 (14.5%)	
2	23008 (18.6%)	17126 (17.9%)	
3	24493 (19.8%)	18657 (19.5%)	
4	26719 (21.6%)	20857 (21.8%)	
5	30801 (24.9%)	25162 (26.3%)	
Area of residence			
Urban	113433 (91.7%)	88212 (92.2%)	
Rural	10267 (8.3%)	7463 (7.8%)	
TRUS-guided biopsy			
Yes	95675 (77.3%)		

No	28025 (22.7%)	
a. Student's t-test		
b. Chi-square test		

Figure 4.11 Cumulative incidence functions for prostate cancer-specific and other-cause mortality for all men with a single negative prostate biopsy



4.3.2.2 Other-cause mortality

The total number of deaths was 27,202 (1,092 due to PCa and 26,110 due to all other causes), accounting for 22.0% of the cohort. The other-cause mortality rates at 5, 10, 15, and 20 years of follow up were 0.0744 (95% CI: 0.0721-0.0765), 0.1807 (95% CI:

0.1792-0.1822), 0.3167 (95% CI: 0.3122-0.3212), and 0.4779 (95% CI: 0.4688-0.4870), respectively. The CIF for other-cause mortality is displayed in Figure 4.11. CIF for all-cause mortality is the sum of the CIFs for PCa-specific and other-cause mortalities. Compared to patients with a single negative TRUS-Bx, the other-cause mortality rates were statistically significantly higher at 5, 10, 15, and 20 years by 0.0169, 0.0304, 0.0381, and 0.0374, respectively.

4.3.2.3 Prostate Cancer Diagnosis

The total number of PCa diagnoses was 21,644, accounting for 17.5% of the total cohort. The PCa diagnosis rates at 5, 10, 15, and 20 years of follow up were 0.1309 (95% CI: 0.1387-0.1331), 0.1877 (95% CI: 0.1849-0.1895), 0.2199 (95% CI: 0.2165-0.2233), and 0.2366 (95% CI: 0.2321-0.2411), respectively. The CIF for PCa diagnosis is shown in Figure 4.12. Compared to patients with a single negative TRUS-Bx, the PCa diagnosis rate was statistically significantly higher only at 5 years by 0.0041.

Figure 4.12 Cumulative incidence function for prostate cancer diagnosis for all men after a single negative prostate biopsy



4.3.2.4 Repeat prostate biopsies

The total number of repeat biopsies was 64,139, with a corresponding incidence rate of 0.07 biopsies per each person-year. The frequency distribution of repeat biopsies among all patients with an initially negative prostate biopsy is shown in Table 4.7, whereas that specific to men subsequently diagnosed with PCa is shown in Table 4.8.

Table 4.7 Frequency distribution of repeat prostate biopsies in all men with an						
initially negative prostate biopsy (n=123,700)						
0	1	2	3	4	5	
80,565	29,476	9,104	2,886	1,035	381	
(65.1%)	(23.8%)	(7.4%)	(2.3%)	(0.8%)	(0.3%)	
6	7	8	9	10+		
133	63	23	18	16		
(0.1%)	(0.05%)	(0.02%)	(0.01%)	(0.01%)		

Table 4.8 Frequency distribution of repeat prostate biopsies in men diagnosed						
with prostate cancer after an initially negative prostate biopsy (n=21,644)						
0	1	2	3	4	5+	
4,285	12,359	3,398	1,082	303	198	
(19.8%)	(57.1%)	(15.7%)	(5.0%)	(1.4%)	(0.9%)	

4.3.2.5 Radical Prostatectomy

The total number of RPs underwent was 7,201, accounting for 5.8% of the total cohort and 33.3% of patients diagnosed with PCa. The rates of undergoing RP at 5, 10, 15, and 20 years of follow up were 0.0483 (95% CI: 0.0468-0.0498), 0.0636 (95% CI: 0.0618-0.0654), 0.0689 (95% CI: 0.0669-0.0709), and 0.0709 (95% CI: 0.0688-0.0730), respectively. The CIF for undergoing RP is shown in Figure 4.13. Compared to patients with a single negative TRUS-Bx, the rates of undergoing RP were statistically significantly lower at 5, 10, 15, and 20 years by 0.0033, 0.0045, 0.0050, and 0.0052, respectively.

Figure 4.13 Cumulative incidence function for undergoing radical prostatectomy for all men after a single negative prostate biopsy



4.3.2.6 Definitive Radiotherapy

The total number of patients who underwent definitive XRT was 4,568, accounting for 3.7% of the total cohort and 21.1% of patients diagnosed with PCa. The rates of undergoing definitive XRT at 5, 10, 15, and 20 years of follow up were 0.0209 (95% CI: 0.0198-0.0220), 0.0381 (95% CI: 0.0365-0.0397), 0.0516 (95% CI: 0.0495-0.0537), and 0.0601 (95% CI: 0.0570-0.0632), respectively. The CIF for undergoing definitive XRT is shown in Figure 4.14. Compared to patients with a single negative TRUS-Bx, the rates of undergoing XRT were non-significantly different at any of the aforementioned time points.

