Temporal Changes in Prostate Biopsy Use in Ontario

Luke T. Lavallée MD, FRCSC

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Department of Epidemiology and Community Medicine
Faculty of Medicine
University of Ottawa

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Abstract

1.1 Introduction

The over-diagnosis and over-treatment of prostate cancer is a major public health concern, and in 2012 the United States Preventive Services Taskforce (USPSTF) recommended against prostate cancer screening. Prostate cancer is usually detected by performing a prostate biopsy. Previously, many men received a biopsy at the first sign of an elevated cancer risk identified by screening. Currently, physicians have more tools are their disposal to select men for biopsy who are likely to have clinically significant cancers, including repeat prostate specific antigen (PSA) testing, PSA density, PSA velocity, PSA free/total ratio, and age-specific cutoffs. These tests allow physicians to reduce the number of unnecessary biopsies performed on lower risk patients. One would expect that the use of these tests, in addition to more selective screening, would decrease the incidence of prostate biopsies in the population.

I hypothesized that in the last 10 years in Ontario: 1) the incidence of prostate biopsy has decreased, 2) the proportion of biopsies that are malignant has increased, and 3) patients receiving biopsies are healthier.

1.2 Methods

I performed a secondary analysis of population-based administrative databases. I validated the prostate biopsy procedure code in the Ontario Health Insurance Plan (OHIP) then used this code to create a cohort of Ontario men who received their first prostate biopsy between 1992 and 2012. Crude and age standardized incidence rates of prostate biopsy were determined for each study year. Era-specific inter-censal population estimates from Statistics Canada were used to

establish the number of men at risk of biopsy each year. Changes over time in prostate biopsy incidence were examined using negative binomial regression by comparing the biopsy incidence of each year to a referent year expressed as incident density ratios. Similar analyses were performed to examine changes over time in the proportion of biopsies that are malignant and the health status of patients receiving biopsy. Health status was determined by calculating the Aggregated Diagnosis Group (ADG) score for each patient.

1.3 Results

The sensitivity of the OHIP prostate biopsy code improved during the study period and was approximately 90% in recent years. The specificity for identifying the first prostate biopsy a patient received was estimated to exceed 95%. The crude and age standardized incidence of prostate biopsy in Ontario gradually increased between 1992 and 2007 and then dropped sharply in 2008 and 2012. Overall, 39% of biopsies were malignant but this proportion increased during the study period. The health status of patients receiving biopsy, as measured by the ADG score, improved over the study period.

1.4 Conclusions

This is the first study to report crude and age standardized prostate biopsy incidence in a population. We found that previously rising biopsy rates decreased significantly in 2008 and 2012 in conjunction with changes to the perceived utility of prostate cancer screening. More years of follow up are required to determine if these changes were transient or the start of broad practice changes.

2 Legend

ADG	–	Aggregated Diagnosis Group
CIHI	–	Canadian Institute for Health Information
DAD	–	Discharge Abstract Database
ERSPC	–	European Randomized Study for Screening of Prostate Cancer
ICES	–	Institute for Clinical Evaluative Sciences
LHIN	–	Local Health Integration Network
LR	–	Likelihood ratio
NACRS	–	National Ambulatory Care Reporting System
OCR	–	Ontario Cancer Registry
OHIP	–	Ontario Health Insurance Plan
OHREB	–	Ottawa Hospital Research Ethics Board
OHRI	–	Ottawa Hospital Research Institute
OMHRS	–	Ontario Mental Health Reporting System
PPV	–	Positive predictive value
PSA	–	Prostate Specific Antigen
RPDB	–	Registered Persons Database
TAC	–	Thesis Advisory Committee
TRUS	–	Trans-rectal ultrasound

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4 Introduction

4.1 Epidemiology of prostate cancer

Prostate cancer is the most common solid organ malignancy in men, with 1 in 6 currently receiving the diagnosis during their lifetime [1]. However, many prostate cancers are classified as low-risk and are unlikely to impact a patient's quality or duration of life. The over-diagnosis and over-treatment of low-risk tumors is a concern [2].

