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The Impact of Ethnicity and Immigration on Prostate Cancer Mortality in Canada

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Abstract

Despite the prevalence of prostate cancer its pathogenesis remains unclear. Marked differences in mortality rates have been observed between countries, however, it is unclear whether the source of the observed differences is driven by underlying genetics, geographic, or social factors. This thesis investigated the impact of ethnicity and immigration on prostate cancer mortality in Canada using the Canadian Census Health and Environment Cohort. South Asian and East Asian men were seen to be at decreased risk of prostate cancer mortality, while no increased risk was observed in black men. These results affirm studies showing lower risks in Asian men; however, they contradict the previously held notion that black men are at increased risk of aggressive disease. Attempts to study the impact of immigration on prostate cancer mortality were limited by small sample sizes and missing data. Efforts to improve linkages and a longer timespan may allow for future analysis.

Keywords

Prostate cancer, prostate cancer mortality, ethnicity, immigration, immigration studies, Statistics Canada, CanCHEC

Summary for lay audience

Prostate cancer is one of the most commonly diagnosed and most deadly male cancers. Despite its prevalence, surprisingly little is known about what causes prostate cancer and who is at an increased risk. This study used a Statistics Canada dataset with detailed demographic and health data to track a cohort of the Canadian population over an 18-year period to determine the impact of ethnicity and immigration on the risk of dying from prostate cancer. In our cohort, Asian-Canadians had lower rates of prostate cancer mortality, while Black-Canadians had equivalent mortality rates to non-visible minority Canadians. This is contradictory to previous studies that showed increased rates of early and aggressive prostate cancer in African Americans. Our study looking at the impact of immigration on prostate cancer mortality showed the dataset to be currently too immature to contribute meaningful data, however this may improve with time.

Our studies demonstrate the importance of considering confounding variables – most importantly socioeconomic factors and access to care when interpreting studies from large datasets. Additionally, they identified potential future avenues of research, specifically trying to understand the underlying cause of the improved mortality rates in Asian Canadians and working to strengthen the dataset to allow more detailed analysis.

Co-authorship statement

The impact of ethnicity on prostate cancer mortality in Canada

Dr Noah Stern:
Project design (80%), data interpretation (80%), manuscript preparation (95%).

Dr Nicholas Power:
Project design, data interpretation, thesis structure.

Dr Michael Haan:
Project design, thesis structure.

Tina Luu Ly:
Project design, technical assistance, statistical analysis, manuscript preparation

Manuscript status: Pending submission for publication

Examining the impact of immigration on prostate cancer pathology and mortality in Canada using the CanCHEC

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Project design, technical assistance, statistical analysis, manuscript preparation

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Table of Contents

List of tables

List of Figures

List of abbreviations, symbols, nomenclature

AJCC	American Joint Committee on Cancer
ASIR	Age standardized incidence ratio
ASMR	Age standardized mortality rates
BC	British Columbia
CanCHEC	Canadian Census Health and Environment Cohorts
CCDB	Canadian Cancer Database
CCR	Canadian Cancer Registry
CMDB	Canadian mortality database
CRA	Canada Revenue Agency
CVSDD	Canadian Vital Statistics Death Database.
DAD	Discharge Abstract Database
DNA	deoxyribonucleic acid
DRE	Digital rectal examination
ERSPC	European Randomized Trial of Prostate Cancer Screening
FDA	Food and Drug Administration
HR	Hazard ratio
IACR	International Agency for Research on Cancer

ICD	International classification of disease
ILGFBP	insulin-like growth factor-binding protein
MRI	Magnetic resonance imaging
NACRS	National Ambulatory Care Reporting Systems
NCCN	National Comprehensive Cancer Network
NCIRS	National Cancer Incidence Reporting System
OR	Odds ratio
PLCO	Prostate, Lung, Colon, and Ovary Trial
PROCESS	Prostate Cancer in Ethnic Subgroups study
PSA	Prostate Specific Antigen
RR	Relative risk
SEER	Surveillance, Epidemiology and End Results
STI	Sexually transmitted infection
TMN	Tumor, node, metastasis
USPSTF	United States Preventative Services Task Force
WHO	World Health Organization

Preamble and Outline

The incidence and mortality of prostate cancer varies markedly across the world. While certain regions are known to have increased rates, defining the true etiology and epidemiology of a cancer among different populations is a constant moving target. It may not be immediately apparent whether an observed difference is due to an inherent genetic predisposition for the disease, exposure to environmental, social, or cultural risk factors, or due to reduced access to healthcare – or a combination of them all.

Population-level datasets and immigration studies provide the opportunity to evaluate the impact of genetic and environmental factors on cancer risks. Observing changes in cancer risks among ethnic and immigrant populations compared to their home or host country allows one to observe the interplay between genetics, the environment, and cancer risks. These studies have the potential to identify novel avenues for improving our understanding of cancer genomics, detection, and treatment. Canada is uniquely situated to answer this question due to its universal healthcare model and diverse population.

This thesis is a multidisciplinary project performed in conjunction with the Department of Surgery at London Health Sciences Centre and the Department of Sociology and Statistics at Western University. The primary aim is to investigate the impact of ethnicity and immigration on prostate cancer mortality in Canada using Statistics Canada's Canadian Census Health and Environment Cohorts (CanCHEC) database.

The thesis is organized in an integrated article format. Chapter 1 introduces the fundamentals of prostate cancer, immigration studies, and the CanCHEC database and provides a literature review of the current understanding of the link between ethnicity, immigration, and prostate cancer. Chapter 2 presents the aims and hypotheses of chapters 3 and 4, two self contained manuscripts using the CanCHEC to investigate the impacts of ethnicity (chapter 3) and immigration (chapter 4) on prostate cancer mortality in Canadian men. Chapters 5 and 6 provide a general discussion, future directions and conclusions on the research questions discussed in earlier chapters.

CHAPTER 1:
Introduction and Literature Review

Prostate Cancer

Prostate cancer is the most common non-cutaneous cancer in Canadian men. 1 in 9 Canadian men will be diagnosed over their lifetime and 1 in 29 will die from prostate cancer.[1] While no contemporary series exists examining the economic impact of prostate cancer in Canada, a study from 2000 estimated the impact of prostate cancer in 5.8 million Canadian men at $4-8 billion over their lifetime. Given the advances in screening, monitoring, and treatment these numbers are expected to have risen substantially.[2]

Diagnosis and staging

In the current Canadian landscape, prostate cancers are most often detected after an elevated prostate specific antigen (PSA) or suspicious digital rectal examination prompts referral to a urologist.[3(p1)] If the patient is found to be high risk after assessment a prostate biopsy is performed for histologic diagnosis. While nuances and controversies exist regarding the role of early detection of prostate cancer screening and treatment, their discussion is beyond the scope of this thesis. The purpose of this section is to provide the reader with a brief understanding of the standard approach often applied by urologists in western nations, as recommended by societal guidelines.

Prostate Specific Antigen

Prostate specific antigen is a serine protease produced nearly exclusively by prostatic luminal epithelial cells that functions to liquify semen and aids in insemination. PSA elevation is thought to occur through disruption of cellular basement membrane and subsequent leakage of PSA into the serum and may be caused by both benign and malignant insults.[4] The sensitivity and specificity of a PSA >4 ng/mL has is 0.90% and

0.72% respectively. Several approaches have been described attempting to improve the performance of PSA including age specific cut-offs, PSA density, PSA velocity, and PSA doubling time.[5,6]

PSA was initially approved by the American Food and Drug Administration (FDA) for monitoring men with prostate cancer in 1986 and subsequently as a diagnostic marker in 1994. With the increased ability to detect early disease, a stage migration was seen in countries with high uptake of PSA screening with an increased diagnoses among younger men with lower stage disease.[7]

Two landmark studies changed the landscape of PSA screening. The Prostate, Lung, Colon, and Ovary Trial (PLCO) was commissioned by the American National Cancer Institute in 1993 to examine the impact of systematic screening on cancer mortality. In the prostate cancer arm the study randomized over 76 000 men 55 to 74 years old randomized to annual PSA testing or no screening. After 7 years of follow-up prostate cancer was detected at a slightly higher rate of 116 per 10 000 person-years in the PSA-screened group compared to 95 per 10 000 person-years in the unscreened group, however no difference in mortality was identified (rate ratio, 1.13; 95% CI, 0.75-1.70).[8] Subsequent re-evaluation of the PLCO data revealed heavy contamination – with up to 90% of the control “unscreened” arm having undergone PSA testing at least once and over 90% having undergone screening during the trial.[9]

In contrast, the European Randomized study of Screening for Prostate Cancer (ERSPC) was a 1993 study involving over 162 000 men aged 55 to 69 also randomized to PSA screening versus no screening. Ultimately, a 21% reduction in prostate cancer-specific

mortality was identified with the number needed to screen at 781 and the number needed to treat at 27. The study concludes the PSA screening can reduce high grade, locally advanced cancers, however this is at the risk of overdiagnosis.[10]

The conflicting results of these studies and the implications of their results have led to fierce debates regarding the role of PSA in the early detection of prostate cancer. Based on the PLCO data the United States Preventative Services Task Force (USPSTF) recommended against PSA screening for the detection of prostate cancer in 2012, with the Canadian Task Force following in 2014.[11,12] This subsequently resulted in a stage migration of newly diagnosed prostate cancers in North America, with fewer, but higher grade cancers being detected.[13,14] During this period incidence rates in white American men decreased over from 67 in 2010 to 48 per 100 000 men in 2016. Similar trends were seen among black (99 to 74 per 100 000 men) and men of other ethnicities (36 to 28 per 100 000 men).[15]

Presently, all major urologic societies, though many generalist societies and national task forces recommend against its use.[11,12,16–19] Current recommendations note that no one true PSA cut-off exists for all individuals and instead encourages a shared decision-making approach incorporating a patient's age, family history, clinical exam and often the use of risk calculators in order to lead discussions with patients.[16–18]

Digital Rectal Exam

Digital rectal examination (DRE) involves a clinician physically examining the prostate for suspicious nodules, indurations, and asymmetries. Prior to PSA testing DREs was an essential tool for screening for prostate cancer. With a sensitivity of 0.51 and a

specificity of 0.59, its role was primarily driven by the lack of a suitable alternative as opposed to a definite clinical value.[20] Many have questioned the role of initial and serial DREs in prostate cancer screening due to a lack of objective supportive data and a lack of clinical benefit.[20,21] Although urologic societal guideline acknowledge the controversy most recognize the potential role in detecting significant disease.[17,18(p1)]

Prostate biopsy

Ultimately, the diagnosis of prostate cancer requires histologic confirmation with a prostatic biopsy. The prostate biopsy allows for the diagnosis of the histopathological subtype, pathological grade, location, volume and if identified, lymphovascular invasion and extraprostatic extension. Current standard of care involves ultrasound guided biopsy through either a transrectal or transperineal approach. Evolving technologies have allowed for improved imaging and sampling of the prostate using magnetic resonance imaging (MRI) guidance to identify lesions using either cognitive or fusion guided biopsy.[22,23]

Grading, staging and risk stratification

Once pathology is established, prostate cancers can be graded and staged, and patients can be risked stratified. Prostate cancers were traditionally graded based on their Gleason score, a composite of the two most abundant pathologic patterns observed. The Gleason score has recently been modified to the Gleason grade group to reflect more contemporary data and vernacular.[24]

Prostate cancer is staged according to tumor, node, metastasis (TNM) classification (Table 1) and stratified into very high, high, intermediate, low and very low risk disease

based on the PSA, clinical stage, and grade group (Table 2).[25] In efforts to improve clinicians' abilities to prognosticate patients, the TNM staging has undergone multiple revisions, most recently in 2017.[26] A patient's risk, coupled with their clinical picture and performance status, allows clinicians to guide further investigations and treatment.

Clinical Tumor	
T0	No evidence of primary tumor
T1a **T1b** **T1c**	Incidental histologic finding in <5% resected tissue Incidental histologic finding in >5% resected tissue Tumor identified by needle biopsy
T2a **T2b** **T2c**	Palpable in one half of one lobe or less Palpable in more than one half of one lobe, but not bilateral Palpable bilaterally
T3a **T3b**	Extraprostatic extension Invades seminal vesicle(s)
T4	Fixed or invades adjacent structures other than seminal vesicles
Pathologic Tumor	
T2	Organ confined
T3a **T3b**	Extra prostatic extension or microscopic invasion of bladder neck Seminal vesicle invasion
T4	Fixed tumor or invades adjacent structures other than seminal vesicles
Nodes	
N0	No positive regional nodes
N1	Metastatic regional nodes
Metastasis	
M0	No distant metastasis
M1a **M1b** **M1c**	Nonregional lymph node(s) Bone(s) Other site(s)

Table 1. Tumor, node, metastasis staging of prostate cancer according to the American Joint Committee on cancer 8th edition based on clinical or histologic (pathology) findings.[26]

Risk Group	Clinical/pathological features		
Very low	T1c AND Grade group 1 AND PSA <10 ng/mL AND Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core AND PSA density <0.15 ng/mL/g		
Low	T1-T2a AND Grade Group 1 AND PSA <10 ng/mL		
Intermediate	Has no high or vary high risk features and has one or more intermediate risk factors (IRF): • T2b-T2c • Grade Group 2 or 3 • PSA 10-20 ng/mL	Favourable intermediate	• 1 IRF • Grade Group 1 or 2 AND • <50% biopsy cores positive
		Unfavourable intermediate	• 2+ IRF • Grade Group 3 and/or • ≥50% biopsy core positive
High	T3a OR Grade Group 4 or 5 OR PSA ≥20 ng/mL		
Very high	T3b or T4 OR Primary Gleason pattern 5 OR >4 cores with Grade Group 4 or 5		

Table 2. Prostate cancer risk stratification according to National Comprehensive Cancer Network (NCCN) criteria.[25]

Risk Factors

Significant efforts have been made attempting to identify underlying genetic or environmental risk factors for prostate cancer. Unfortunately, few definitive and even fewer actionable factors have been discovered. Of all factors investigated only age, family history, ethnicity and certain genetic mutations have shown a consistent association with prostate cancer.