Figure 4.14 Cumulative incidence function for receiving definitive radiotherapy for all men after a single negative prostate biopsy



4.3.2.7 Androgen Deprivation Therapy

The total number of patients who received ADT was 6,114, accounting for 4.9% of the total cohort and 28.2% of patients diagnosed with PCa. The rates of receiving ADT at 5, 10, 15, and 20 years of follow up were 0.0280 (95% CI: 0.0270-0.0290), 0.0513 (95% CI: 0.0498-0.0528), 0.0690 (95% CI: 0.0669-0.0711), and 0.0809 (95% CI: 0.0777-0.0841), respectively. The CIF for receiving ADT is shown in Figure 4.15. Compared to patients with a single negative TRUS-Bx, the rates of receiving ADT were non-significantly different at the aforementioned time points.

Figure 4.15 Cumulative incidence function for receiving androgen deprivation therapy for all men after a single negative prostate biopsy



Time from first negative biopsy (Years)

Chapter Five General Discussion

5 General Discussion

5.1 Summary of Major Findings

This was the first population-based study that examined long-term outcomes in North American patients with a single negative TRUS-Bx. Our cohort of 95,675 men with a single negative TRUS-Bx is also the largest series of such patients to date, and our median follow-up of 8.1 years is also the longest.

5.1.1 Prostate Cancer-Specific Mortality

We demonstrated that the 20-year cumulative incidence of PCa-specific mortality was 1.8%. The risk of PCa-specific mortality is significantly influenced by patient age at time of first negative TRUS-BX, with the 20-year cumulative incidence of death increasing more than 30-fold from 0.2% in those aged 40-49 years to 6.9% in those aged 80 years or older. Patients of higher socioeconomic status (i.e. neighborhood income quintile) and those living in an urban residence were significantly less likely to die of PCa.

5.1.2 Prostate Cancer Diagnosis

We found that the 20-year cumulative incidence of PCa diagnosis was 23.7%. As previously mentioned, the lifetime risk of PCa diagnosis among Canadian men is about 1 in 8 (12.5%) ("Prostate cancer statistics", 2017). Thus, these patients have about a two-

fold increased risk of PCa diagnosis. This suggests that the increased pre-test/pre-biopsy probability of PCa, due to an elevated PSA level and/or positive DRE, is driving additional diagnostic work up in these patients, leading to increased cancer detection. Further analysis is needed to discern the Gleason score of cancers diagnosed in these patients. Similar to PCa mortality, age was a significant predictor of PCa diagnosis, with the cumulative incidence increasing from 16% by 20 years in those ages 40-49 at time of first negative TRUS-Bx to around 23-24% in those ages 50-79. Patients of higher neighborhood income quintiles and those living in an urban residence had a higher risk of PCa diagnosis. We theorize that these are patients who are more likely to follow up with their physician, get diagnosed more frequently, and as discussed in section 5.1.1, less likely to die of their disease. The validity of this hypothesis will need to be confirmed in future studies.

5.1.3 Repeat Prostate Biopsies

The incidence rate of undergoing a repeat prostate biopsy was 0.07 biopsies per personyear. Almost 35% of patients underwent at least one repeat prostate biopsy, with patients undergoing up to 11 repeat biopsies. Interestingly, of patients subsequently diagnosed with PCa, 20% did not undergo a repeat biopsy, which suggests that these patients were either histologically diagnosed incidentally via a TURP, a cystoprostatectomy for a bladder tumor, a biopsy of a distant metastatic lesion (i.e. not a prostate biopsy), were presumed to have PCa due to elevated PSA levels and signs and symptoms extremely suggestive of PCa, or the diagnostic biopsy was not captured by the OHIP registry (one of the limitations of administrative databases that will be discussed later).

5.1.4 Treatment Outcomes

Despite the initial negative TRUS-Bx, 7.6% of patients eventually received treatment in the form of RP, 6.1% underwent definitive radiotherapy, and 7.2% received ADT within

20 years of follow up. Among patients who underwent RP, 19% and 14% of patients received salvage XRT and adjuvant ADT, respectively, within 20 years of their surgery, suggesting that at least 19-20% of patients had failed surgery, which is a proportion comparable to that seen in previously published series (Hull et al., 2002). Among patients who underwent XRT, the 20-year rate of receiving adjuvant ADT was 19%, which was not significantly different than the corresponding rate in patients who underwent RP.

5.1.5 Sensitivity Analyses

The purpose of conducting these sensitivity analyses was to assess whether our decision to restrict our cohort to men with a single negative TRUS-BX, as opposed to all patients with a single negative biopsy, had any significant implications on rates of various health outcomes. TRUS-Bx, as opposed to a finger-guided biopsy, is currently the accepted standard of care, and our decision to restrict primary analysis to patients with a negative TRUS-Bx stems from our intention to create as contemporary a cohort as possible. We do recognize that biopsying technique in a proportion of our patients was different than that currently recommended in clinical practice, and this will be further discussed in a later section. Nonetheless, we believe that the decision to restrict the primary cohort to those who had a TRUS at time of biopsy, as opposed to also including patients who had a presumed finger-guided biopsy, will increase the external validity/applicability of our results to contemporary cohorts.