4.2 Prostate cancer screening – a changing landscape

Population-based prostate cancer screening has occurred since the introduction of the serum prostate specific antigen (PSA) test in the 1990's. PSA screening led to a dramatic increase in the number of prostate cancers diagnosed, a decrease in the proportion of prostate cancers that had an advanced stage, and a decrease in prostate cancer-specific mortality [3]. While screening seemed to result in early disease detection, the detection of clinically indolent tumors is concerning because the diagnosis and treatment of these low-risk patients has unclear benefits and may result in patient harm. Indeed low-risk cancer patients may have anxiety due to their diagnosis, morbidity from their prostate biopsy, and morbidity from their cancer treatments.

Over the last decade, three randomized controlled studies and numerous observational studies have indicated that screening does not benefit all men [4–6]. These data have led many to question the benefit of population-based prostate cancer screening programs. Specifically, there seems to be a limited benefit of using PSA to screen men over 70 or those with less than a 10 to 15 year life expectancy. Because of the known risks of prostate cancer screening and unclear

benefits, some groups have recommended completely *against* screening for all men [7,8]. There is currently a lack of consensus by medical organizations on the best approach for prostate cancer screening [9].

4.3 Screen-positive patients – uncoupling screening and prostate biopsy

Critical to the performance of any screening test is the appropriate use and interpretation of test results. The definitive diagnosis of prostate cancer is usually made by performing a trans-rectal ultrasound (TRUS) guided prostate biopsy. Prostate biopsies are associated with physical morbidity and may be a source of anxiety for patients [10,11]. The indications for prostate biopsy are poorly defined, but it is usually prompted by an 'abnormally elevated' PSA blood concentration or abnormal physical examination (digital rectal examination). Previously, many men received a biopsy if there was any elevation in PSA above a concentration threshold. Currently, physicians may be more discriminative in selecting patients for biopsy by using other factors such as repeat PSA testing; PSA density (PSA concentration/prostate volume), and PSA kinetics; PSA Free/Total ratio, and age-specific PSA thresholds [12,13]. One would expect that the use of these ancillary factors, in addition more refined patient selection for screening, would decrease the number of prostate biopsies being performed over time in a particular population.

5 Study proposal to define current practice patterns for prostate biopsy in Ontario

I believe that the incidence of prostate biopsy is decreasing in Ontario due to: i) a lack of clear benefit of prostate cancer screening ii) more selective biopsy referrals by physicians and iii) a greater awareness of the risks of over-diagnosis and over-treatment of prostate cancer. I also believe that more careful selection of men for biopsy has increased the proportion of biopsies that are malignant. Finally, I believe that the health status (life expectancy) of men receiving biopsy has improved over time since urologists (and, possibly, other physicians) are selecting men who are more likely to benefit from treatment [14].

This study will describe the use of prostate biopsy in Ontario over time to determine if physician practices are changing. Specifically, it will determine if the following statistics have changed over time: i) incidence of prostate biopsy (primary outcome); ii) proportion of biopsies that are malignant (secondary outcome); iii) health status of men receiving biopsy (secondary outcome).

5.1 Significance of the proposed thesis

Characterizing the use of prostate biopsy at a population-based level will inform health care providers and administrators. Clinicians will benefit from a greater understanding of population-level practice patterns because they will see the impact of changes in their practice patterns at a population level. Health care administrators may use these data to understand the impact of changes in physician behavior and improve resource allocation or identify trends requiring attention via policy change or education.

Population level statistics regarding prostate cancer incidence and mortality are available from Ontario and other jurisdictions [1,15]. This study will augment these data in several ways. First, it will examine prostate cancer incidence over a time period in which prostate cancer screening recommendations, and possibly practice patterns, have changed [8]. Second, it will examine if clinicians are selecting men in better health to receive biopsy in response to data indicating these men are more likely to derive benefit from the diagnosis and treatment of prostate cancer. Third, the proportion of biopsies that are malignant over time will provide indirect evidence that physicians are using PSA kinetics or other methods to better select men for biopsy.