An individual's risk of prostate cancer has been shown to increase drastically with age. Autopsy studies have estimated the prevalence of prostate cancer to increase with each

decade, from 5% in men under 30 to over 40% in men over the age of 70 and nearly 60% in men over 80.[27,28] However, given the slow growing and often indolent nature of the disease, prostate cancer screening is not recommended by any societal guideline in men with life expectancies under 10 years while some recommend against screening any man over the age of 70.[16–18]

Family history positive for prostate cancer been shown to drastically increase the risk of developing prostate cancer. The son of an affected father has a relative risk (RR) of prostate cancer 2.17 times higher than an individual without an affected relative. The risk continues to increase with an affected brother (RR 3.37) or with more than two first degree relatives (RR 5.08).[29] While the correlation between family history and prostate cancer has been considered absolute, there has been a recent interest in exploring whether these men are any increased risk of aggressive disease. A large Swedish population-based study utilized their national prostate cancer database to determine the risk of developing low risk, non-low risk and high-risk prostate cancer in men with relatives diagnosed with prostate cancer. The study found that these men had a 30-60% probability of developing prostate cancer by age 75, however approximately half of these were low risk disease. Interestingly the risk of developing aggressive prostate cancer correlated with the risk of their relative's disease and the number of family members affected, indicating a potential genetic predisposition for aggressive disease.[30] These observed increases have led most major urologic societies to encourage clinicians to consider earlier prostate cancer screening in men with family history of prostate cancer.[16–18]

While the familial risk of prostate cancer indicates some genetic component, hereditary mutations likely account for less than 15% of prostate cancers.[31] Attempts to identify causative mutations have been met with mixed results, highlighting the potential polygenic nature of the disease with rare variants causing high risk disease.[32] For example mutations to the BRCA2 gene is estimated to give a 5 to 7 fold risk of developing prostate cancer, while only present in <1% of the general population.[33,34,35(p1)] Ongoing research continues to identify potential mutations involved in prostate cancer mutagenesis, however few actionable discoveries have been identified.

Significant efforts have been placed both retrospectively and prospectively to identify modifiable risk factors of prostate cancer. Small or retrospective studies identify a potential novel target; however, the larger or confirmatory studies fail to show conclusive results (Table 3).

Risk Factor	Observed impact
Androgens	CAG repeat polymorphism on androgen receptor increases risk of prostate cancer (OR 1.2-1.3), but no relation between serum androgens levels and prostate cancer risk.[37,37] Finasteride (medication affecting the androgen pathway) decreases risk of prostate cancer, but increases the detection of high grade disease.[38]
Estrogens	Low incidence of prostate cancer in cultures, vegetarians with high intake of phyto-estrogens[39] Polymorphism in estrogen-related genes associated with increased risk of prostate cancer (OR 1.26-1.63)[40]
Inflammation and infection	Chronic inflammatory response leading to dysplasia, hyperproliferation, DNA damage. Premalignant lesions seen on histology.[41]
Insulin-like growth factor axis	High serum insulin levels associated with increased risk of prostate cancer.[42] IGFBP-2 may promote cell growth, resistance to chemotherapy, but does not affect risk of developing prostate cancer.[43,44]
Leptin	High leptin concentration in men with high volume, advanced disease.[45,46]
Obesity	Weak positive association with aggressive disease (RR 1.05 per 5 kg/m^2) potentially through insulin, insulin-like growth factor-1 and leptin[42,45,47]
Sexual activity	No impact of age of first intercourse, marriage Increased risk with increased frequency (>3 per week, RR 1.2)[48]
Sexually transmitted infections	Increasing number of partners increases risk of prostate cancer (>20 partners, RR 1.2)[48] Increased risk with history of STI (OR 1.6) and history of multiple STDs (>3, OR 3.3)[49]
Smoking	No increased incidence, but may have a role in lethality, biochemical recurrence, and disease progression.[50–52]
Vasectomy	Increased risk of prostate cancer post vasectomy (RR 1.4-1.6), though the risk disappears with proper patient matching.[53–56]
Vitamin D **Vitamin D receptor**	Higher incidence of prostate cancer in northern latitudes, prostate cancer mortality inversely related to UV exposure, but no impact of vitamin supplementation.[57–59]
Vitamin E	Supplementation may increase (HR 1.17) or have no impact on prostate cancer risk.[60–62]

Table 3. Selected risk factors for prostate cancer showing inconclusive results. OR: odds ration; DNA: deoxyribonucleic acid; RR: relative risk; IGFBP-2: insulin-like growth factor-binding protein 2; STI: sexually transmitted infection.

Incidence

Prostate cancer is the second most commonly diagnosed male cancer worldwide, accounting for 14.5% of all malignancies in men, second only to lung cancer.[63] It is the most commonly diagnosed cancer in 105 countries and the leading cause of cancer death in 46 countries. Globally, prostate cancer is responsible for 1.3 million new cases and 359 000 deaths annually.[63] Varied rates of prostate cancer are seen, with rates highest in Europe and North America and lowest in South-East Asia.[63] Efforts to understand the cause of these variable rates have met significant resistance controlling for genetic, geographic, and social confounding variables.

To address the uncertain etiology of prostate cancer one approach would be to compare incidence rates between countries. Identifying a population with aberrant cancer risks could allow one to investigate the potential protective or contributory factors. Unfortunately, attempts to objectively study the cause for the varied rates are hindered by multiple obstacles - most notably by the paucity of high-quality data and variable and fluctuating rates of PSA screening.

Data sources and estimates

The Cancer Incidence in Five Continents (Volume X) is an investigational report published by the International Agency of Cancer and International Agency for Research on Cancer (IACR) aiming to publish comparable population-level cancer data to allow for international comparisons.[64] Given their mandate to publish strictly high-quality data, over 20% of their received data was rejected. This resulted in a disproportionate underrepresentation of developing and African countries and an overrepresentation of

developed and predominantly Caucasian countries. The latest volume captures only 14% of the world's population, including 2% of African, 6% of Asian, and 8% of Central and South American populations. Whereas 95% of North American, 78% of Oceanic, and 42% of European populations are included.[64]

Given this paucity of a high-quality comparative data the IACR worked in conjunction with the World Health Organization (WHO) to establish GLOBOCAN as a method to report *best available* data. Currently, GLOBOCAN provides estimates of cancer incidence and cancer-specific mortality for 184 countries. GLOBOCAN utilizes nine methods to estimate cancer incidences with varying degrees of accuracy ranging from the utilization of national incidence databases (highest quality) to average estimation from neighbouring countries (lowest quality).[65] This uncertainty of data quality makes translation of true cancer incidence and mortality difficult. Alternatively, the use of national databases with diverse populations allows one to observe rates within communities and allows for comparisons between groups with more similar geographic and social exposures. The American Surveillance, Epidemiology and End Results (SEER) program covers nearly 35% of the American population with reasonable representation from white, African American, Hispanic, and Asian populations allowing for comparisons of ethnic rates within a single system.[15]

GLOBOCAN estimates prostate cancer to have a world-wide age standardized incidence ratio per 100 000 men (ASIR) of 29.3. Estimates vary widely from 11.5 in Asia to 73.7 and 79.9 in North America and Oceania respectively (Figure 1).[63] The nations with the highest ASIR were the French Caribbean islands of Guadeloupe (189.1) and Martinique

(158.4) followed by Ireland (132.2). Lowest rates were reported in Bhutan (1.0), Nepal (1.1) and Yemen (1.8).[18] Similarly, SEER estimates the highest rates in American black men and lowest rates in Asian men.[15]

The Prostate Cancer in Ethnic Subgroups study (PROCESS) performed in the United Kingdom looked at a cohort of men diagnosed with prostate cancer between 1997 and 2001 in London and Bristol. They demonstrated a prostate cancer incidence rate 3 times higher in black men compared to white men, with no difference between black men of African and Caribbean descent.[66]

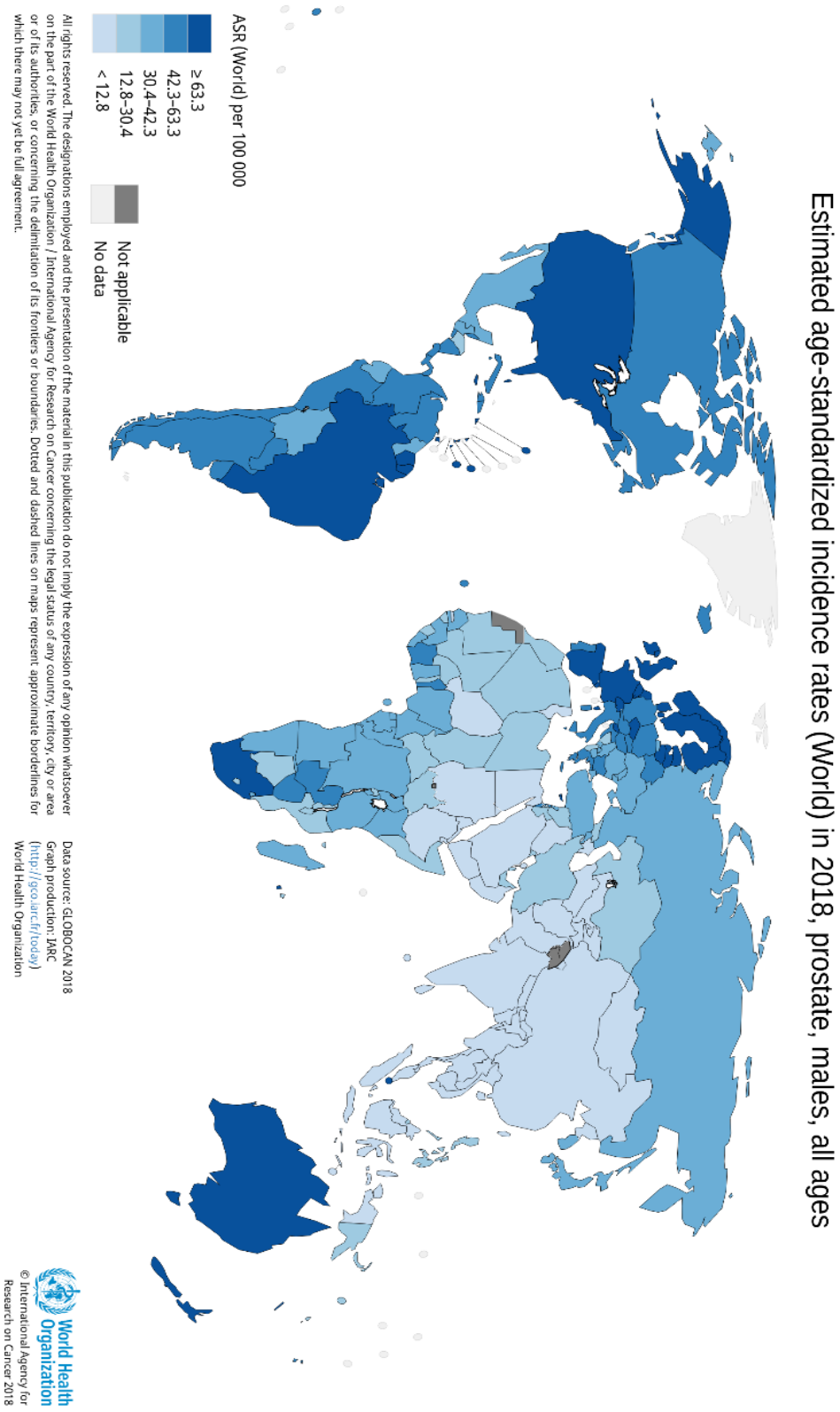

Figure 1. Variation of age standardized rates of prostate cancer incidence by country. ASR: Age standardized rate. IARC: International Agency for Research on Cancer. Source: GLOBOCAN 2018[67]

Impact of PSA on prostate cancer incidence

With the adoption of PSA-based screening there has been an increased detection and subsequent stage migration of prostate cancers as patients more often present with lower grade and organ-confined tumors.[7] This resulted in marked spike in prostate cancer incidence in countries as screening rates rose. Rates of prostate cancer quickly spiked in the United States in both white men (ASIR 35.8 to 79.2) and black men (ASIR 58.1 to 121.6) between 1985 and 2000 (Figure 2. Age-standardized incidence rate of prostate cancer among white (blue), black (orange), and men of other ethnicities (grey) in the United States from 1975-2016. Rates are per 100 000 and age-adjusted to the 2000 United States Population (single ages to 85+) standard. Source: SEER 9.[15]Figure 2).[15] This rate subsequently fell to 47.6 in white men and 74.0 in black men following recommendations by the USPSTF initially against PSA for prostate cancer screening in all men (D recommendation) in 2008 and 2012 to individualized screening in select men after discussing the risks and benefits (C recommendation) in 2018.[12,68,69] A similar pattern of prostate cancer incidence can be seen in the Canadian population (Figure 3).[70] While PSA screening has been adopted more heavily in North America, lower, delayed and variable rates are seen in Europe and Asian countries.[71] Currently, Japan is the only Asian country with guidelines on prostate cancer screening, advocating for a shared decision making approach as of 2008.[72,73] Despite its significant impact on the region, sub-Saharan African countries have shown low uptake of PSA screening and poor overall awareness of the risks of prostate cancer.[74–76] Most South and Latin American

governing bodies recommend against PSA screening, while Mexico recommends screening men over 50 years of age.[77]