The rationale behind moving away from a finger-guided/targeted biopsy towards a systematic TRUS-Bx is that this latter technique allows for increased cancer detection (Hodge et al., 1989), which should ideally lead to timely intervention in appropriate patients, and consequently, improved mortality outcomes. This is supported by our results whereby patients who had a negative biopsy of any type had higher PCa-specific mortality rates at 5, 10, and 15 years of follow up, compared to those with specifically a negative TRUS-Bx. The rate difference of 0.0021 at 15 years in these patients accounts for about a 15% higher rate compared to those with a negative TRUS-Bx, which is quite

clinically significant. The lack of a statistically significant difference at 20 years is likely due to the majority of patients being censored prior to attaining that follow up duration.

These patients also had higher PCa diagnosis rates at five years of follow up. This is likely due to the inferior sensitivity of these initial finger-guided biopsy techniques that miss a higher proportion of present cancers, with subsequent biopsy attempts detecting these initially missed cancers. Despite the presence of statistically significant differences, we must highlight that the absolute rate differences, in the range of 0.0006 to 0.0041, are not particularly clinically significant. It is also worth noting that despite the baseline characteristics of these patients being statistically significantly different than those of our primary cohort, these differences are, as well, not clinically significant (e.g. median age 63 vs. 64, urban residence 92.2% vs. 91.7%) and primarily reflect the large sample size of our cohort.

5.2 Assessment of Study Hypotheses

Prior to conducting the study, we hypothesized that the PCa-specific mortality rate at 20 years will be 0.03. We found that the actual rate in our cohort was 0.018 (95% CI: 0.0160-0.0201), which is significantly different than 0.03, both clinically and statistically, and thus we reject our initial hypothesis. Based on results from the study by Klemann et al., we had postulated that due to geographic differences in management techniques among physicians, the cancer mortality rate in our cohort would be almost half of theirs. However, it seems that the actual mortality rate in our cohort was even lower, suggesting that the differences in management styles have an even more profound impact on mortality outcomes than previously anticipated.

We also expected that the overall mortality rate would be around 0.67, similar to that in the Danish cohort (Klemann et al., 2017). The actual rate at 20 years was 0.4587 (95% CI 0.4496-0.4678), which was significantly lower than predicted, leading us to reject our

initial hypothesis. This reveals that our cohort was much healthier to start with than we had anticipated.

Given the more frequent use of PSA testing and earlier/more aggressive detection of PCa in North America, we anticipated that the PCa diagnosis rate at 20 years in our cohort would be 0.20, as opposed to 0.11 in Danish men (Klemann et al., 2017). The actual rate at 20 years was significantly higher at 0.2373 (95% CI: 0.2328-0.2418), which causes us to reject our initial hypothesis. This strongly suggests once again that the geographic differences in follow up of these patients have an even more profound impact on PCa diagnosis rates than previously anticipated.

We hypothesized that 50% of patients will undergo repeat biopsies, whereas the actual proportion was only 35.1%. Using the chi-square test, the two values were statistically significantly different (p<0.01), and the absolute difference (15%) was also clinically significant.

We predicted that the combined 20-year rate of undergoing either RP and/or XRT would be around 0.15. The actual 20-year rate was 0.1372 (95% CI: 0.1350-0.1424), which was statistically significantly lower than 0.15. However, the absolute difference was not that clinically significant. Nonetheless, we reject our null hypothesis on statistical grounds. The 20-year rate of ADT use was 0.0723 (95% CI: 0.0691-0.0756), which was significantly lower than our predicted rate of 0.10. As previously mentioned, ADT is used for patients with either locally or distally advanced disease (i.e. non-localized disease), and as such is considered by many researchers/urologists as a surrogate for adverse prognosis. The fact that the actual rate of ADT use was lower than what we had predicted implies that the long-term rates of diagnosis of non-localized disease in these patients is lower than what we had expected as well.

As predicted, increasing age at index biopsy, increasing socioeconomic status (i.e. neighborhood income quintile), and living in an urban residence were associated with a higher risk of PCa diagnosis on multivariate regression analysis. However, lower cADG

score (i.e. healthier medical status) was not associated with increased risk of PCa diagnosis. Conversely, increasing age, lower socioeconomic status, and rural residence were all associated with increased PCa-specific mortality on multivariate regression analysis.

5.3 Comparison with Current Literature

As discussed in Chapter 1, Klemann et al. recently published a similar population-based outcomes study of all Danish men undergoing their first TRUS-Bx (Klemann et al., 2017). For the purposes of this discussion, we will restrict all comparisons to the portion of Danish men with specifically a negative TRUS-Bx. The most striking difference in results between the two studies is the PCa-specific mortality rates. While 1.8% of our study cohort had died of PCa by 20 years of follow up, the corresponding rate in Danish men was 5.2%, which is almost three-fold higher. Similarly, the 20-year PCa diagnosis rate was almost 24% in our cohort, with a corresponding rate of only 11% in the Danish cohort. The higher cancer diagnosis rate among Canadian men suggests that these patients are followed up more intensively after their initial negative result, compared to Danish men. It is likely that men in our cohort underwent more frequent serum PSA measurements and repeat biopsies, although this cannot be verified without data on such procedures from both cohorts. The impact of this increased cancer detection, and subsequent timely treatment, seems to be positively reflected in superior cancer mortality rates among Canadian men, suggesting that this more intensive follow up may lead to improved PCa outcomes. However, as previously discussed in Chapter 1, screening/diagnostic procedures for PCa do have other economic and health-related adverse effects that must be taken into consideration as well.