6 Study questions and hypotheses

6.1 Study questions

- Are administrative codes in the Ontario Health Insurance Program (OHIP) for prostate biopsy valid to identify men who receive a prostate biopsy in Ontario?
- Is the incidence of prostate biopsy in Ontario decreasing?
- Is the proportion of malignant prostate biopsies increasing?
- Is the health status of Ontario men undergoing prostate biopsy improving?

6.2 Study hypotheses

- Administrative billing codes in OHIP for prostate biopsy are valid for identifying men who receive a prostate biopsy in Ontario.

- The incidence of prostate biopsy has decreased in Ontario in the last 10 years.
- The proportion of malignant prostate biopsies has increased in Ontario in the last 10 years.
- The health status of men receiving prostate biopsy has improved in Ontario in the last 10 years.

7 Study methods

7.1 Study design

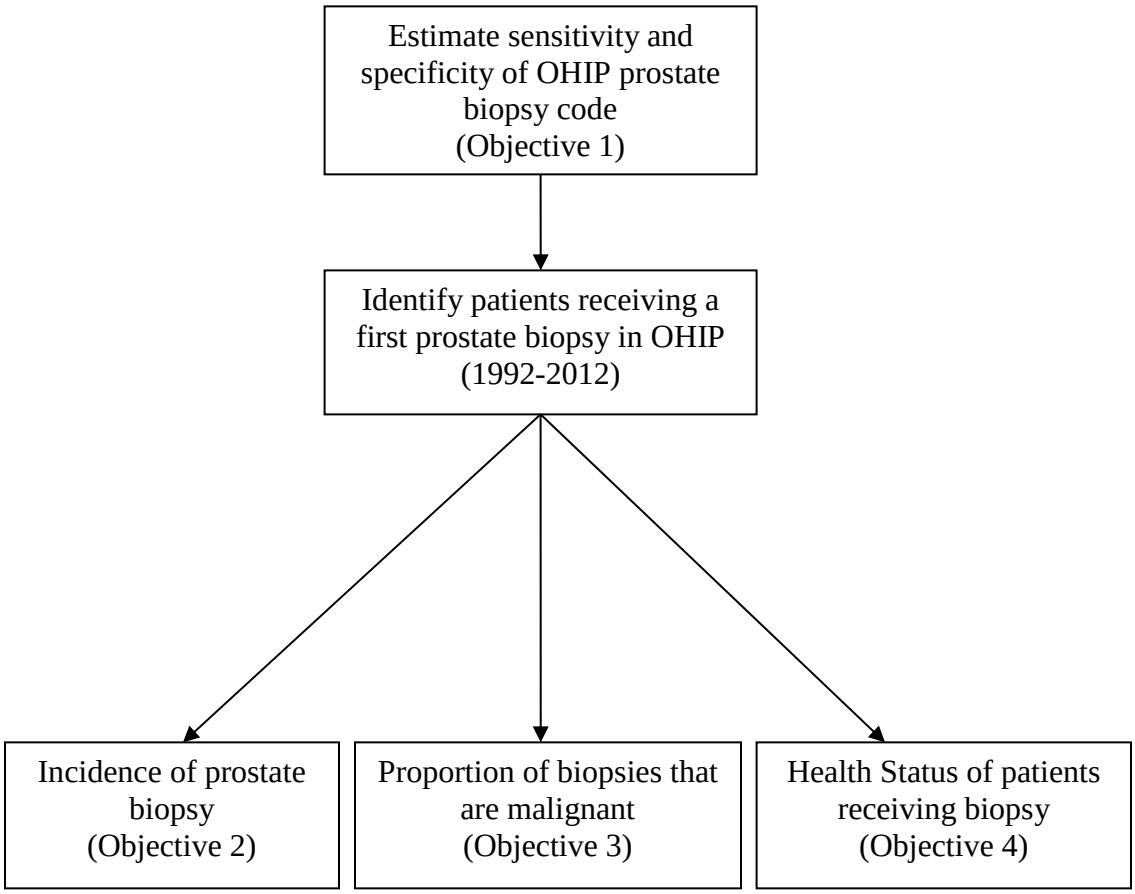
This study was a secondary analysis of population-based administrative databases. A cohort of Ontario men who underwent prostate biopsy was identified using health administrative data housed at the Institute for Clinical Evaluative Sciences (ICES). These databases were linked deterministically using encrypted health care numbers.