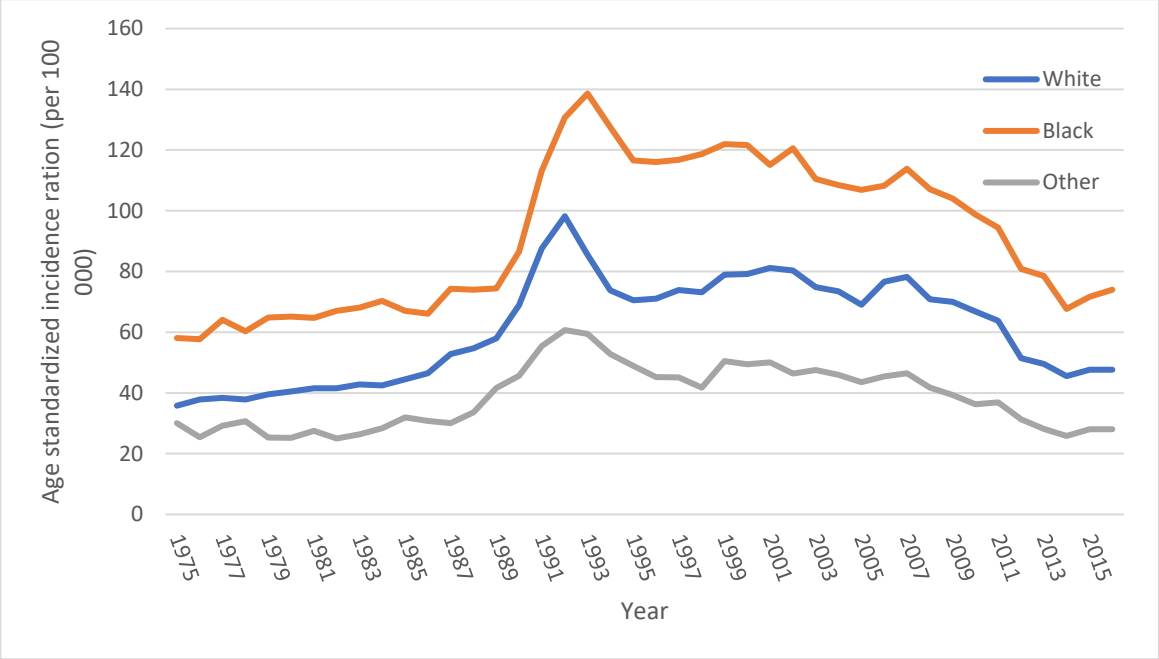

Figure 2. Age-standardized incidence rate of prostate cancer among white (blue), black (orange), and men of other ethnicities (grey) in the United States from 1975-2016. Rates are per 100 000 and age-adjusted to the 2000 United States Population (single ages to 85+) standard. Source: SEER 9.[15]

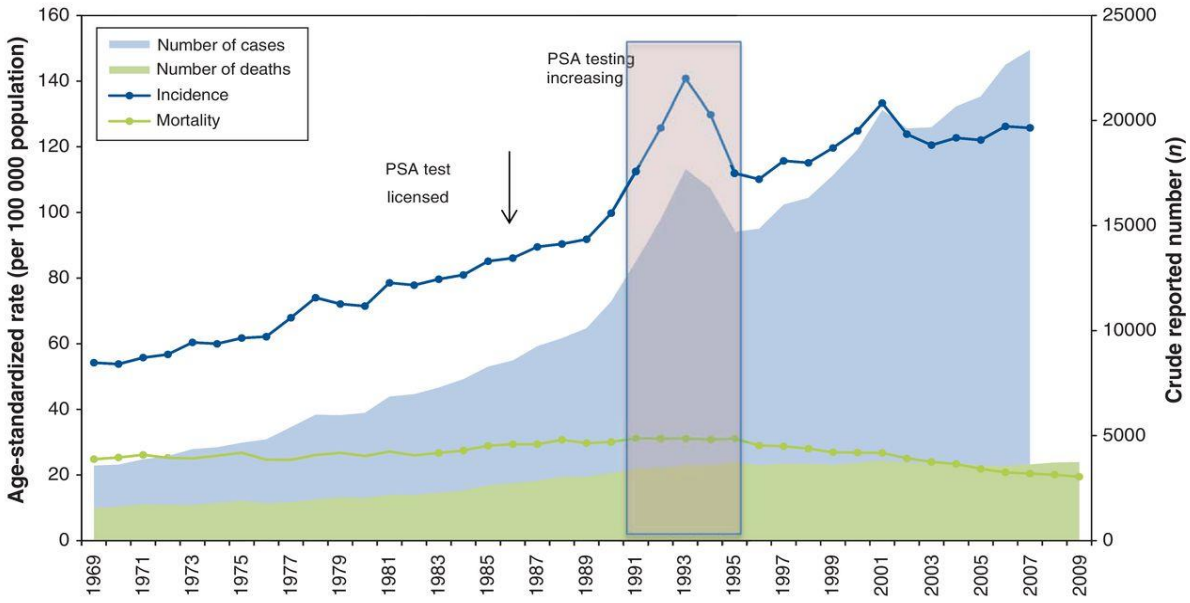

Figure 3. Age-standardized incidence and mortality, number of cases and deaths from prostate cancer in the pre and post PSA era in Canadian men, 1969-2009, Canada. Source: Dickinson et al 2016.[70] Reprinted with permission.

Using prostate cancer incidence as a comparator

The changing landscape of PSA screening and its subsequent impacts of prostate cancer incidence limits the ability to use prostate cancer incidence as a global and temporal comparator of prostate cancer between countries and over time.[71,78] Similar difficulties exist when trying to use prostate cancer incidence within countries due to varied screening rates and beliefs within communities.[79,80] When using incidence alone, it is unclear whether the increased rates observed in African and Caribbean nations are due to inherent genetic risks of prostate in these men, a shared environmental exposure, increased systemic screening, or a combination of these variables and more. Overall, the current academic consensus appears to mirror published GLOBOCAN and SEER estimates with men of African descent believed to be at higher risk, while men of Asian

descent are at lower risk, though the underlying data and strength of these recommendations remain questionable.

Mortality

Prostate cancer is the 6th leading cause of cancer related death worldwide, accounting for 7% of all cancer deaths.[63] GLOBOCAN data estimates prostate cancer to be the leading cause of male cancer-specific mortality in 53 countries with nearly 360 000 deaths from prostate cancer in 2018 (Figure 4).[63] In Canada 4200 men are expected to die of prostate cancer in 2020, accounting for 1 in 9 cancer related deaths.[1]

Global data sources and estimates

Like the disparities seen in the incidence of prostate cancer, varied rates of prostate cancer-specific mortality are observed worldwide. Using the GLOBOCAN database, age standardized mortality rates (ASMR) of prostate cancer range from highs of 48 and 42 per 100 000 men in Barbados and Jamaica to less than one in Yemen and Napal.[63] Unfortunately, it has been exceedingly difficult to separate sociocultural impacts on access to medical care from true genetic and environmental risk factors for disease.

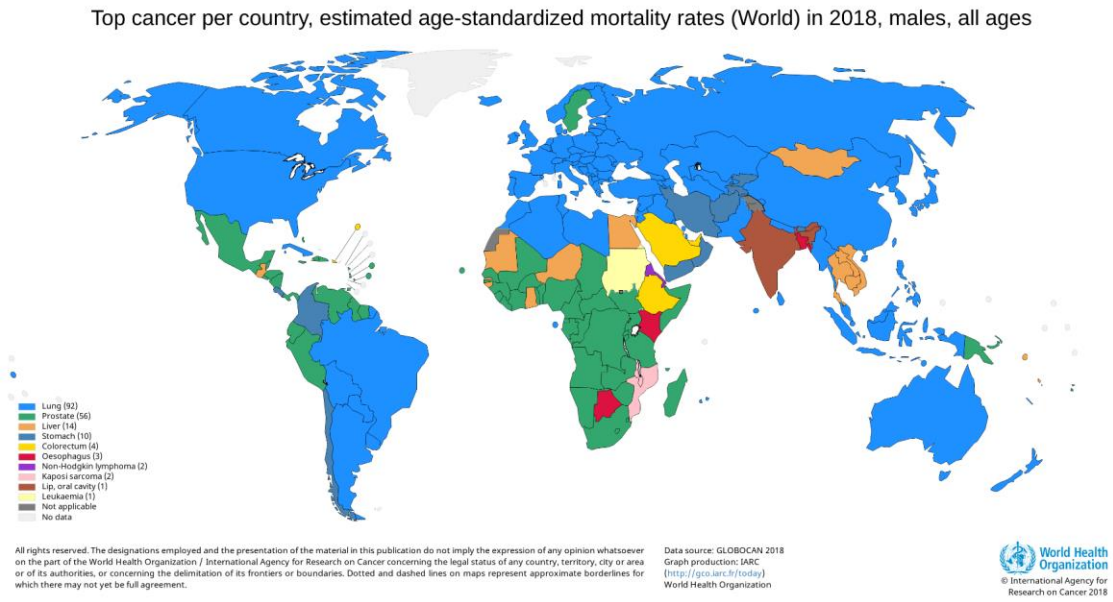

Figure 4. Global map of the most common cause of male cancer mortality by country in 2018. The number of countries represented are noted. ASR: Age standardized rate. IARC: International Agency for Research on Cancer. Source: GLOBOCAN 2018.[67]

The most extensive comparison of cancer survival across countries began in 1999 as a collaboration between the American Centers for Disease Control and Prevention and the British Department of Health and Cancer Research UK. It was initially established to investigate differences in cancer survival between European and American individuals diagnosed with prostate, breast, and colorectal cancers between 1990 and 1994.[81] This project evolved into the c*ancer survival in five continents (CONCORD)*. It is the first global comparison of cancer survival involving population-based cancer registries from all five continents covering nearly 300 million individuals.

Given the differences in life expectancy across the globe, CONCORD estimated relative survival as the ratio between observed mortality and expected mortality. Expected

mortality rates were calculated by creating life tables for each population studied, controlling for sex, region, and race.[82]

The original CONCORD study identified marked differences in prostate cancer survival across ethnically similar countries of equivalent Human Development Index and even different regions within countries (Figure 5). Across Europe, 5-year survival in men diagnosed with prostate cancer between 1990-1994 ranged from as low 37% in Poland to highs of 86% in Austria. While not as drastic, geographic differences are seen in Canada and the United States, ranging from 78% in Saskatchewan to 89% in British Columbia and from 86% in New York to 93% in Atlanta.[81]

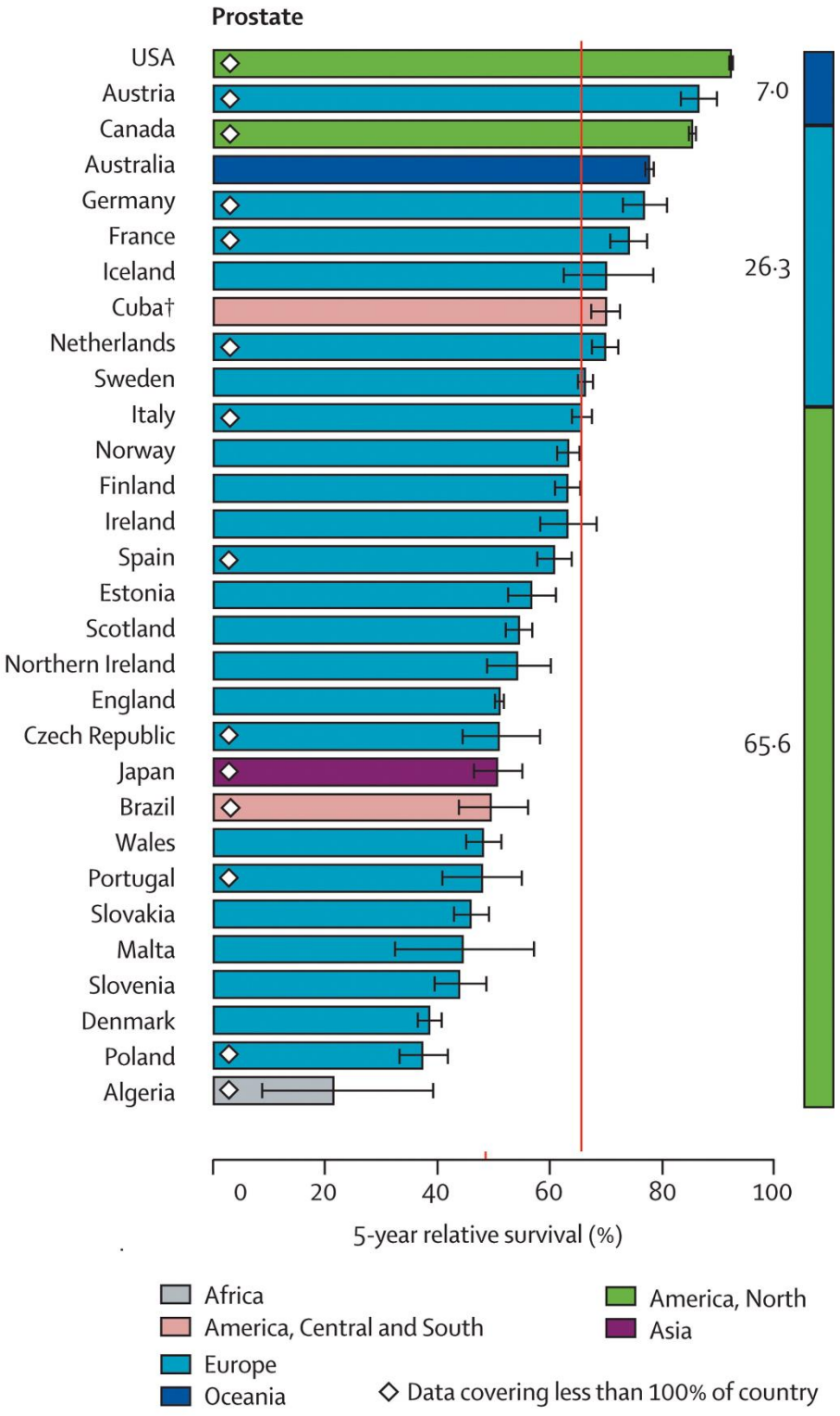

Figure 5. National differences in age standardized 5-year relative survival of men diagnosed with prostate cancer from 1990-94. Source: CONCORD Study 2008.[81] Reprinted open source figure.

The CONCORD-3 is the most recent update encompassing nearly 1 billion individuals, 18 cancers and 322 registries across 71 countries. This 2018 update estimates cancer survival from 2000 to 2014 and used a similar approach to CONCORD and CONCORD-2, estimating relative survival after calculating background mortality risk utilizing life tables. The CONCORD-3 showed an overall trend of improved 5-year prostate cancer survival, especially amongst developed nations. A total of 41 countries had 5-year net prostate cancer survival rates over 90% and a further 17 in the 80-89% range. Canada specifically improved from 85% between 1990-1994 to 94% in 2010-2014 (Figure 6).[81,83]

Unfortunately, no CONCORD study has been able to capture high volume African or Asian data. Only 6 African countries submitted data to CONCORD-3 and only 2 700 men were ultimately included in the study. Of the men included, 4.3% were lost to follow up and 37% were censored. Asian countries had better overall representation in CONCORD-3 with 397 000 men included, however 42% of these men were from Japanese registries. This is compared to 2 700 000 North American and 2 300 000 European men. Of the African data available, majority is single centre data with poor generalizability.