There were also other notable differences between the two cohorts. The median age of men in our cohort was 63 years, whereas that in the Danish cohort was higher at 67 years. As demonstrated in our results section, increasing age at index biopsy was a significant predictor of worse PCa-specific mortality outcomes. Thus, the higher PCa-specific mortality rates in the Danish cohort may be due in part to the older age of its individuals at index biopsy.

The proportion of positive first biopsies in our cohort was 42.2% (derived from study flow chart in Figure 4.1), while that in the Danish cohort was significantly higher at 54.6%. This suggests that Danish patients who undergo a TRUS-Bx have a higher pretest probability of PCa diagnosis (e.g. higher pre-biopsy PSA levels), compared to Ontario men, and that Ontario-based physicians have a lower threshold for biopsying patients, compared to their Danish counterparts. It is likely that Danish patients who underwent a TRUS-Bx had higher pre-biopsy PSA levels than their Ontario counterparts. This is significant as Klemann et al. demonstrated that pre-biopsy PSA levels are important predictors of long-term PCa-specific mortality cumulative rates: 0.7% after 15 years for those with PSA concentrations of 10 ug/L or less compared to 17.6% for those with concentrations greater than 20 ug/L (Klemann et al, 2017). Thus, the differences in PCa-specific mortality rates between the two cohorts may also in part be due to differences in pre-biopsy PSA levels. Absence of PSA data for our patients precludes definitive assessment of this hypothesis.

Also, the 20-year overall mortality rate among Danish men was also much higher at 66%, compared to only 44% in our cohort. This suggests that our cohort of men with a negative TRUS-Bx was a significantly healthier one to start with, and all subsequent health outcome rates must be interpreted in light of these differences. Nonetheless, these significant differences in cancer detection and mortality rates may reflect differences in management patterns between these geographic regions. The major differences between our study's cohort/results and those of the study by Klemann et al. are summarized in Table 5.1.

Table 5.1. Summary of the major differences between our study and that by Klemann et al.

	Our Study	Klemann et al.
Number of men with	95,675	27,181
single negative TRUS-Bx		
Median patient age at	63	67
index biopsy (years)		
Median cohort follow-up	8.6	5.9
time (years)		
20-year PCa-specific	1.8%	5.2%
mortality rate		
20-year overall mortality	44%	66%
rate		
20-year PCa diagnosis rate	24%	11%
Percentage of first TRUS-	42%	55%
Bx that were malignant		

5.4 Critical Appraisal of Study Methodology

Health administrative databases are a unique source of patient-level health information. As a result of the increased digitization of health care provision, they offer the possibility of tracking a patient's course through the health care system. These databases however are, by definition, created for purposes other than research, and this can have implications on their data completeness and accuracy (van Walraven et al., 2012). In addition, specific patient cohorts (e.g. men with a negative TRUS-Bx) were not pre-defined in ICES databases. For these reasons, we implemented specific inclusion and exclusion criteria to maximize data validity and accuracy.

5.4.1 Study Inclusion and Exclusion Criteria

The definitions for a TRUS-Bx and negative TRUS-Bx were chosen with the limitations of health administrative databases in mind. After identifying codes for prostate biopsy using the ICES data dictionary, our definition for TRUS-Bx included having a pelvic/abdominal ultrasound within two days of a biopsy (+/- two days). Physicians (radiologists/urologists) who perform the TRUS-Bx should theoretically have submitted billing claims for both the biopsy and the ultrasound at the same time. These physicians have a financial incentive to submit billing claims for both procedures, or else they will not be compensated for their services. However, due to anticipated inaccuracies/inefficiencies in recording the exact dates procedures were performed, we implemented this time window to ensure that we don't misclassify TRUS-Bx as fingerguided biopsies and erroneously exclude patients. There is nonetheless an issue to consider when using this definition. There is the possibility that a patient underwent a pelvic/abdominal ultrasound for a different reason (e.g. evaluation for benign prostatic hyperplasia) and the actual biopsy was not TRUS-guided. However, based on discussions with an experienced urologist, we do not anticipate this issue to be of major concern, and the majority of patients with both billing codes are highly likely to have undergone a TRUS-Bx. Ideally, this should be ascertained in the future using a validation study that assesses the proportion of patients with both billing codes who truly underwent a TRUS-Bx or a specific procedure code for TRUS-Bx should be developed.