7.2 Study objectives

- **Objective 1** - Determine the validity of administrative codes in OHIP for identifying men who received a prostate biopsy in Ontario.
- **Objective 2** - Determine if the incidence of prostate biopsy in Ontario has changed between 1992 and 2012.
- **Objective 3** - Determine if the proportion of prostate biopsies that are malignant has changed between 1992 and 2012.
- **Objective 4** - Determine if the health status of men undergoing prostate biopsy in Ontario has changed between 1992 and 2012.

A study flow chart is presented in **Figure 1**.

Figure 1: Study flow chart



7.3 Data sources

Two data sources were used in this study. The majority of analyses were performed using datasets housed at the Institute for Clinical Evaluative Sciences (ICES). A portion of Objective 1 (prostate biopsy code validation) used data from The Ottawa Hospital Department of Radiology procedure records.

ICES houses population-based collections of administrative datasets concerning health care physician services claims, health care encounters, cancer diagnoses, and surgical procedures [16]. Most datasets start in July 1991. The Ontario Health Insurance Plan (OHIP) database records all remunerated health-care services provided in Ontario and records patient identifiers, physician identifiers, service date, and service identifier. The Discharge Abstract Database (DAD) records demographic, diagnostic, and procedural data for all hospital encounters. The Registered Persons Database (RPDB) records demographic information and date of death for all Ontarians. The Ontario Cancer Registry records all primary cancer diagnoses (and certain second cancers) and the diagnosis source and is complete through December 2012. Finally, the National Ambulatory Care Reporting System (NACRS) records all visits to emergency departments starting in 2002 [14].

The Ottawa Hospital Department of Radiology procedure records were used to identify all patients at The Ottawa Hospital for whom a prostate biopsy procedure code was submitted to OHIP. This database is prospectively maintained by the Department of Radiology and is comprehensive.

7.4 Validating the prostate biopsy code(s) in the Ontario Health Insurance Plan database (Objective 1)

The first objective of this study was to determine if the prostate biopsy procedure code (Z712) in the Ontario Health Insurance Plan (OHIP) was valid for identifying patients who received a prostate biopsy in Ontario. The code is considered valid if it accurately identifies prostate biopsies being performed. If validated, this code can be used to determine the incidence of prostate biopsy in Ontario.

To examine population incidence using administrative data in a valid way, the code used to determine incidence must have a high positive likelihood ratio (+LR). A high +LR indicates that a patient who has the code in the administrative dataset has a high likelihood of actually having undergone the procedure, in this case prostate biopsy. The +LR is calculated with the following equation:

Equation 1: Positive likelihood ratio (+LR)

$$Positive\ Likelihood\ Ratio = \left[\frac{Sensitivity}{(1 - Specificity)}\right]$$

In this equation, "sensitivity" is the proportion of prostate biopsies that had the procedure code and "specificity" is the proportion of men *without* prostate biopsy who *did not* have the procedure code. Therefore, administrative codes should have both a high sensitivity and a high specificity to produce a large +LR and be considered valid.

7.4.1 Determining the sensitivity of the Ontario Health Insurance Plan prostate biopsy procedure code (Z712)

The first step for determining the sensitivity of the code was identifying a gold standard (reference) cohort against which the code can be compared. All index cancer diagnoses in Ontario are recorded in the Ontario Cancer Registry (OCR). The source of the diagnosis is also recorded (e.g. histology, cytology, cancer clinic chart, etc.). The OCR is a regulated registry and has been previously shown to be highly accurate. I identified all men in Ontario whose prostate cancer diagnosis was based on histology using the DXCONFIRM variable in OCR. Duplicate records were excluded. This created a cohort of patients with pathologically confirmed prostate cancer based on tissue histology. This cohort was used as the **gold standard reference group** to measure the sensitivity of the OHIP prostate biopsy procedure code (Z712) in Ontario.