CONCORD provides the ability to trend mortality over time, which provides useful information to track initiatives and improvements within a country. However, the lack of standardized treatment and screening practices and low proportion of African (<2%) and Asian (<6%) men captured by high quality population-based registries limit the ability to compare between ethnically distinct countries.[64] This leads to uncertainty whether the high rates of prostate cancer mortality seen in African nations are due to the underlying

genetic risk factors in the population, access to healthcare, or environmental exposure to an unknown risk factor.

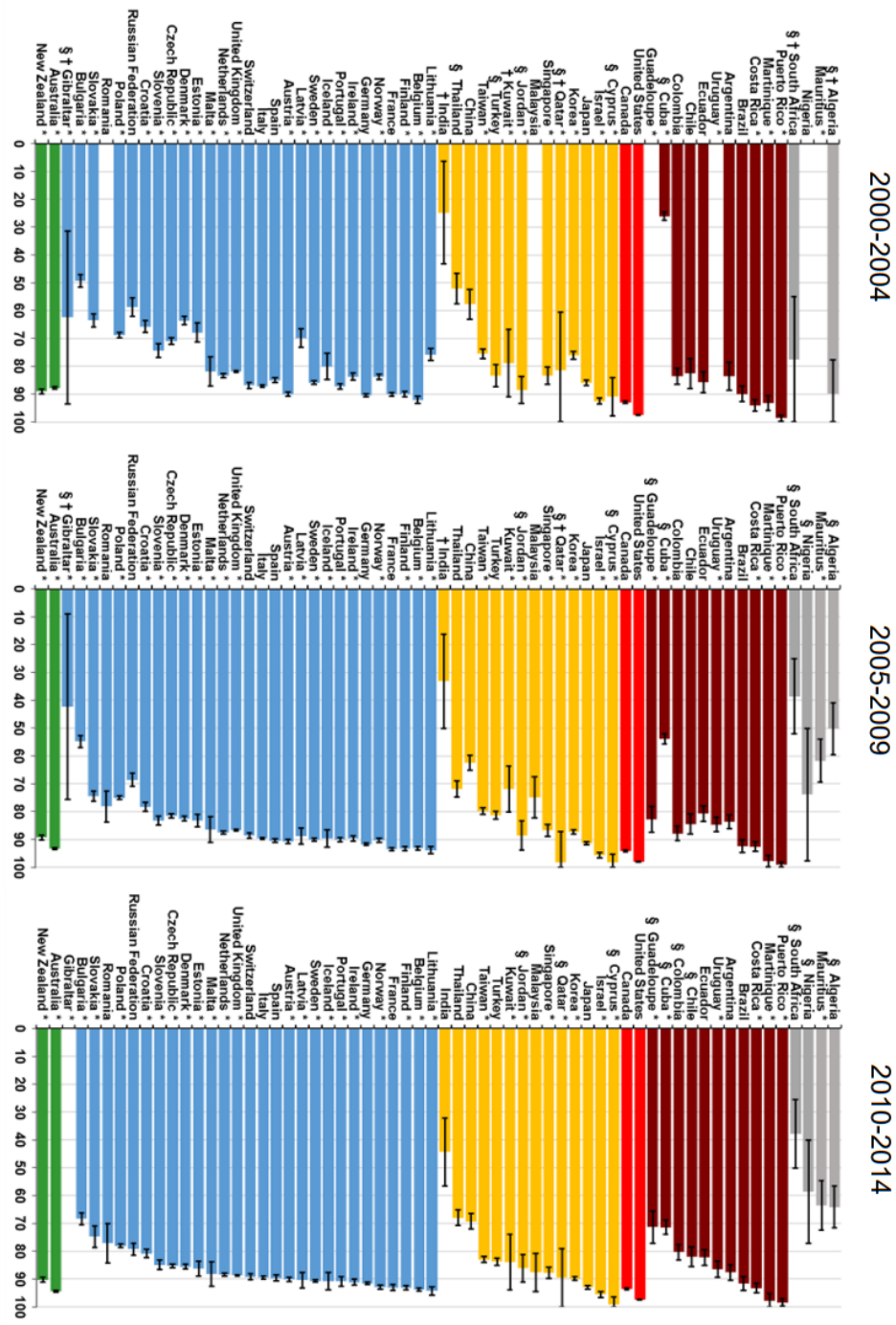

*Figure 6. Changes in 5-year net survival in adults diagnosed with prostate cancer over 5-year periods by country. *Data with 100% coverage of national population. †National estimates not age standardised. §Estimates flagged as less reliable source. Maroon: South America. Red: North*

America. Yellow: Asia. Blue: Europe. Green: Oceania. Grey: Africa. Source: CONCORD-3.[83] *Reprinted with permission.*

National estimates of prostate cancer mortality

An alternative to using international data is to study the impact of ethnicity on prostate cancer within a country with diverse populations and population-based datasets. Many comparators use the easily accessible American SEER database, however one must acknowledge its inherent biases and inability to fully control for confounders – most notably socioeconomic status and access to care in the United States.[84,85]

Analysis of the CONCORD study and the SEER database reveals a trend of increased mortality among black American men with a 5-year survival of 86%, compared to 92% in white men. This trend remained consistent across states, with the difference between white and black prostate cancer survival ranging from 5% in Florida to 16% in Rhode Island.[81]

Miller *et al.* used the SEER as well as state-specific databases to investigate the incidence and mortality rates among American Asian and Pacific Islander communities. Age-adjusted mortality rates among Asian communities were consistently ⅓ to ½ lower than non-Hispanic white men. Lowest rates were seen in Korean and Japanese men at 11 and 18 per 100 000 compared to 28 per 100 000 for non-Hispanic white men.[86]

Using England's population-based mortality datasets linked to hospital censuses and records have allowed the investigation of the lifetime risk of dying of prostate cancer in the United Kingdom. It found the lifetime risk of both being diagnosed with and dying from prostate cancer was doubled in black men compared to white men. In the same

study Asian men demonstrated lower lifetime prostate cancer incidence (8% vs 13%) and mortality (2% vs 4%). A significant limitation was the inaccuracy and absence of accurate ethnicity data, necessitating multiple assumptions be made.[87]

Using prostate cancer mortality as a comparator

In contrast to the fluctuations seen in prostate cancer incidence, prostate cancer mortality in Canada has remained more stable over time with approximately 3000 deaths per year and an ASMR that progressively decreased from 45 in 1992 to 26 in 2015 (Figure 7).[88] This stability makes prostate cancer mortality a more reliable temporal marker to investigate the impacts of ethnicity and immigration on prostate cancer mortality.

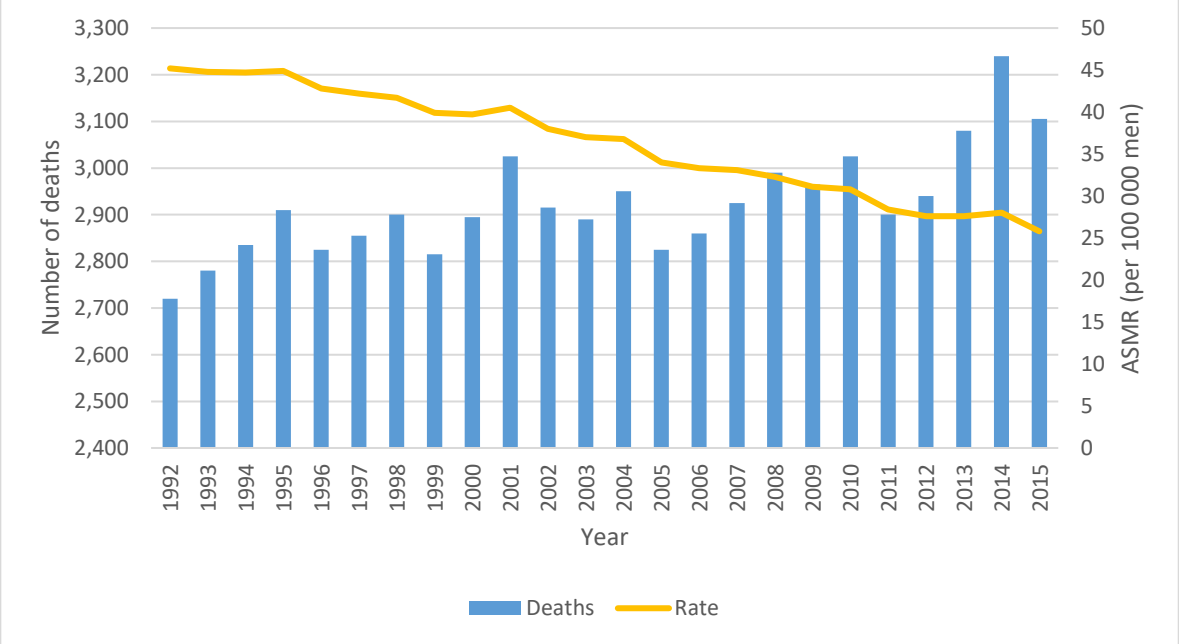

Figure 7. Number of prostate cancer deaths and age-standardized mortality rate in Canada from 1992 to 2015. ASMR: Age-standardized mortality rate. Source: Leblanc et al. Reprinted open source figure.[88]

Impact of immigration on prostate cancer

Many studies have attempted to use population-based registries to compare prostate cancer mortality between nations in hopes of identifying at-risk and protected groups. An alternative method to a investigate cancer's etiology is through immigration studies. Comparing an immigrant population to their home country assesses the impact of different environments on genetically similar individuals. In contrast, comparing immigrant populations to their host countries assesses the impact of the same environment on genetically differing populations.

Immigration studies are most useful when there is a notable difference in the dependent variable – either largely different environments or genetic pools. While these studies can address a wide range of questions, a unique niche has been developed investigating more nuanced, or multifactorial determinants of cancer risk.

An early immigration study involving Statistics Canada datasets investigated the rates of cancer mortality among the six largest immigrant populations in Ontario from 1969 to 1973. It found no appreciable difference in cancer mortality in the Canadian population compared to the British, Italian, German, Dutch, Polish, and Soviet immigrant groups.[89]

A 2007 study used the SEER database to compare prostate cancer incidences among Korean-Americans compared to native South Koreans as the risk amongst South Koreans in among the lowest in developed nations with age standardized incidence rates of 5-6 per 100 000 men.[90] It found Korean-American immigrants had increasing risks of prostate cancer compared to native Koreans, however the risks did not reach that of

white Americans. This suggests a potential environmental driver of prostate cancer through westernization, though the exact mechanism is yet to be determined.

Many of the more thorough immigration studies have been performed in Sweden by leveraging their high-quality, population-based datasets with extensive demographic and medical data. A 2009 study compared the risk of prostate cancer amongst Swedish born and foreign born men from 1961 to 2004.[91] Foreign born men had incidence rates 43% lower than the Swedish population, however a significant time effect was observed. Men who immigrated greater than 35 years prior had a risk of prostate cancer closer to that of the native Swedish population compared to those with less time in Sweden 35 years.

Perhaps most intriguing as it contradicts the notion that African men are at increased risk of early and aggressive disease was a 2013 Swedish database study. The study involved over 690 000 first generation immigrants to Sweden with over 13 000 cases of prostate cancer identified. It demonstrated men of Middle Eastern, Asian, North African, and Chilean descent had not only a lower risk of developing prostate cancer, but also had higher disease specific survival (hazard ratio 0.6). The authors conclude that these discrepancies seen cannot be accounted for by observed clinical features or risk factors and that an underlying protective mechanism may be at play.[92]

Canadian immigration and ethnicities

Canada is uniquely situated to investigate the impacts of ethnicity and immigration on cancer. With nearly 250 000 economic immigrants, sponsored immigrants, and refugees

arriving yearly, the Canadian population is comprised of over 250 unique ethnic origins.[93,94] The proportion of immigrants grew from nearly 20% in 2006 to 22% in 2016 and is expected to reach over 25% by 2031.[93,95]

Three major waves of immigration helped define the Canadian landscape. The first wave in the early 1900s comprised primarily of white European farmers attracted to the Canadian government's offer of free land to settle western Canada. A second more heterogeneous, but still predominantly white wave occurred in the 1930-1950s coinciding with the Great Depression and World War II. The third wave began in 1962 and continues to this day with changes to Canadian immigration policy to encourage immigration from non-European countries. Most importantly the policy changed the primary admission criteria from race and country of origin to skills and potential productivity.[96,97] Changes to ethnic restrictions on Canadian immigration laid the foundation for Canada to become the diverse nation seen today. Allowing economic immigrants resulted in a sharp increase in the number of Black Canadians with 300 000 West Indie immigrants and 150 000 African immigrants arriving between 1950-1995.[98]

The healthy immigrant effect

One major caveat to the interpretation of immigration studies is the *healthy immigrant effect.* The principle of the healthy immigrant effect is that those who are ill and infirmed are both less likely to seek out immigration opportunities and less likely to be welcomed by accepting countries. This leads to the selection of an immigrant population that is on average healthier than the standard population.

This effect has been clearly demonstrated in the Canadian population with both lower all-cause age standardized mortality rates for immigrant men (1006 vs 1305 per 100 000 person-years) and women (610 vs 731 per 100 000 person-years) and lower all-site cancer risk (standard incidence rates 0.25-0.31).[95,99]

For often debated reasons the healthy immigrant effect diminishes over time. It is thought that a combination of new life stressors, unhealthy western diet and the adoption of new risky behaviors like tobacco, alcohol, and illicit drug use may play a predominant role in weakening the initially protective effects.[100–102] While the root causes of the healthy immigrant effect may be beyond the scope of this paper its impact must not be ignored.

Canadian Cancer Registry

Statistics Canada has been the custodian of Canada-wide cancer statistics since 1969, beginning with the *National Cancer Incidence Reporting System* (NCIRS). Initially the NCIRS was an event-based registry involving nine of ten provinces, with Ontario joining in later years.[103] Since 1992, Statistics Canada has adopted a person-oriented database now known as the *Canadian Cancer Registry* (CCR). The CCR is an amalgamated registry maintained by Statistics Canada with data from the 10 Canadian provinces and 3 territories registering all primary cancer diagnoses.[104] The advantage of a person-oriented database is the ability to longitudinally track individuals over time. These records can subsequently be linked to mortality data, allowing for calculation of cancer incidence and survival over time. While the registry is an excellent resource for clinicians and healthcare leaders in Canada, it provides limited demographic data to allow for

detailed exploration of potential underlying risks and trends in Canadian subpopulations.