As for negative TRUS-Bx, the definition chosen was a record of a TRUS-Bx, as previously defined, and no record of PCa diagnosis in OCR within three months of the date of the biopsy. This three-month window was implemented for reasons similar to those for implementing a two-day window for a TRUS-Bx. Generally, date of diagnosis in OCR corresponds to the date the diagnostic biopsy was performed (i.e. if biopsy is performed on day one and diagnosis is histologically confirmed one week later, date of cancer diagnosis is recorded as day one). So it appears that there is no need to implement any time window. However, after discussions with multiple health services researchers who frequently use ICES data, there was a consensus that date inaccuracies are inevitable
and some cases may not be "back-dated" to the date of the diagnostic biopsy. For that reason, a time window was implemented. Three months was chosen to ensure that all PCa diagnoses linked to a TRUS-Bx were captured, and that all included men in the cohort truly had a negative biopsy. The use of this three-month window, however, does introduce a potential for an immortal person-time bias, a form of selection bias. By definition, no outcomes can occur during this time frame. In other words, a patient can not be diagnosed with PCa, die of PCa or any other reason, or receive treatment for PCa. Thus, any enrolled patient has actually survived free-of-outcome for three months. In addition, it is possible, although unlikely, that a patient may have underwent a repeat biopsy during these three months. This repeat biopsy may have still been negative, in which case a patient would still have been included in the cohort. If it were positive, then the patient would probably be erroneously excluded from the cohort, as the first biopsy would have been truly negative. Despite these theoretical concerns, we do not believe that they are a significant threat to the internal validity of our study. Patients rarely undergo repeat biopsies within such a short time frame, especially since the introduction of the 12-core systematic TRUS-Bx template, and thus it is highly unlikely that any patients were subsequently diagnosed with PCa and undergone subsequent therapy within three months of the first negative biopsy. Also, as discussed in Chapter 1, PCa typically has a long natural history and does not cause mortality within such a short time frame. Thus, we can be reassured that the benefits of applying such a time window significantly outweigh the theoretical risk of introducing an immortal person-time bias.

As mentioned in Chapter 3, we used the OHIP billing claim for implantation of hormone pellets (G342) to identify men who received ADT, and this billing claim was also used as part of our definition for a presumed diagnosis for PCa. However, this code does not identify men who received oral ADT and has only been validated in men older than 65 years of age (Bhindi et al., 2014). Thus, its validity in patients younger than this age, who formed a significant proportion of our cohort, has yet to be ascertained. However, given its validity in older patients, we assumed that the same would apply for younger patients. The implications of this decision are uncertain, however we do not anticipate that our choice introduced any element of a selection bias. Regardless, by implementing this code

to identify ADT use in our cohort, we were unable to account for oral ADT use among men in our cohort.

We chose to exclude patients younger than age 40 years as these patients do not typically undergo screening for PCa and subsequent diagnostic biopsies. It is possible that such men may have undergone screening/testing and have records of OHIP billing codes for a prostate biopsy; however, the circumstances under which such patients received a biopsy are likely to be atypical, and not the focus of this study.

We also excluded patients who did not have a valid IKN at time of study. Since Ontario offers public healthcare coverage to all its residents, the vast majority of patients would have been considered. Those who might have been excluded include marginalized populations such as homeless men, who are highly unlikely to receive screening for PCa in the first place. Also, it was not possible to track the health records of men who sought health care out of province, although these men represent an extremely small proportion of Ontarians and this is thus unlikely to have significantly affected our results.

As part of our study exclusion criteria, we eliminated patients with sex recorded as female. This may seem as an unnecessary step, as the prostate gland is exclusively a male reproductive organ. However, administrative databases are prone to data entry errors and steps to ensure highest possible data validity are recommended. Five hundred and seventy-eight patients were excluded because of a recorded female sex. It is likely that these patients were either males who were falsely entered as females or were females who underwent a different procedure that was falsely recorded as a prostate biopsy. This highlights one of the limitations of health administrative databases and the importance of implementing as many steps as necessary to ensure data validity.

5.4.2 Study Timeline

Our study timeline was dictated by several factors. First, we wanted to implement a lookback window, prior to enrolling any patients, to ensure that all included patients had no previous record of a prostate biopsy (i.e. the negative TRUS-Bx was the first negative one recorded) and no prior history of PCa (e.g. patients on AS protocols usually undergo repeat biopsies even after histologic diagnosis of PCa). To ensure that these two conditions were met, availability of data records from OHIP, OCR, and CIHI DAD was necessary. Information from OHIP, OCR, and CIHI DAD were available from 1991,1964, and 1988, respectively ("ICES Data Dictionary", 2017). Thus, 1991 was the earliest date that both these conditions could be ascertained. Based on the clinical judgment of experienced physicians and health services researchers, as well as common practice in other health services research studies, we decided that a look-back window of at least three years would be enough, as patients who did not receive a biopsy within this time frame were highly unlikely to have received one earlier. Similarly, a history of PCa diagnosis, as defined in Chapter 3, was ascertained in OCR records up till 1964 and CIHI DAD records up till 1988. Thus, the earliest possible date to enroll patients was January 1994 (three years after January 1991). The accrual window extended from this date up until October 2014 as OCR data was not complete after this point. Thus, it was not possible to ascertain whether a TRUS-Bx performed after this time point was truly negative. Thus, we applied this date restriction for accrual. However, patients were followed up for all possible outcomes up until Dec 31, 2015, as data on various events was available in these databases up till that point.