The OHIP database was queried to identify all prostate biopsy procedures billed using code **Z712 (the code to be validated)** in Ontario during the study period. Duplicate codes billed on the same day for the same patient were excluded. Patients and procedures identified in OHIP were deterministically linked to the gold standard reference cohort of histologically confirmed prostate cancers using unique ICES key numbers.

I then determined the proportion of patients with histologically confirmed prostate cancer who had a Z712 code submitted to OHIP within 1 week of their prostate cancer diagnosis. With the terminology presented in **Table 1**, I calculated the sensitivity of the prostate biopsy code using **Equation 2**:

Table 1: Methods used to calculate the sensitivity of the OHIP prostate biopsy code (Z712)

		Prostate Cancer histologic diagnosis in OCR (gold standard)	
		+	**-**
Code Z712 in OHIP (Code to be validated)	**+**	**A - True Positive (Available)**	B - False Positive (Not applicable)
	-	**C - False Negative (Available)**	D - True Negative (Not applicable)

Equation 2: Sensitivity

$$Sensitivity = \left[\frac{True\ Positives}{True\ Positives + False\ Negatives}\right] * 100\%$$

Sensitivity was calculated for the entire cohort and also stratified by year. Additional sensitivity analyses were performed to determine if varying the time interval for detecting a prostate biopsy code before and after the histologic cancer diagnosis would change the sensitivity of the code. Intervals of 14 and 21 days were used.

A proportion of patients with a histologic diagnosis of prostate cancer in the OCR did not have a prostate biopsy code recorded in OHIP. While a histologic diagnosis of prostate cancer is most commonly derived from prostate biopsy tissue, other sources of tissue may provide histologic confirmation of disease including specimens from: a trans-urethral resection of the prostate (TURP), cystoscopy with trans-urethral prostate biopsy, or biopsy/resection of tissue from another part of the body if metastatic disease is present. Patients who have a histologic diagnosis confirmed using one of these alternative tissue sources would not be expected to have a prostate biopsy code in OHIP within 1 week of their diagnosis. These patients would be inappropriately included as **false negatives** in the sensitivity calculation (**Table 1**).

To incorporate these data in my calculation of code sensitivity, I used two methods to examine additional OHIP codes for patients that did not have an OHIP prostate biopsy code. First, for these patients, I examined all the OHIP codes recorded within 1 week of their prostate cancer diagnoses in the OCR. I then arranged these in order of descending frequency to identify the **most common non-prostate biopsy OHIP codes** that may have led to the histologic diagnosis of prostate cancer. Second, I created a list of all alternative **OHIP codes that may be associated with the provision of prostate tissue** (e.g. trans-urethral resection of the prostate) and thus may represent the source used for histologic confirmation of prostate cancer. The list of alternative codes was created using the Ontario Ministry of Health and Long Term Care Schedule of Benefits [17]. This list included two diagnostic imaging codes (intracavitary ultrasound and ultrasound guided biopsy) since these are usually performed at the time of prostate biopsy and may have been submitted by providers in place of the prostate biopsy procedural code.

OHIP codes identified using each of these two methods were compared and a final set of alternative codes was created. This set of codes was applied to the cohort of men with an OCR histologic diagnosis of prostate cancer who did not have an OHIP prostate biopsy code. I identified patients for whom any one of these OHIP codes was recorded within 1 week of their prostate cancer diagnosis. Each patient could only be counted once. Patients who had one of these codes billed within 1 week of histologic diagnosis of prostate cancer were removed from the denominator of the sensitivity equation for the prostate biopsy (Z712) code (**Equation 2**) because they had alternative explanations (i.e. non-prostate biopsy sources) for their diagnosis. The resulting new sensitivity was termed the **corrected sensitivity** of the code.