Canadian Census Health and Environment Cohort

To address the deficiency of health data with detailed demographic statistics, Statistics Canada commission the *Canadian Census Mortality and Cancer Follow-Up cohort.* This was the first study of its kind to investigate the impact of sociodemographic factors on cancer incidence, morbidity, and mortality in Canada. The study linked the 1991 long form census, Canadian mortality database (CMDB), Canadian Cancer Database (CCDB) and annual tax files allowing the analysis of detailed health and demographic data between 1991 and 2001.[105] The study found marked differences in mortality races based on education, socioeconomic status, and ethnicity.[106]

The *Canadian Census Health and Environment Cohort* (CanCHEC) expanded on the Mortality and Cancer Follow-Up cohort by including data from the 1991 long-form censuses, the 2011 National Household Survey, the Canadian Vital Statistics Death Database, the Canadian Cancer Registry, the Discharge Abstract Database, the National Ambulatory Care Reporting System, and postal code files. Table 4 shows selected variables of interest provided by each dataset. More detail and the methodology of dataset linkages having been extensively documented by Peters *et al* and Wilkins *et al.*[105–107]

Dataset	Relevant variable available
1991 Long form census	Age Ethnicity Immigration status Country of birth Education Income
Historic Tax Summary Files (1984-2011)	Postal code Tax filings for censoring
CCR (1992-2015)	Primary malignant tumor diagnosis Age at diagnosis Tumor characteristics
CVSDD (1991-20011)	Cause of death Date of death Age at death

Table 4. Sources of select analyzed variables in the 1991 CanCHEC database. CCR: Canadian cancer registry. CCDB: Canadian cancer database. CVSDD: Canadian Vital Statistics Death Database.

1991 Long Form Census

The 1991 Canadian Census of Population was administered to all Canadians on June 4, 1991 and ultimately covered over 96% of the Canadian population. The individuals not captured were estimated to be primarily young, mobile, low income, Aboriginal, or homeless.[106] The census included a mandatory short-form portion administered to all respondents that included basic demographic and family data and a long-form portion administered to 20% of eligible respondents. The long-form questionnaire included respondents age, detailed ethnic data including home language, religion, ethnic origin and place of birth, education, employment, and economic data. Linkage within the

CanCHEC specified individuals must be aged 25 or older at the time of the census with taxes filed in 1990 or 1991. Individuals who were institutionalized were also excluded.

Historic Tax Summary Files

The T1 family file covers 96% of the Canadian population and includes basic tax and demographic data including annual income, age grouping, and postal code and is updated annually.[108,109] To form the T1 family file an individual's T1 tax return, T4 tax file and federal child benefit (where applicable) are combined and used to attribute non-filing spouses, partners, and children. The data is collected by Canada Revenue Agency (CRA) and reported to local and national bodies including Statistics Canada.

The historic tax summary files included in CanCHEC allow for the longitudinal tracking of individuals regardless of name changes or movement throughout the country. These files also allowed for accurate censoring of individuals due to death or emigration.

Canadian Cancer Registry

The Canadian Cancer Registry (CCR) is a collated registry collecting administrative data from the 10 provincial and 3 territorial cancer registries. It contains cancer data on all permanent and non-permanent residents of Canada and has been reported annually since 1992. The CCR is maintained by the Canadian Council of Cancer Registries, a collaboration between the provincial and territorial cancer registries and Statistics Canada. The council standardizes and codifies the reported elements of the CCR.

As a person-based registry the CCR is able to longitudinal track an individual and includes all primary cancer diagnoses over a patient's lifetime.[104] It includes all primary borderline and malignant tumors classified according to the International Statistical

Classification of Diseases and Related Health Problems (ICD 9 and 10 where applicable). The CCR also includes tumour characteristics and basic demographic data.

Canadian Vital Statistics Death Database

The Canadian Vital Statistics Death Database (CVSDD) is updated annually and tracks deaths of Canadian residents and non-residents who died in Canada. The database has been maintained by Statistics Canada since its first publication in 1921 and has gradually included progressively more comprehensive data. Its most recent updates include data from all provinces and territories and classifies causes of death according to ICD criteria. Until 2010 the database also included Canadians who died in American states, however this practice has since been discontinued.[110]

The database is made possible by mandatory collection, classification, and reporting of all deaths within provinces and territories. These results are subsequently communicated by appropriate bodies to Statistics Canada. The CVSDD reports patients' demographic and death data including birthplace, date of death, age at death, cause of death, location (province or territory at time of death), and autopsy data where appropriate.

Summary and rationale

The incidence and mortality of prostate cancer continues to evolve worldwide. It is unclear whether these changes are through direct genetic impacts, shared environmental exposures, or systemic differences in healthcare practices and access. Previous attempts to answer these questions have been limited by poor quality data and confounding variables. Ultimately, this provided mixed results and uncertain

conclusions. Overall, these studies appear to suggest increased risks of prostate cancer mortality among black men and decreased risk among Asian men, though the underlying cause of these differences is unknown.

With the recent release of a Canada-wide database linking demographic, economic and health data we can explore ethnocultural impacts on cancers in Canada. Access to the CanCHEC dataset provides the unprecedented ability to longitudinally tract 20% of the Canadian population over an 18-year period. This leverages Canada's diverse and immigrant heavy population, as well as its universal access to care to investigate the impact of ethnicity and immigration on prostate cancer mortality in Canada.

CHAPTER 2:
Aims and Hypotheses

The primary purpose of this study was to investigate the impact of ethnicity and immigration on prostate cancer mortality in Canadian men. The findings are presented as an integrated article with two independent manuscripts. The specific aims and hypotheses of each manuscript are presented below.

Study 1: aims and hypotheses

Chapter 3 presents the first study: *The impact of ethnicity on prostate cancer mortality in Canada*. This study utilizes the 1991 CanCHEC dataset to assess the relationship between ethnicity and prostate cancer – accounting for age, education, immigration status, and region. Given the strengths of the dataset, all cancer diagnoses between 1992 and 2010 can be followed to death as long as the individual remained in Canada and continued to file taxes. This allows for the calculation and comparison of all-cause and cancer-specific mortality between different ethnic groups. The purpose of this study was to use Canadian data to reaffirm or challenge previous conclusions using population level data in an ethnically diverse, equal access healthcare system.

Hypothesis 1

We hypothesize that Asian-Canadian men will have a lower all-cause and cancer-specific mortality. Previous high quality population-level studies from ethnically homogenous Asian nations such as Japan and Korea, as well as American SEER dataset studies have consistently shown decreased prostate cancer mortality as compared to American or ethnically homogenous European and Scandinavian nations.[63,90,92,111] These patterns hold true in both registry and immigration studies and appear to function independent of PSA screening rates.[92,112]

Hypothesis 2

In line with previously published data and guideline recommendations, we hypothesize that black Canadians will have a higher all-cause and prostate cancer-specific mortality.[16–18,113,114] As compared to studies investigating prostate cancer mortality in Asian, European, and Scandinavian men, studies focusing on prostate cancer mortality in black men struggle with confounding variables, most notably poor quality and access to care, socioeconomic barriers to healthcare, different treatment patterns, and high rates of comorbidities.[115–117]

Study 2: aims and hypothesis

The second study is presented in Chapter 4, *Examining impact of immigration on prostate cancer mortality in Canada using the CanCHEC*. This study was performed using similar methodology to the first study. It uses the CanCHEC dataset in order to assess the impacts of immigration on prostate cancer mortality in men in Canada. Given the likely multifactorial nature of prostate cancer this study attempts to further explore potential biologic and geographic impacts on prostate cancer mortality by investigating cohorts of similar genetic profile in a new environment. If a genetic predisposition plays a dominant role than prostate cancer mortality should be similar to rates seen in home countries and remain stable over time. If environmental risk factors play a dominant role than rates should be lower on immigration and increase depending on length of stay in Canada.

Hypothesis 1

Given the multifactorial nature of prostate cancer, mortality rates in Asian immigrant men will initially be decreased compared to white Canadian men, however these rates

will increase over time. This is in line with what has been seen in American studies using the SEER dataset where rates in Asian men approach, but never eclipse the rates seen in white men.[90]

Hypothesis 2

Similarly, we hypothesize that immigrant black men will have a higher rate of prostate cancer-specific mortality. While majority of the studies have been observational and retrospective this community is believed to be at higher risk for early and aggressive disease.[16–18] We expect this rate to progressively decline over time, but remain elevated, given the presumed genetic predisposition to aggressive disease.

CHAPTER 3:
The impact of ethnicity on prostate cancer mortality in Canada

Abstract

Purpose: Prostate cancer is one of the most common non-cutaneous cancers diagnosed worldwide. Attempts to identify at risk populations have shown men of Asian descent to be protected, while men of African and Caribbean descent appear to be at an increased risk, though the cause of this disparity is largely unknown. It is unclear whether there is genetic, geographic, or social factors influencing prostate cancer mortality in these communities. The diverse Canadian population, single-payer healthcare model, and Statistic's Canada's population-level data lends itself well to investigate the impact of ethnicity on prostate cancer mortality.

Methods: Using Statistics Canada's Canadian Census Health and Environment Cohort (CanCHEC) we identified all men diagnosed with prostate cancer between 1992-2010. Cox proportional-hazards models were used to calculate hazard ratios (HR), predicting the association between the survival time of those with prostate cancer and ethnicity, controlling for age, immigration status, education, and province/territory.

Results: 51 530 cases of prostate cancer were identified with 21 785 705 total deaths and 7 925 deaths caused by prostate cancer. On multivariate analysis South Asian (HR 0.53 CI 0.36-0.76 p=0.0006) and East Asian (HR 0.62 95% CI 0.49-0.78 p=<0.0001) men had lower risks of prostate cancer-specific compared to non-visible minority men. No increased risk of prostate cancer mortality was seen in Black Canadian men (HR 0.83 95% CI 0.67-1.02 p=0.068). A higher level of education and location in Canadian had significant impacts on prostate cancer mortality.

Conclusion: In our Canadian cohort, black ethnicity does not confer increased risks of prostate cancer mortality while South and East Asian men appear to have factors protective against prostate cancer mortality.

Introduction

Prostate cancer is the most common non-cutaneous cancer in the Western world with an estimated 1 in 9 Canadian men expected to be diagnosed over their lifetime and 1 in 29 are expected to die from prostate cancer.[1] Despite extensive research, the only well established and accepted risk factors for prostate cancer remain age, family history, ethnicity and certain genetic mutations. Men of Asian descent appear to have lower rates and less aggressive disease while men of African descent have been demonstrated to have earlier onset, more aggressive disease with prostate cancer-specific mortality rates 80% higher than the white population.[114,118,119]

Internationally, prostate cancer mortality rates vary widely with rates nearly four times higher in African nations compared to Asian nations.[120] Unfortunately, it has been exceedingly difficult to separate the impacts of social, cultural and economic barriers on access to medical care from true genetic and environmental risk factors for the disease.

The purported increased risk of early, aggressive disease have led to the classification of men of African descent as *high risk* by the both American and European urologic associations with subsequent recommendations of more aggressive screening practices in these men.[16,18] However, the underlying data for these recommendations lacks high quality evidence, leaving the foundation for these recommendations uncertain. Some suggest that adjusting for nonbiologic differences including screening practices, socioeconomic status and access to healthcare may account for the disparities seen in the black population and recommend caution when drawing conclusions from these observational studies.[84,85,116]

Canadian data is uniquely suited to contribute to determining the impacts of ethnicity on prostate cancer mortality due in part to its diverse population and universal healthcare model. Using the Canadian Census Health and Environment Cohort (CanCHEC) we investigated the impacts of sociodemographic factors and their impacts on cancer mortality over an 18-year period. While causal linkages are not possible with population-based studies they can add high quality data to the question of ethnic impacts on prostate cancer mortality.

Methods

Study Design: This retrospective cohort study uses the 1991 CanCHEC to investigate the role of ethnicity on the likelihood of dying among those with prostate cancer in Canada between 1992 and 2010.

Data source: The 1991 CanCHEC is a population-based database including data from the 1991 long-form censuses linked to the Canadian Cancer Registry (1992-2010), Canadian Vital Statistics Death Database (1921-2016), and historic tax summary files (1984-2011), amongst others.[121] Further detailing of the CanCHEC as well as its linkage methodology is thoroughly described by Peters *et al.*[107]

Patient population: This study included all men involved in the 1991 long form census with complete demographic data diagnosed with prostate cancer between 1992 and 2010. A diagnosis of prostate cancer was established using the International Classification of Disease coding of 185 before 2000 (ICD-9CM) and C61 from 2000 onwards following the update to ICD-10-CM. As a person-oriented dataset, individual

cancer diagnoses and deaths are reported annually and linked. Individuals with missing demographic data and prostate cancer diagnoses prior to 1992 were excluded.

Variables: Our focal independent variable was ethnic minority group as determined from responses to the 1991 Census. Categoric grouping was necessary to ensure adequate sample size to adhere to Statistics Canada reporting guidelines in accordance with the 1985 Statistics Act.[122] The ethnic minority groups were categorized into 6 groups as (1) Black (2) South Asian (3) East Asian (Chinese, Korean, and Japanese) (4) Southeast Asian and Filipino (5) West Asian or Arabs, and (6) not a visible minority, with the non-visible minority group acting as a reference category for regression models. Control variables were immigrant status, age, education, and Canadian region of residence as determined from the 1991 Census.

Statistical methods: Frequency distribution of all-cause and prostate cancer-specific mortality was calculated and chi-squared tests for independence were conducted for each contingency table. Cox Proportional-Hazards Models were also used to predict the association between the survival time of those with prostate cancer and our covariates. Hazard ratios, 95% confidence intervals, and p-values are reported. Both a univariate analysis testing the effect of each individual independent variable and multivariate analysis testing the effect of independent variables, while accounting for our control variables was performed. All analyses were conducted using SAS 9.4 and vetted prior to release in accordance with Statistics Canada Research Data Centre protocols. This study was approved by the institutional review board of the University of Western Ontario.

Results

In total there were 51 530 cases of prostate cancer diagnosed between 1992 and 2010. 29 705 of these men died with 7 925 of these deaths caused by prostate cancer. Table 5 shows baseline characteristics of men with prostate cancer in our cohort.