We could have extended this look-back window further by enrolling patients from 1995 or 1996 and onwards, ensuring a longer window to look for these exclusion criteria and potentially increasing the validity/specificity of our study cohort. However, we also wanted to maximize duration of follow up for these patients in order to define the longterm rates of the various outcomes of interest (i.e. since patients were enrolled from 1994, the longest follow up duration possible was 21 years, whereas if patients were enrolled from 1996, the longest possible follow up would have been 19 years). We believe that setting the look-back window at a minimum of three years gave us the optimal balance between assessing for exclusion criteria and maximizing long-term follow up durations.

5.5 Study Limitations

Our study has several notable limitations. As discussed in the previous section, several procedures were implemented to minimize these risks; however, some of these were unavoidable.

5.5.1 Selection bias

A selection bias refers to a systematic error in selection of individuals such that proper randomization is not achieved and the resulting sample being not representative of the target population. This leads to results different than what would have been obtained had the entire target population been included. As discussed in Section 5.4.1, there was a potential risk for immortal-person time bias, a type of selection bias. However, we do not believe that this had any significant impact on the validity of the study's findings.

5.5.2 Information bias

The major source of information bias in our study, similar to all other studies utilizing health administrative databases for research purposes, is misclassification errors. This occurs when exposure and/or outcome status is incorrectly specified, resulting in inaccurate patient records.

These errors may occur at several levels. For example, for a certain disease, represented by a diagnostic code, to be correctly entered into an administrative database several steps need to be accurately completed. The treating physician must correctly diagnose the patient. He or she must then clearly document the disease in the patient's chart. The health records abstractor must then identify and correctly interpret the documented diagnosis, followed by assigning the correct code for the disease (van Walraven et al., 2012). One error in any of these steps would lead to a misclassification error. The possibility of such errors occurring was well demonstrated when we applied the female sex exclusion criteria and 578 patients were subsequently excluded. No female could have possibly undergone a prostate biopsy, thus signifying that this was a misclassification error. Similar errors are likely to have occurred with our other exposure/outcome definitions.

As discussed in Section 5.4.1, we used a unique definition to identify men with negative TRUS-Bx. There is currently no validated algorithm to identify this cohort. We thus needed to rely on the judgments of an experienced practicing urologist and health services researchers to choose our definition. Consequently, the validity of our definition is uncertain. Exposure to negative TRUS-Bx status may thus have been erroneously assigned. Future studies that evaluate the validity of our definition are necessary.

The validation study of OHIP billing claims for PCa procedures reassured us that such procedures are well captured in this database, with the subsequent risk for information bias being low (Simunovic et al., 2005). However, the reliability of OHIP with regards to capturing radiotherapy sessions is somewhat disappointing (Alibhai, 2001) and suggests that the actual rates of undergoing definitive radiotherapy in our cohort were likely to be considerably higher than what we found.

5.5.3 Confounding Bias

There are several important confounders that we were unable to account for. As discussed in Chapter 1, serum PSA level is the major screening tool for PCa. Patients with higher screening levels are at increased risk of PCa diagnosis (Vickers et al., 2010) and most importantly, are significantly more likely to die of PCa, as demonstrated in the Danish study (Klemann et al., 2017). Thus, risk-stratifying our cohort by PSA level would have been an effective way of comparing the rates of different outcomes across these strata and would have allowed treating physicians to individualize the risk of these events to their patients, based on their PSA levels. Unfortunately, PSA levels are currently not available in ICES databases and for that reason we were unable to risk-stratify our cohort.

Similarly, the risk of PCa diagnosis is strongly influenced by patient ethnicity (Bechis et al., 2010; Jayadevappa et al., 2011). Ontario is populated by a diverse pool of ethnicities ("2006 Census", 2009), and categorizing the men in our cohort by ethnicity would have allowed us to assess the impact of this variable on the various outcomes in our study. However, accurate ethnicity data is unavailable at ICES, and thus precluded us from carrying out this analysis.

The technique of biopsying patients (finger-guided versus TRUS-guided), as well as number of cores taken, has changed significantly since the early 1990's, as discussed in Section 1.7.1. Since men in our cohort were enrolled starting 1994, this strongly suggests that our patients underwent varying biopsy techniques/templates. We attempted to minimize this variability by restricting our cohort to men who specifically had a negative TRUS-Bx. Our sensitivity analyses demonstrated that when this restriction was not applied, and all men with a negative prostate biopsy were included, the PCa diagnosis rates were not clinically significantly different. We could not however control for the number of cores that were obtained, and this is likely to have influenced our results. The potential impact of this temporal change in number of cores sampled could have been evaluated by assessing whether there were any time trends with regards to the various study outcomes. Specifically, whether patients who underwent biopsies at different time points in the study period had differences in the cumulative incidences of the various study outcomes, which could be a reflection of the impact of changes in number of cores sampled on disease outcomes. Similarly, temporal changes in the relative frequencies of finger-guided versus TRUS-Bx over the study period could have been assessed to further demonstrate changes in biopsying technique over the years and to evaluate the temporal changes in patient exclusion due to having undergone a finger-guided biopsy.