7.4.2 Determining the specificity of the Ontario Health Insurance Plan prostate biopsy procedure code (Z712)

As stated in section 7.4, to be valid a code must have a high positive likelihood ratio (+LR). The +LR is exquisitely sensitive to changes in specificity. As the specificity approaches 1, the +LR increases dramatically, and thus so does the validity of the code (**Equation 1**). Specificity is calculated using the following equation:

Equation 3: Specificity

$$Specificity = \left[\frac{True\ Negatives}{True\ Negatives + False\ Positives}\right] * 100\%$$

It was not possible to identify true negatives (exclude prostate biopsy in men without a prostate biopsy code) or false positives (men with the prostate biopsy code who did not receive a biopsy) using population-based health administrative data. However, I was able to indirectly examine the specificity of the prostate biopsy code by determining **the positive predictive value (PPV)** of the code in a separate study cohort. PPV is calculated using the equation:

Equation 4: Positive predictive value (PPV)

$$Positive\ Predictive\ Value = \left[\frac{True\ Positives}{True\ Positives + False\ Positives}\right]$$

Determining the PPV requires identification of true positive (code for prostate biopsy present and patient received a prostate biopsy) and false positive cases (code for prostate biopsy present but patient did not receive a prostate biopsy). The **false positive rate** derived from the PPV calculation can be used to examine the specificity of the code; this is because, as the false positive rate decreases to zero, the specificity approaches 1 (**Equation 3**). In other words, a code that has a very high positive predictive value (because it has a small number in the B-cell of the 2x2 contingency table - **Table 2**) will invariably have a very high specificity (since it is the number in the B-cell that determines the specificity value). The specificity is usually higher than the positive predictive value in 2x2 contingency tables since the proportion of subjects in the population *without* the condition (i.e. the sum of the B-cell and the D-cell) usually exceeds those *with* the condition (i.e. the sum of the A-cell and C-cell). In such a case, the value of the B-cell will decrease the positive predictive value to a much greater extent than the specificity (because the sum of the A-cell and B-cell is usually much less than the sum of the B-cell and D-cell).

Therefore, the specificity will exceed the positive predictive value in the vast majority of situations. As such, I can use this information to infer that the specificity of the code of interest will usually exceed its positive predictive value.

7.4.3 Determining the positive predictive value (PPV) of the Ontario Health Insurance Plan prostate biopsy procedure code (Z712) in a cohort of patients at The Ottawa Hospital

I calculated the PPV of the prostate biopsy code using a cohort of patients for whom a prostate biopsy code had been submitted to OHIP. For all patients in this cohort, I reviewed the electronic medical record to verify if these patients had a biopsy recorded. I identified all men at The Ottawa Hospital for whom a prostate biopsy code (Z712) was submitted to OHIP between February 1st 2007 and October 30th 2014. The Ottawa Hospital is a tertiary care cancer referral center for a health region of approximately 1 million people. Prostate biopsies are performed by radiologists and all procedure codes are recorded and submitted using a central claims system. I obtained a patient identification number and procedure date for each prostate biopsy performed in the study period.

A stratified random sample was then created from the complete prostate biopsy cohort using the RAND( ) function in Microsoft Excel (Redmond, Washington). The electronic medical record of patients with the thirty smallest randomly generated numbers *from each year* was then reviewed to determine if they truly had undergone prostate biopsy. This was determined by reviewing all radiology reports for that patient on the day identified on the OHIP claim. Patients for whom the report identified a prostate biopsy was performed were classified as having had the

procedure (True positive). If a prostate biopsy had not been performed, I classified these as false positives, and I recorded the reason and/or alternative procedure identified from the report.

Table 2: Methods used to calculate the positive predictive value of the OHIP prostate biopsy code (Z712)

		Prostate biopsy recorded in medical record	
		+	**-**
Prostate biopsy code (Z712) submitted to OHIP	**+**	**A - True Positive (Available)**	**B - False Positive (Available)**
	-	C - False Negative (Not Applicable)	D - True Negative (Not Applicable)

These data allowed me to calculate the overall and year specific positive predictive value of the prostate biopsy code using **Equation 4**.

Next I used the false positive rate derived from the PPV to estimate the specificity of the prostate biopsy code using various simulation models. As explained in S**ection 7.4.2**, a low false positive rate usually results in a high specificity based on **Equation 3**.