Table 6 and Table 7 show univariate and multivariate hazard ratios of death due to all cause and prostate cancer. Our univariate analyses show that all ethnic minority groups with prostate cancer were less likely to die from any cause and prostate cancer specifically than non-ethnic minorities.

A similar trend was seen on multivariate analysis. After accounting for immigrant status, age, education and Canadian region of residence, Black (HR 0.76 95% CI 0.67-0.87), South Asians (HR 0.83 99% CI 0.69-0.99), and East Asian (HR 0.65 95% CI 0.57-0.74) men with prostate cancer were significantly less likely to die of any cause as compared to non-visible minorities. For prostate cancer-specific mortality, South Asian (HR 0.53 95% CI 0.0.36-0.76) and East Asians (HR 0.62 95% CI 0.49-0.79) were seen to be at lower risk compared to non-ethnic minorities. Interestingly, black men were shown to not be at increased risk of prostate cancer death with a lower risk of prostate cancer mortality on univariate analysis (HR 0.47 95% CI 0.39-0.58) and no significant difference in risk on multivariate analysis (HR 0.83 95% CI 0.67-1.02).

A geographic disparity was demonstrated on multivariate analysis with the West Coast having a protective effect (HR 0.82 95% CI 0.77-0.87) and the prairie provinces having an increased risk (HR 1.081 95% CI 1.02-1.14).

	Died from any death (n=21 785)	p-value	Died from prostate cancer (n=7 925)	p-value
Minority Categories		<.0001		<.0001
Not a visible minority	21 045		7 675	
Black	235		95	
South Asian	125		30	
East Asian	215		70	
Southeast Asian and Filipino	55		15	
West Asian and Arabs	110		35	
Immigrant Status		<.0001		<.0001
Not an immigrant	16 695		6 130	
Immigrant Status	5 095		1 795	
Age Categories		<.0001		<.0001
25-34	25		20	
35-44	325		185	
45-54	1 740		750	
55-64	6 105		2 225	
65+	13 590		4 750	
Education Categories		<.0001		<.0001
No high school	12 235		4 420	
High school	6 210		2 270	
Postsecondary non-university	1 495		575	
University degree	1 845		660	
Canadian Region		<.0001		<.0001
Central Canada	12 385		4 520	
East Coast	1 900		665	
Prairies	4 090		1 645	
British Columbia	3 390		1 085	
Territories	25		10	

Table 5. Baseline characteristics of men with prostate cancer who died of any cause or of prostate cancer in the CanCHEC between 1992 and 2010.

	Univariate				Multivariate			
	HR	**95% CI**		**p-value**	**HR**	**95% CI**		**p-value**
Minority Categories *(ref= Not a visible minority)*								
Black	0.422	0.371	0.48	<.0001	0.76	0.67	0.87	<.0001
South Asian	0.494	0.415	0.588	<.0001	0.83	0.694	0.988	0.0362
East Asian	0.601	0.525	0.688	<.0001	0.65	0.567	0.744	<.0001
Southeast Asian and Filipino	0.534	0.411	0.695	<.0001	0.82	0.631	1.069	0.1438
West Asian and Arabs	0.714	0.591	0.862	0.0004	1.14	0.941	1.374	0.1842
Immigrant Status *(ref= Not an immigrant)*								
Immigrant Status	0.896	0.868	0.925	<.0001	0.88	0.852	0.91	<.0001
Age Categories *(ref= 25-34)*								
35-44	1.894	1.246	2.879	0.0028	1.9	1.251	2.89	0.0026
45-54	4.666	3.106	7.01	<.0001	4.53	3.015	6.806	<.0001
55-64	14.9	9.933	22.33	<.0001	13.8	9.188	20.66	<.0001
65+	58.35	38.93	87.46	<.0001	52.9	35.27	79.28	<.0001
Education Categories *(ref= No high school)*								
High school	0.577	0.559	0.595	<.0001	0.83	0.801	0.852	<.0001
Postsecondary non-university	0.452	0.428	0.476	<.0001	0.74	0.698	0.778	<.0001
University degree	0.361	0.344	0.379	<.0001	0.61	0.576	0.636	<.0001
Canadian Region *(ref= Central Canada)*								
East Coast	0.995	0.948	1.044	0.8261	0.95	0.902	0.995	0.0308
Prairies	1.069	1.032	1.107	0.0002	0.98	0.943	1.012	0.1917
British Columbia	1.087	1.047	1.129	<.0001	0.91	0.88	0.949	<.0001
Territories	0.729	0.492	1.079	0.1146	1.13	0.761	1.669	0.5502

Table 6. Univariate and multivariate analysis of all-cause mortality in men diagnosed with prostate cancer between 1992-2010 in the 1991 CanCHEC. ref: Reference. HR: Hazard ratio. CI: Confidence interval.

	Univariate				Multivariate			
	HR	**95% CI**		**p-value**	**HR**	**95% CI**		**p-value**
Minority Categories *(ref= Not a visible minority)*								
Black	0.474	0.387	0.581	<.0001	0.83	0.672	1.015	0.0683
South Asian	0.314	0.218	0.453	<.0001	0.53	0.364	0.76	0.0006
East Asian	0.549	0.434	0.694	<.0001	0.62	0.49	0.787	<.0001
Southeast Asian and Filipino	0.447	0.277	0.722	0.001	0.68	0.422	1.105	0.1201
West Asian and Arabs	0.651	0.469	0.903	0.0102	1.03	0.737	1.426	0.8827
Immigrant Status *(ref= Not an immigrant)*								
Immigrant Status	0.863	0.819	0.91	<.0001	0.87	0.827	0.924	<.0001
Age Categories *(ref= 25-34)*								
35-44	1.345	0.836	2.165	0.2219	1.35	0.84	2.177	0.2136
45-54	2.507	1.584	3.967	<.0001	2.45	1.548	3.877	0.0001
55-64	6.661	4.224	10.5	<.0001	6.2	3.928	9.772	<.0001
65+	23.49	14.91	37	<.0001	21.5	13.61	33.81	<.0001
Education Categories *(ref= No high school)*								
High school	0.593	0.563	0.623	<.0001	0.83	0.789	0.874	<.0001
Postsecondary non-university	0.49	0.449	0.535	<.0001	0.78	0.712	0.849	<.0001
University degree	0.366	0.337	0.397	<.0001	0.6	0.549	0.648	<.0001
Canadian Region *(ref= Central Canada)*								
East Coast	0.956	0.881	1.037	0.2742	0.91	0.833	0.982	0.017
Prairies	1.177	1.113	1.246	<.0001	1.08	1.021	1.144	0.0072
British Columbia	0.951	0.89	1.016	0.1358	0.82	0.765	0.874	<.0001
Territories	0.796	0.426	1.485	0.4729	1.18	0.63	2.194	0.6119

Table 7. Univariate and multivariate analysis of prostate cancer-specific mortality in men diagnosed with prostate cancer between 1992-2010 in the 1991 CanCHEC. ref: Reference. HR: Hazard ratio. CI: Confidence interval.

Discussion

This longitudinal cohort study is the largest to assess the impact of ethnicity on mortality rates in Canadian men with prostate cancer. After controlling for potential confounding variables, non-visible minority Canadians were at the highest risk for all-cause and prostate cancer-specific mortality. South and East Asian men were found to have lower risks of prostate cancer-specific mortality while other ethnicities showed no significant increased risk or protection compared to the non-visible minority group.

Our study demonstrated no increased risk of prostate cancer-specific mortality in Canadian black men. Black men have traditionally been classified as a high risk population with increased rates of early and aggressive disease.[113,114] Unfortunately, the scarcity of high quality outcomes data on black men has led to the majority of these conclusion being drawn from American administrative datasets where controlling for confounding variables can be exceedingly difficult.[84,85,123] This is especially important in American studies given that American black men are known to have lower socioeconomic status, higher rates of comorbidities, and are less likely to be offered definitive therapy as compared to a non-Hispanic white men.[113,124,125] These concerns have led some to question whether black men are truly at increase risk of prostate cancer mortality or whether there are social and societal barriers driving the observed poor outcomes.

The results of this study are consistent with recent pooled analyses of the American Surveillance, Epidemiology, and End Results Program (SEER), Veteran Affairs health systems data and randomized control studies, as well as single institution studies that

found no evidence of a racial predisposition to aggressive disease once confounding variables were controlled.[116,125] Specifically, adjusting for nonbiological differences including socioeconomic status and access to healthcare eliminated the observed increased risk seen amongst American black men for prostate cancer-specific mortality.

A significantly lower hazard ratio was seen among South and East Asian men on both univariate and multivariate analysis, while the protective effect of Southeast Asian and Filipino as well as Western Asian and Arab ethnicity seen on univariate analysis disappeared when confounding variables were accounted for. Published data on these populations remain controversial as well given mixed uptake of PSA screening in their home countries.[111,126,127] Overall, Asian men are have been shown to be at lower risk with age adjusted mortality rates 2.3 times lower as compared to non-Hispanic white men though they may present later due to cultural and social barriers to healthcare access.[128] There does appear to be further risk stratification within the Asian populations. Retrospective analysis of men undergoing hormone therapy showed improved overall and cancer specific survival in Japanese men compared to white men.[129] This may indicate a potential underlying genetic or cultural protective factor with respect to tumor biology or response to treatment.

There have been few studies investigating the geographic disparity of prostate cancer mortality in Canada. Using data published by the Canadian Cancer Society, projected age-standardized mortality rates vary from lowest in Quebec, Ontario, and British Columbia (20-22 per 100 000 men) to their highest in Saskatchewan, Manitoba and Newfoundland (28-30 per 100 000 men), though no statistical analysis have been

performed to indicate the significance of these values.[130] Our data showed a small coastal protective effect with lower all-cause and prostate cancer-specific mortality seen in the East and West coast provinces once confounding variables were controlled, while Alberta and Manitoba showed slightly higher risk of prostate cancer-specific mortality.

Several limitations to this study should be acknowledged. As with all population and administrative data, the retrospective nature and subsequent linkage of these datasets limits the ability to draw definitive causal conclusions. The inability to further stratify individuals beyond broad ethnic groups may miss variable rates within each subset. Additionally, the CanCHEC was unable to provide family history, PSA, or treatment modality that may act as uncontrolled confounders in the studied population. Finally, the absence of cancer grading, staging, pathology, and treatment data limit the ability to comment on potential variations on how different ethnicities present and are treated in Canada. This data has been added to later versions of the CanCHEC and will hopefully yield results in the coming years. This study is the largest Canadian cohort to investigate the impacts of ethnicity on prostate cancer mortality. The large sample size, long follow up, and equal access healthcare model provided the power necessary to overcome confounding social determinants of health observed in previous studies.

Conclusion

As compared to non-visible minority Canadian men with prostate cancer, black men showed no increased risk of prostate cancer-specific mortality. Black, South Asian and East Asian all had lower risks of all-cause mortality and South Asian and East Asian showed lower risks of prostate cancer-specific mortality. A slight geographic effect was

noted with lower risks of prostate cancer and all cause mortality in the East and West coasts of Canada and higher rates in the Prairies. These results contradict earlier studies suggesting black men may have a biologically distinct form of aggressive prostate cancer and highlights the importance of addressing socioeconomic and cultural barriers to healthcare.

CHAPTER 4:
Examining the impact of immigration on prostate cancer pathology and mortality in Canada using the CanCHEC

Abstract

Purpose: Prostate cancer is the second most common cancer diagnosed worldwide, however mortality rates vary markedly by country. Men of African and Caribbean descent appear to have increased risks of prostate cancer mortality, while men of Asian descent have lower risks compared to Caucasian men. It is unclear whether this disparity is from a shared genetic factor, from geographic or social practices, or from screening and treatment patterns. Immigration studies provide an opportunity to examine the impact of genetics and the environment on the risk of prostate cancer mortality over time.

Methods: This study used Statistics Canada's Canadian Census Health and Environment Cohort (CanCHEC) to investigate the impact of ethnicity and immigration on prostate cancer mortality. Bivariate analyses were used to predict the association between survival time of non-visible minority men (diagnosed 2004-2007) and visible minority men (diagnosed 2004-2010) and covariates including immigration and tumor characteristics. Sample size concerns necessitated grouping of men of different visible minority populations.

Results: In total 2 335 non-visible minority and 165 visible minority men with prostate cancer died of any causes. Of these men 1 095 non-visible minority and 60 non-visible minority men died from prostate cancer. Results could not be further stratified by visible minority status due to low sample size and missing data.

Conclusions: While CanCHEC provides access to the variables necessary to determine the impact of immigration on prostate cancer mortality over time in Canada, it remains too

immature to draw definitive conclusions. Increased follow up times and improved data linkages may provide more promising results in the future.

Introduction

Prostate cancer is the second most commonly diagnosed male cancer worldwide with a global age-standardized incidence rate of 29 per 100 000 individuals.[63] Variable mortality rates for prostate cancer are seen globally. The highest rates are seen in predominantly African, Latin American and Caribbean nations, while lower rates are seen in European, North American and Asian countries.[63] Efforts to understand these differences have met resistance in controlling for the interplay between potential underlying genetic, environmental, and socio-economic factors.

Immigration studies provide opportunities to examine the impacts of genetics and the environment on individuals' risk for cancer. Comparing cancer characteristics and mortality rates between immigrant Canadians and their home country allows one to elucidate whether the observed differences may be caused by genetic variants which result in more aggressive disease or through socioeconomic factors resulting in poorer access to care, screening, or treatment patterns. Should genetic impacts be a predominant factor driving mortality rates, no differences should be seen between home and host country and the length of time since immigration should not impact mortality rates. If the differences are caused by environmental factors – either through exposure to a risk factor, screening practices or other socio-economic factors – rates should initially mirror the home country before approaching the rate of Canadian men.

This study uses the Canadian Census Health and Environment Cohort (CanCHEC) to investigate the impact of immigration on prostate cancer mortality in Canada. The CanCHEC linked long form census data with detailed health, socioeconomic, pathology,

and survival data. Exploring differences in pathology and mortality data allows for the investigation of whether biological or social factors drive the observed ethnic differences in prostate cancer survival. Presumably, the observed differences in mortality rates are multifactorial; however, the ability to document definitive differences between groups provides avenues for further research.