Also, due to the retrospective nature of the study, we were unable to control for the triggers/clinical indicators for repeat biopsy. The decision to undergo repeat biopsy, and potentially subsequent treatment, is secondary to shared decision-making between the patient and treating physician. Different patients have different preferences and not all physicians follow up their patients at similar intensities. However, by using "real world" data, we believe that this is actually a strength of our study that increases the external validity of our results.

5.5.4 Other Limitations

We used average neighborhood income quintile as a surrogate of each individual's income, education level, and socioeconomic status. This characteristic is well established as significant health predictor in the population (Braveman et al., 2010). We theorized that patients of different socioeconomic backgrounds were likely to have different preferences with regards to following up with their physician after their negative biopsy and consequently undergoing repeat biopsies. However, this is limited by the assumption that all individuals in the same neighborhood have the same, exact income and education levels, which is likely not true.

Research studies utilizing data from health administrative databases often have very large sample sizes. While this is a powerful tool for researchers to take advantage of, this can create tension between statistical significance and clinical significance, as even small, clinically unimportant absolute differences may be associated with highly statistically significant results. In their review article that addresses biases in administrative database research, van Walraven and Austin, two experienced health services researchers, recommend, "Writers should avoid interpreting the importance of differences based solely on P-values because small differences do not become more meaningful with additional zeroes in the P-value." (van Walraven et al., 2012) They recommend the use of CIs to help differentiate between clinical and statistical significance. CIs are generated around absolute or relative differences and force both the readers and writers to actually

note the differences between the populations, highlighting clinical rather than statistical significance (van Walraven et al., 2012). We believe that by adopting this approach in our sensitivity analyses, as well as highlighting the absolute value of the subdistribution HR in our regression analyses, as opposed to the p-value only, we were able to avoid this potential pitfall, while still maximizing the advantages from our large sample size.

Chapter Six Conclusions

6 Conclusions

This is the first population-based study that assesses long-term outcomes in a North American cohort of men with a single negative TRUS-Bx. After 20 years of follow-up, 1.8% of these men die from PCa, 23.7% get diagnosed with PCa, 7.6% undergo RP, 6.1% receive definitive XRT, and 7.2% receive ADT. Patients of older age at time of negative biopsy are more likely to be diagnosed with and die from PCa, whereas patients of higher socioeconomic status and those living in an urban residence are more likely to get diagnosed with and less likely to die from PCa. The PCa mortality and diagnosis rates were significantly different than what we had expected based on results from previous studies, with the mortality rates significantly lower and the diagnosis rates significantly higher. These results highlight the impact of geographic variations in clinical practice techniques on patient outcomes. Practicing North American physicians can use results from this study to accurately inform their patients with a negative TRUS-Bx of their various long-term outcomes. Given that older patients are at higher risk of being diagnosed with and die of PCa, physicians may also choose to follow-up these older patients more closely.

Chapter Seven Future Directions

7 Future Directions

As a next step, we will ensure that knowledge transfer occurs by sharing the results of this study with the rest of the medical community. We will present our findings at various international conferences such as the annual American Urological Association Meeting. We also plan on publishing our results in a peer-reviewed journal, ensuring that our results become available to as wide an audience as possible.

Despite our best efforts at bridging the current knowledge gap, a number of questions remain unanswered and further steps can be taken in the future to address these remaining gaps in the literature. As discussed in Section 5.5.3, one of our limitations was the lack of serum PSA levels for our patients. There are currently plans in place to import patient PSA measurements from various labs in Ontario into ICES, allowing us in the future to risk-stratify patients based on their PSA levels.

Future studies should determine the GS of cancers diagnosed in North American patients subsequent to a negative TRUS-Bx. Determining the GS, and consequently which cancers were clinically significant, would allow us to assess the aggressiveness of these tumors and what proportion of patients could have theoretically avoided definitive therapy in favor of active surveillance or watchful waiting. Future population-based studies should also assess whether a relationship between number of diagnostic biopsies performed and GS in diagnosed cancers exists. Histopathological/grading information for tumors is not currently available in OCR. These data, however, can be obtained by reviewing medical charts of individual patients and noting down the GS of diagnosed tumors. Plans are in place for this to be performed in the future, which would allow us to answer these two important questions.

As discussed in the limitations section, there is confounding bias that we have not accounted for in our regression analysis. Any future study that formally assesses predictors of PCa diagnosis and mortality will need to account for all logical confounders/predictors in order to minimize residual confounding. It is important to evaluate other potential factors that could be associated with rates of PCa diagnosis and mortality, such as intensity of follow up with an urologist or family physician. If increased intensity of follow up with a physician is shown to be associated with improved cancer outcomes, then this could prompt physicians to follow up such patients more closely after their initial negative biopsy. It would also be interesting to evaluate whether intake of drugs such as metformin and statin could decrease the risk of PCa diagnosis and/or mortality. These drugs have been shown in some studies to decrease the risk of PCa diagnosis (Bansal et al., 2012; Sayyid et al., 2016), and whether they have a similar impact in patients following a negative TRUS-Bx is yet to be determined. If shown to decrease PCa diagnosis and/or mortality rates, this can serve as the basis for prospective RCTs that evaluate the efficacy of these drugs in patients with negative TRUS-Bx, similar to the concept of the Metformin Active Surveillance (MAST) trial which aims to evaluate whether metformin intake has any impact on time to disease progression in PCa patients on AS protocols ("ClinicalTrials.gov- MAST", 2017).