Methods

Study design: This retrospective cohort study uses the 1991 CanCHEC data to investigate the impact of immigration on the mortality rate among men with prostate cancer in Canada.

Data source: The 1991 CanCHEC is a population-based database which includes linked data from the 1991 long-form census, the Canadian Cancer Registry (1992-2010), Canadian Vital Statistics Death Database (1921-2016), and historic tax summary files (1984-2011), among others.[121] Further detailing of the CanCHEC, as well as its linkage methodology, is thoroughly described by Peters *et al.*[107]

This study was performed in two phases: the first phase looking at non-visible minority Canadian men and the second phase investigating visible minority Canadians. Phase 1 involves all non-visible minority men involved in the 1991 CanCHEC diagnosed with prostate cancer between 2004-2007. These dates were selected to allow access to tumor characteristics including TMN staging, grading, and tumor size, which are only available during this time period. Phase 2 involved men whom identified as a visible minority on the 1991 long-form census. Due to small sample size concerns, Phase 2 was expanded to contain diagnoses from 2004-2010 in accordance with Statistics Canada

reporting guidelines and the 1985 Statistics Act.[122] The CanCHEC allows for longitudinal tracking of an individual's cancer diagnoses and cause of death. A diagnosis of prostate cancer was established using the International Classification of Disease coding of C61.

Statistical methods: Frequency distribution of all-cause and prostate cancer-specific mortality was calculated for both Phases, and *t* tests or chi-squared tests for independence were conducted where appropriate. Bivariate analyses were also used to predict the association between the survival time of those with prostate cancer and covariates. All counts were weighted and rounded to base 5, and percentages were based on weighted, rounded counts. Where the weighted frequency of a cell did not contain 10 individuals, categories were aggregated where necessary to increase the cell count per Statistics Canada guidelines. Hazard ratios, 95% confidence intervals, and *p* values are reported. All analyses were conducted using SAS 9.4 and vetted prior to release in accordance with Statistics Canada Research Data Centre protocols. This study was approved by the institutional review board of the University of Western Ontario.

Results

In total, 11 580 non-visible minority Canadian men were diagnosed with prostate cancer between 2004-2007. 1 095 died from prostate cancer and 2 335 died from any cause.

	Died from any cause (n=2,335)	**Did not die** (n=9,245)	**p-value**
Age			
(mean)	63	51	
(median)	64	51	<.0001
Education (%)			<.0001
No high school	54	33.6	
Highschool	31.1	36.6	
Post-secondary non-university	6.6	11.6	
University	8.4	18.2	
Canadian Region of Diagnosis (%)			0.0002
Central Canada	61.4	58.7	
East Coast	7.5	10.4	
Prairies	17.1	17.9	
West Coast	13.9	12.8	
Territories		0.1	
Immigrant Status (%)			0.7677
Not an immigrant	79	79.4	
Immigrant	20.8	20.6	
Tumour Grade (%)			<.0001
G1/G2	5.8	14.8	
G3/G4	13.3	13.8	
Unreported	80.7	71.4	
T Stage (%)			<.0001
T1	2.8	4.9	
T2	1.9	4.2	
T3	1.1	1	
T4	0.4		
Unreported	93.6	90	
N Stage (%)			<.0001
N0	1.7	3.1	
N1 - N3	0.4		
Unreported	97.8	97.2	
M Stage (%)			<.0001
M0	2.1	4.6	
M1	1.7		
Unreported	95.9	95.4	
Tumour Size (%)			<.0001
0 - 1.9 cm	0.6	2.4	

1.9 - 4.9 cm	0.6	0.7	
> 5 cm		0.4	
Unreported	98.5	96.4	

Table 8 and

	Not a Minority (n=3,575)	**Minority** (n=165)	**p-value** [3]
Age			
(mean)	61	58	
(median)	63	58	<.0001
Education (%)			<.0001
No high school	52.7	33.3	
Highschool	31.2	33.3	
Post-secondary non-university	7.3	12.1	
University	8.8	21.2	
Canadian Region of Diagnosis [4] **(%)**			0.0005
Central Canada	61.1	72.7	
West Coast (BC)	14.3	18.2	
Other	24.8	12.1	
Immigrant Status (%)			<.0001
Not an immigrant	79.4	12.1	
Immigrant	20.6	87.9	
Tumour Grade (%)			0.3669
G1/G2	6.3	6.1	
G3/G4	16.4	12.1	
Unreported	77.5	78.8	

Table 9 show baseline characteristics of non-visible minority and visible minority men diagnosed with prostate cancer in our cohort.

Parameter	**Hazard Ratio**	**95% Hazard Ratio**	**p-value**

		Confidence Limits		
Age	1.123	1.118	1.128	<.0001
Education (ref=No high school)	1.036	0.543	1.979	0.9145
Highschool	0.59	0.514	0.676	<.0001
Post-secondary non-university	0.513	0.409	0.643	<.0001
University	0.328	0.261	0.411	<.0001
Canadian Region of Diagnosis (ref=Central Canada)				
East Coast	0.769	0.611	0.967	0.0248
Prairies	1.006	0.855	1.183	0.9427
Territories	0.869	0.157	4.805	0.8718
West Coast	1.092	0.914	1.305	0.3317
Immigrant (ref=not an immigrant)	1.126	0.975	1.302	0.107
Tumour Grade (ref=unreported)				
G1/G2	0.147	0.098	0.22	<.0001
G3/G4	0.995	0.842	1.175	0.9505
T Stage (ref=unreported)				
T1	0.544	0.373	0.793	0.0016
T2	0.339	0.202	0.569	<.0001
T3	1.923	1.242	2.976	0.0034
T4	8.54	4.489	16.244	<.0001
N Stage (ref=unreported)				
N0	0.677	0.428	1.071	0.0953
N1 - N3	10.762	6.258	18.508	<.0001
M Stage (ref=unreported)				
M0	0.503	0.331	0.765	0.0013
M1	13.966	10.072	19.364	<.0001
Tumour Size (ref=unreported)				
0 - 1.9 cm	0.178	0.069	0.462	0.0004
2 - 4.9 cm	0.606	0.24	1.534	0.2907
> 5 cm	0.802	0.306	2.101	0.6528

Table 10 and

Parameter	Hazard Ratio	95% Hazard Ratio Confidence Limits		p-value
Age	1.105	1.084	1.127	<.0001
Education (ref=No high school)				
Highschool	0.753	0.419	1.351	0.3411
Post-secondary non-university or university	0.411	0.212	0.799	0.0087
Canadian Region of Diagnosis (ref=Central Canada)				
Other	1.218	0.61	2.431	0.576
West Coast (BC)	0.998	0.496	2.008	0.9961
Immigrant (ref=not an immigrant)	0.78	0.366	1.663	0.5201

Table 11 show bivariate analysis of all-cause and prostate cancer-specific mortality. Among non-visible minority Canadians, immigration status had no impact on all-cause or prostate cancer-specific survival. Increasing age, tumor grade, size, and TNM staging all had significant impact on all-cause and prostate cancer-specific mortality.

Among visible minority men 165 died from any cause and 60 died from prostate cancer.

	Not a Minority (n=3,575)	**Minority** (n=165)	**p-value** [3]
Age			
(mean)	61	58	
(median)	63	58	<.0001
Education (%)			<.0001
No high school	52.7	33.3	
Highschool	31.2	33.3	
Post-secondary non-university	7.3	12.1	
University	8.8	21.2	
Canadian Region of Diagnosis [4] **(%)**			0.0005
Central Canada	61.1	72.7	
West Coast (BC)	14.3	18.2	
Other	24.8	12.1	
Immigrant Status (%)			<.0001
Not an immigrant	79.4	12.1	
Immigrant	20.6	87.9	
Tumour Grade (%)			0.3669
G1/G2	6.3	6.1	
G3/G4	16.4	12.1	
Unreported	77.5	78.8	

Table 9 shows baseline characteristics of visible minority men with prostate cancer in our cohort. Unfortunately, due to small sample size concerns, significant censoring of the data was required. In accordance with Statistics Canada guidelines, the results could not be reported by visible minority group. Among visible minority Canadians, immigration status did not have a significant impact on all-cause or prostate cancer-specific mortality. Visible minority groups had lower rates of both all-cause and prostate cancer-specific mortality (Figure 8).

	Died from any cause (n=2,335)	Did not die (n=9,245)	p-value
Age			
(mean)	63	51	
(median)	64	51	<.0001
Education (%)			<.0001
No high school	54	33.6	
Highschool	31.1	36.6	
Post-secondary non-university	6.6	11.6	
University	8.4	18.2	
Canadian Region of Diagnosis (%)			0.0002
Central Canada	61.4	58.7	
East Coast	7.5	10.4	
Prairies	17.1	17.9	
West Coast	13.9	12.8	
Territories		0.1	
Immigrant Status (%)			0.7677
Not an immigrant	79	79.4	
Immigrant	20.8	20.6	
Tumour Grade (%)			<.0001
G1/G2	5.8	14.8	
G3/G4	13.3	13.8	
Unreported	80.7	71.4	
T Stage (%)			<.0001
T1	2.8	4.9	
T2	1.9	4.2	
T3	1.1	1	
T4	0.4		
Unreported	93.6	90	
N Stage (%)			<.0001
N0	1.7	3.1	
N1 - N3	0.4		
Unreported	97.8	97.2	
M Stage (%)			<.0001
M0	2.1	4.6	
M1	1.7		
Unreported	95.9	95.4	
Tumour Size (%)			<.0001
0 - 1.9 cm	0.6	2.4	
1.9 - 4.9 cm	0.6	0.7	
> 5 cm		0.4	
Unreported	98.5	96.4	

Table 8. Demographic and clinical data for non-visible minority Canadian men diagnosed with prostate cancer between 2004-2007 in the 1991 CanCHEC.

	Not a Minority (n=3,575)	**Minority** (n=165)	**p-value** [3]
Age			
(mean)	61	58	
(median)	63	58	<.0001
Education (%)			<.0001
No high school	52.7	33.3	
Highschool	31.2	33.3	
Post-secondary non-university	7.3	12.1	
University	8.8	21.2	
Canadian Region of Diagnosis [4] **(%)**			0.0005
Central Canada	61.1	72.7	
West Coast (BC)	14.3	18.2	
Other	24.8	12.1	
Immigrant Status (%)			<.0001
Not an immigrant	79.4	12.1	
Immigrant	20.6	87.9	
Tumour Grade (%)			0.3669
G1/G2	6.3	6.1	
G3/G4	16.4	12.1	
Unreported	77.5	78.8	

Table 9. Demographic and clinical data for visible minority Canadian men diagnosed with prostate cancer 2004-2010 who died of any cause in the 1991 CanCHEC.

Parameter	Hazard Ratio	95% Hazard Ratio Confidence Limits		p-value
Age	1.123	1.118	1.128	<.0001
Education (ref=No high school)	1.036	0.543	1.979	0.9145
Highschool	0.59	0.514	0.676	<.0001
Post-secondary non-university	0.513	0.409	0.643	<.0001
University	0.328	0.261	0.411	<.0001
Canadian Region of Diagnosis (ref=Central Canada)				
East Coast	0.769	0.611	0.967	0.0248
Prairies	1.006	0.855	1.183	0.9427
Territories	0.869	0.157	4.805	0.8718
West Coast	1.092	0.914	1.305	0.3317
Immigrant (ref=not an immigrant)	1.126	0.975	1.302	0.107
Tumour Grade (ref=unreported)				
G1/G2	0.147	0.098	0.22	<.0001
G3/G4	0.995	0.842	1.175	0.9505
T Stage (ref=unreported)				
T1	0.544	0.373	0.793	0.0016
T2	0.339	0.202	0.569	<.0001
T3	1.923	1.242	2.976	0.0034
T4	8.54	4.489	16.244	<.0001
N Stage (ref=unreported)				
N0	0.677	0.428	1.071	0.0953
N1 - N3	10.762	6.258	18.508	<.0001
M Stage (ref=unreported)				
M0	0.503	0.331	0.765	0.0013
M1	13.966	10.072	19.364	<.0001
Tumour Size (ref=unreported)				
0 - 1.9 cm	0.178	0.069	0.462	0.0004
2 - 4.9 cm	0.606	0.24	1.534	0.2907
> 5 cm	0.802	0.306	2.101	0.6528

Table 10. Bivariate associations for prostate cancer mortality in non-visible minority Canadian men diagnosed between 2004-2007 in the 1991 CanCHEC. ref: Reference.

Parameter	Hazard Ratio	95% Hazard Ratio Confidence Limits		p-value
Age	1.105	1.084	1.127	<.0001
Education (ref=No high school)				
Highschool	0.753	0.419	1.351	0.3411
Post-secondary non-university or university	0.411	0.212	0.799	0.0087
Canadian Region of Diagnosis (ref=Central Canada)				
Other	1.218	0.61	2.431	0.576
West Coast (BC)	0.998	0.496	2.008	0.9961
Immigrant (ref=not an immigrant)	0.78	0.366	1.663	0.5201

Table 11. Bivariate associations for prostate cancer mortality among visible minority Canadian men diagnosed between 2004-2010 in the 1991 CanCHEC. ref: Reference. HR: Hazard ratio. CI: Confidence interval.

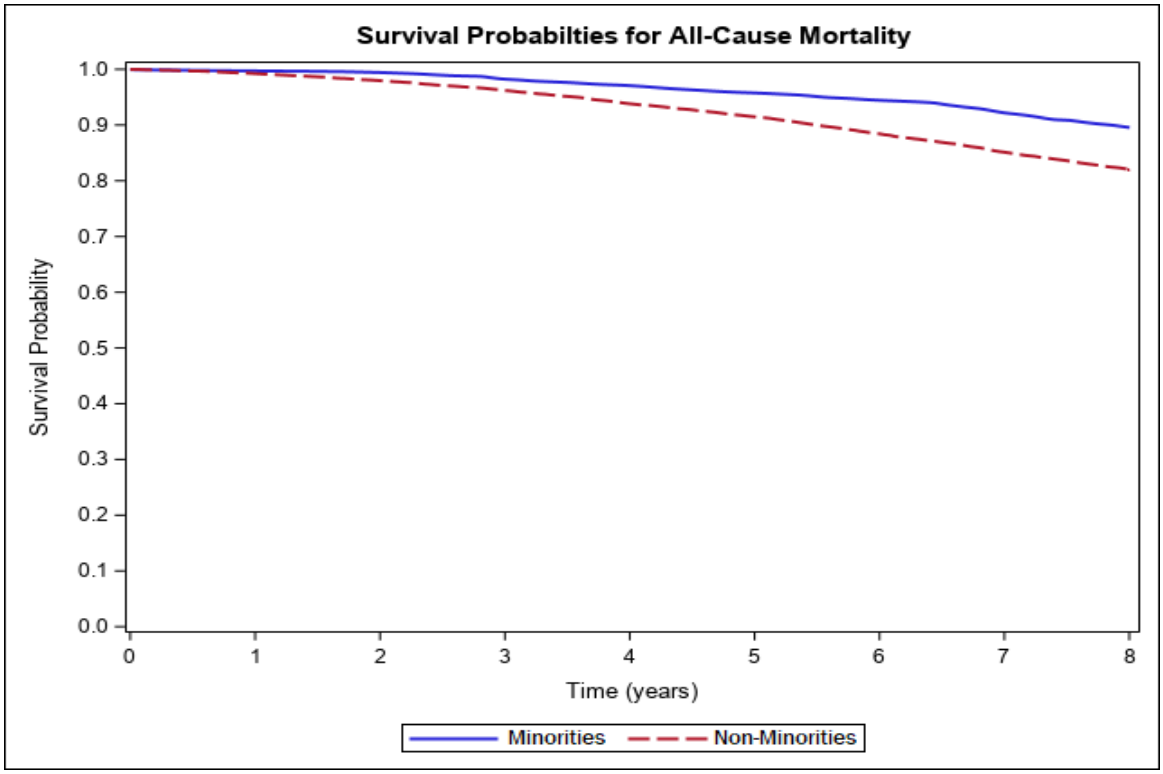

Figure 8. Survival probabilities for all-cause mortality among visible (diagnosed 2004-2010) and non-visible minority (diagnosed 2004-2007) men diagnosed with prostate cancer in the 1991 CanCHEC.

Discussion

This study was the first to investigate the impact of immigration status on prostate cancer-specific mortality using the CanCHEC data. Our findings suggest that although the CanCHEC gives access to the variables necessary, the data is too immature for proper analysis. The dataset has a maximum follow-up of six years and has 77.5-78.8% of tumor characteristics missing in both visible and non-visible minority cohorts. Due to the short follow-up and low sample size currently available no meaningful conclusions can presently be drawn.

11 580 non-visible minority Canadians were diagnosed with prostate cancer between 2004-2007, with 1 095 dying from the disease. With an adequate sample size in this cohort we were able to utilize grading and staging information available in the CanCHEC. In this population, and in line with the endorsement by the American Joint Committee on Cancer, prostate cancer-specific mortality increased with increasing grade and TMN stage.[26]

In our sample, 881 immigrant Canadians with prostate cancer died with 385 dying from prostate cancer. Of the men that died of prostate cancer only 50 were from the visible minority cohort. Additionally, nearly 80% of the patients who did die had missing pathology data. The high rate of missing pathology data coupled with the low mortality rate resulted in significant changes to the initial research question in order to acquire data with a sample size large enough to satisfy Statistics Canada guidelines for publication. Importantly, this restricted us from publishing analyses capable of

stratification by ethnicity and immigration status we believe would be necessary to address the primary question of this project.

Major limitations to this study were small sample sizes, missing data, and a short follow-up period. Prostate cancer is known to have a long, indolent course. A Swedish study which looked at the natural history of prostate cancer over a 21-year period in patients with low-grade disease found a substantial increase in prostate cancer-specific mortality over time.[131] Analysis of 21-year follow-up data found prostate cancer-specific mortality nearly tripling – from 15 per 100 000 person-years six years prior, to 44 per 100 000 person-years.[131] Among the immigrant men in the CanCHEC there are over 130 000 Europeans, 18 000 Chinese and 14 000 South Asians.[132] With time, the data from these cohorts will continue to mature. We believe that with a longer period of study and follow up, coupled with complete pathology data the CanCHEC dataset may be powered to assess the impact of immigration on prostate cancer mortality in Canada.

Our results show no evidence of a healthy immigrant effect in both all-cause and cancer-specific mortality. This is contradictory to previous studies using both Canadian administrative and census data. Ontario-specific hospital administrative data has been used to demonstrate a lower all-cause and cancer-specific mortality among immigrants as compared to native Canadians diagnosed with one of six index cancers, though data was not stratified by cancer type.[133] Similarly, the Canadian Census Mortality and Cancer Follow-up Study looked at all-cause mortality among Canadian immigrants and found lower mortality rates among immigrants compared to Canadians; however, marked differences between country of origin were seen.[134] The significant censoring, missing

data and subsequent small sample sizes currently available likely makes CanCHEC underpowered to address these questions.

With the deficiencies noted above corrected, the CanCHEC data may eventually have the ability to further stratify the effect of immigration on mortality by ethnicity and cancer type. Ultimately, this could provide insight into underlying genetic, environmental, and socio-economic determinants of health in Canada.

Conclusion

In conclusion, the current CanCHEC data is too underpowered and immature to assess the impact of immigration on prostate cancer mortality in Canada. Nonetheless, it remains a unique and powerful dataset with significant potential as it encompasses high-level demographic, cancer, and survival data in a first-world, single-payer system. Given the long time-course needed to see significant survival differences in prostate cancer it is unsurprising that the short follow-up and missing pathology data available through the CanCHEC is unable to properly assess the impact of immigration on prostate cancer mortality in Canada. Future efforts to expand captured pathologic data, coupled with the results from longer follow-up, may improve the power of CanCHEC and identify disparities between immigrant and Canadian populations.

CHAPTER 5:
General conclusions and future directions

This research project is the first which attempts to use the CanCHEC dataset to determine the impact of ethnicity and immigration on prostate cancer mortality in Canada. As one of the largest person-based datasets in Canada the CanCHEC reflects enough statistical power to reliably detect rare events in small populations. This study aims to add longitudinal data, from a diverse population in a single-payer healthcare system, to a debate inundated with poor-quality data.

Our first study on the impact of ethnicity on prostate cancer mortality in Canada provided some support as well as some challenges to previously held certainties in prostate cancer epidemiology. Our study supports the notion that South and East Asian communities may have a biologically distinct form of prostate cancer, resulting in improved outcomes. Previous studies which investigated ethnic differences in the presentation and outcomes of prostate cancer observed that, while Asian men often present with more advanced and higher risk disease, no difference or improved outcomes are observed as compared to white men.[127,135,136] The largest genetic study, which was performed by the International Consortium for Prostate Cancer Genetics, used pooled data and statistical modelling to use linkage analysis to identify loci which impart increased risk for developing prostate cancer. Unfortunately, less than 2% of the data was comprised of Asian families, making application of the identified linkages to the Asian population questionable.[137] Smaller studies of Asian men have identified other potentially provocative and protective loci, however the impact of these loci remains unclear.[127,138,139] Given the marked heterogeneity and likely polymorphic nature of

prostate cancer, separating legitimate protective factors from false signals remains exceedingly difficult.

Our study also identified no increased risk of prostate cancer mortality among black Canadians. Traditionally, black men have been considered a high-risk population for prostate cancer with early and aggressive disease seen in black Americans, and high rates of prostate cancer mortality seen in predominantly black African and Caribbean countries.[15,63] Efforts to understand the source for these disparities have suggested social, genetic, and environmental factors, though few definitive factors have been proven. Similar to Asian men, there is an under-representation of black men in genomic studies.[140] This has resulted in a poor understanding of any underlying genetic mechanisms which result in the observed increased mortality rates. Several studies which look at ethnic variations of prostate cancer mutations have found significant differences in allelic frequency which correspond with the presumed risk of prostate cancer, with Asian men having lowest rates of polymorphisms and African men having higher rates compared to Caucasian men.[141]

While these patterns were identified, the significance of these genotypic variations and how they impact prostate cancer biology remain unknown. Therefore, the conclusions that observed mutations in black men result in more aggressive disease assumes that black men are in fact at increased risk of aggressive disease. Results from our study contradict these assumptions and stress the importance of social determinants of health. In a single-payer, universal healthcare system, black men appear to have no increased risk of prostate cancer. These results concur with contemporary analysis of

American datasets which show no significant differences in prostate cancer mortality among black Americans once confounding variables – most importantly socioeconomic status and access to healthcare – are controlled.[116]

Our study defined ethnicity as the ancestral and cultural roots of an individual, as self-selected in the 1991 census, leaving the onus on the individual to select (or write in) one or more of the provided ethnic groups. Using this definition may further confound the issue by grouping individuals from similar, but certainly distinct genetic backgrounds. For example, the non-visible minority cohort pools all individuals of minority status including those of European, Irish, Scottish, and Scandinavian descent without further stratification. Similarly, all Black men are treated as a single entity, despite having unique cultures, ethnic practices, and genetic makeup. It is certainly possible that the differences seen in our results compared to previously published studies lie in a unique Canadian population. Canada has a lower proportion of Caribbean Black men, with just over 40% identifying as Caribbean on the 2006 census whereas the American population has a more even representation at 53% African and 47% Carribean.[93,142] Previous genetic analyses have found African American and Caribbean communities carry distinct markers as admixed groups – deriving genetic components from both Western African and European origins. African American communities show 70-80% African ancestry whereas Caribbean communities have higher rates as high as 80-90%.[143,144] Both groups also contain differing rates of heterogeneity and Asian ancestry. To date no comparable study has been performed in the Canadian population. If one is to believe that certain groups have a genetic predisposition for certain disease traits, pooling distinct

communities into “Black”, “Asian”, and “Other” does researchers a disservice as it confounds the data and masks the results.

CanCHEC has the ability to stratify beyond ethnicity to country of origin. With longer follow-up and increasing sample size the potential exists to explore the impact of individual sub-regions on prostate cancer mortality. By identifying at risk and protected communities one can more closely investigate whether it is underlying genetics, environmental, or social factors such as PSA screening rates, driving the observed mortality differences.

A significant limitation to using the CanCHEC to investigate the impact of ethnicity on prostate cancer mortality is the inability to identify and to control for family history. Given the known propensity for not only an increased incidence, but more aggressive familial-linked prostate cancer the inability to control this factor adds in an uncontrolled confounding variable.[30] An over-representation of non-visible minority individuals with a family history or an underrepresentation among visible minority groups may be falsely elevating the mortality rate seen in the non-visible minority group or falsely decreasing the rate seen in the Black population.

The 1991 CanCHEC is a powerful and under-utilized tool that can identify disparities in mortality rates across geographic, ethnic, and socio-economic groups.[107] To date, the dataset has been used to investigate a variety of subjects, ranging from the effects of profession on cancer risks, to the impacts of pollution, ethnicity, or living near green spaces and overall mortality.[145,145–151]

Given the power of the dataset, we investigated the impact of immigration on prostate cancer mortality. Unfortunately, significant sample size limitations impaired our ability to draw any meaningful conclusions. It is important to note that while our current attempt failed, future attempts to address the impact of immigration on cancer mortality using the CanCHEC may succeed through increased sample size and longer follow-up. The number of individuals captured by each CanCHEC cohort continues to climb – from 2.6 million in 1991, to 6.5 million in 2011.[152] This increased sample size, in conjunction with long-term follow-up, may sufficiently power CanCHEC to draw more conclusive results, despite prostate cancer's long latency period.

Another significant limitation to investigating the impact of immigration on prostate cancer mortality in Canada using the CanCHEC data was the high degree of missing pathological data – as high as 79% in our sample. Efforts to reduce this missing data, coupled with increased sample size and long-term follow-up, may allow for a more definitive evaluation.

Statistics Canada continues to actively link datasets as new research questions and data gaps are identified. Following a needs assessment identifying the value of linking treatment data to cancer outcomes, the Canadian Cancer Treatment Linkage Project pilot was formed. The goal of the pilot was to investigate the feasibility of linking the Canadian Cancer Registry to the Discharge Abstract Database (DAD) and National Ambulatory Care Reporting Systems (NACRS). The project was able to successfully link over 90% of files, with linkage rates improving with more recent data.[153] CanCHEC datasets from 2006 onwards have been linked to the DAD, and the 2011 cohort has

been linked to the NACRS. Adding treatment data, ideally with pathology data, may provide more insight into the observed differences in prostate cancer mortality across different groups.

CHAPTER 6:
Conclusions

In conclusion, this study was the first to use the CanCHEC to investigate the impacts of ethnicity and immigration on prostate cancer mortality in Canada. Our study found that Asian ethnicity had a protective effect, while Black men showed no increased rates of prostate cancer-specific mortality. In its current form, the CanCHEC is under-powered to investigate the impact of immigration; however, this may improve with longer follow-up and improved data linkages. This study demonstrates the difficulties and the significant risks drawing conclusions from observational data and the power of CanCHEC to challenge previously accepted dogma and to investigate rare outcomes on a national level.

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Curriculum Vitae

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Post-secondary education and degrees

2018-2022 (expected)	**FRCSC** Urology, Western University, London ON
2019-2020	**MSc** Surgery, Western University, London ON
2014-2018	**MD** Schulich School of Medicine and Dentistry, London Ontario
2010-2014	**BSc** (Hons) Life Sciences Specialization, Queen's University, Kingston ON

Honours and awards

2019	Dr John Denstedt Masters' of Surgery Research Excellence Award
2019	Surgery Tuition Award
2017	Western Graduate Research Scholarship
	Best Student/Fellow Presentation JK Wyatt Urology Residents Research Day
2014	Peer Reviewed Poster Award, Biomedical and Molecular Sciences Research Day
2014	Pharmacology and Toxicology prize for Proficiency in Research Course
2011	Dean's Special Award

Research Grants

2019	Resident Research Grant: The impact of immigration on genitourinary cancer incidence in Canadian communities

Related work experience

2018-present	Urology resident, London Health Sciences Centre

Publications

Nair S, **Stern N**, Dewar M, Siddiqui K, Smith E, Gomez AJ, Moussa M, Chin J. *Salvage open radical prostatectomy for recurrent prostate cancer following MRI-guided transurethral ultrasound ablation (TULSA) of the prostate: Feasibility and Efficacy*. Scand J Urol 2020;1-5; doi:10.1080/21681805.2020.1752795

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