It thus becomes clear that despite our best efforts, a lot of important questions remain unanswered. Future studies that address these deficiencies will be crucial in advancing the exciting fields of urology and health services research.

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Appendices

Appendix A. University Health Network Research Ethics Board approval for our study

Q	Toronto Genera Toronto Westerr Princess Margar Toronto Rehab	l c ct	Research Ethics Board 10th Floor, Room 1056 700 University Ave Toronto, Ontario, M5G 1Z5		
			Phone: (416) 581-7849		
Notification of REB Approval for Access to Retrospective Data for Research Purposes					
Date:	Date: February 18th, 2016				
To:	Dr. Neil Fleshner				
	Room 130, 3rd Floor, 610 Univ	versity Avenue, Princess Margaret Cancer C	Centre		
	Toronto, Ontario, Canada				
	MDG ZINI9				
Re:	16-5082-CE				
	Determining the Natural Histor	y of Men with Initially Negative Prostate Bio	psies		
	-				
REB Review Type:		Expedited			
REB Initial Approval Date:		February 18th, 2016			
REB Expiry Date:		February 18th, 2017			
Documents Approved:					
Protocol		Version date: May 1st, 20	015		

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement; ICH Guideline for Good Clinical Practice E6(R1); Ontario Personal Health Information Protection Act (2004); Part C Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations and the Medical Devices Regulations of Health Canada. The approval and the views of the REB have been documented in writing.

Furthermore, members of the Research Ethics Board who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

Best wishes on the successful completion of your project.

Sincerely,

Jack Holland, MD FRCPC Co-Chair, University Health Network Research Ethics Board

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University Health Network

NOTIFICATION OF REB RENEWAL APPROVAL

Date:	February 27, 2017		
То:	Neil E Fleshner Room 130; 3rd Floor, Room 130, 610 University Avenue; Princess Margaret Cancer Centre; 610 University Avenue, M5G 2M9; Toronto, Ontario, Canada		
Re:	16-5082 Determining the Natural History of Men with Initially Negative Prostate Biopsies		
REB Review Type: REB Initial Approval Date: REB Renewal Approval Effective Date: Lapse In REB Approval:		Delegated February 18, 2016 February 18, 2017 N/A	

The University Health Network Research Ethics Board has reviewed and approved the Renewal (16-5082.1) for the above mentioned study.

February 18, 2018

Best wishes on the successful completion of your project.

Sincerely, Marina Mikhail Ethics Coordinator, University Health Network Research Ethics Board

For: Alan Barolet Co-Chair, University Health Network Research Ethics Board

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement; ICH Guideline for Good Clinical Practice E6(R1); Ontario Personal Health Information Protection Act (2004); Part C Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations and the Medical Devices Regulations of Health Canada.

REB Expiry Date:

Appendix B. University of Toronto Research Ethics Board approval for our study



We are writing to advise you that the Office of Research Ethics (ORE) has granted administrative approval to the above-named research protocol. The level of approval is based on the following role(s) of the University of Toronto (University), as you have identified with your submission and administered under the terms and conditions of the affiliation agreement between the University and the associated TAHSN hospital:

- Graduate Student research hospital-based only
- Storage or analysis of De-identified Personal Information (data)

This approval does not substitute for ethics approval, which has been obtained from your hospital Research Ethics Board (REB). Please note that you do not need to submit Annual Renewals, Study Completion Reports or Amendments to the ORE unless the involvement of the University changes so that ethics review is required. Please contact the ORE to determine whether a particular change to the University's involvement requires ethics review.

Best wishes for the successful completion of your research.

Yours sincerely,

Daniel Gyewu REB Manager

Research Oversight and Compliance Office - Human Research Ethics Program McMurrich Building, 12 Queen's Park Crescent West, 2nd Floor, Toronto, ON MSS 1S8 Canada Tel: +1 416 946-3273 • Fax: +1 416 946-5763 • ethics.review@utoronto.ca • http://www.research.utoronto.ca/for-researchers-administrators/ethics/ **Appendix C.** Specific codes used to identify procedures/events in OHIP and CIHI DAD

Procedure	Code			
OHIP				
Prostate biopsy	Z712, Z713, S644, E780			
Pelvic/abdominal ultrasound	J128, J135, J138, J149, J162, J180			
Radiation therapy	X336, X310, X311,X312, X313,			
	X322			
Brachytherapy	S640 till 2007, afterwards X323,			
	X324, X325			
Implantation of hormone pellets	G342			
Healthcare contact with an urologist	A355, A935, A356, A353, A354,			
	C355, C935, C356, C353, C354,			
	C352, C357, C359			
CIHI DAD				
Bilateral orchiectomy	CCP Code: 74.31; CCI Code:			
	1QM89			
Radical prostatectomy	CCP: 72.4, CCI: 1QT91			