7.4.3.1 Sensitivity analysis

In the validation cohort from The Ottawa Hospital, all prostate biopsies were performed by radiologists however this is not true of all centers in Ontario. The proportion of prostate biopsy codes submitted to OHIP by urologists and radiologists was determined overall and stratified by year so that we could determine how our specificity estimates apply to the Ontario population.

7.5 Incidence of prostate biopsy in Ontario (Objective 2)

7.5.1 Study cohort

I identified prostate biopsies performed in Ontario using procedure codes in the OHIP database. Characterization of prostate biopsy codes in OHIP performed in section 7.4 indicated that using fee code Z712 (needle biopsy of prostate) was the best way to identify prostate biopsies.

7.5.2 Exclusion criteria

Patients aged less than 40 are not frequently diagnosed with prostate cancer and are not typically included in prostate cancer screening cohorts and were excluded from this analysis. At the time of data extraction, OHIP had incomplete records for the years 1991 and 2013 so these years were excluded. Duplicate records for a biopsy performed on the same patient on the same date were also excluded.

Some patients receive greater than 1 prostate biopsy for cancer detection. Other patients receive greater than 1 biopsy after their diagnosis of cancer as part of an active surveillance program [18]. The purpose of this study was to examine prostate biopsy incidence in the context of prostate cancer screening; therefore, the study cohort was **limited to a patient's first prostate biopsy**.

Men may receive a diagnosis of prostate cancer prior to receiving a prostate biopsy. This may occur if they have tissue removed from other body sites (metastases) or from other surgical procedures that procure prostate tissue (ex: trans-urethral resection of the prostate). The diagnosis may also rarely be made on the basis of overwhelming clinical indicators including but

not limited to: a highly elevated prostate specific antigen level (PSA) or convincing physical exams/imaging study. **Men with a diagnosis of prostate cancer registered in the OCR prior to their first biopsy were excluded**.

7.5.3 Crude incidence of prostate biopsy

The **crude number** of prostate biopsies performed in Ontario each year from January 1992 to December 2012 was determined. Incidences were stratified by age groups starting at age 40 using 5 year intervals. Men aged 90 and above were grouped together. The proportion of annual biopsies contained in each age group was also determined.

To ensure I had complete OHIP data for the entire study period up to December 2012, I explored monthly biopsy counts in OHIP for years 2011-2013. If monthly biopsy counts at the end of 2012 and beginning of 2013 were consistent (no significant unexplained drop) this would indicate that the data extracted from OHIP was complete, that is the data I extracted from OHIP included all biopsy codes from 2012, and any changes observed in the data are due to practice change rather than incomplete data.

To ensure the changes in biopsy counts over time were not due to the increase in sensitivity of the biopsy code observed over time, I calculated an adjusted biopsy count by dividing the biopsy count in a study year by the code sensitivity in the same study year; I termed this the **code sensitivity adjusted biopsy count** (**Equation 5**). For example, a biopsy count of 1000 biopsies using a code that had a sensitivity of 75% would actually be 1333 biopsies after applying the sensitivity-adjusted calculation (1000/0.75=1333); this would be equivalent to a biopsy count of 1200 with a code sensitivity of 90% (1200/0.90 = 1333). This adjustment should remove the influence of code sensitivity and allow me to compare biopsy counts in each year to

one another to ensure changes over time are due to practice changes and not changes in code characteristics in the database.

Equation 5: Code sensitivity adjusted biopsy count

$$Code\ Sensitivity\ Adjusted\ Biopsy\ Count = \left[\frac{Biopsy\ Count\ in\ Study\ Year}{Sensitivity\ of\ Biopsy\ Code\ in\ Study\ Year}\right]$$

The age-specific crude incidence of prostate biopsy was determined for each study year. The **numerator** was the unadjusted number of men having a prostate biopsy in each year for each age group. The **denominator** was the number of men alive at the start of the year in the given age group for each given year (**Equation 6**). The denominator was determined using year-specific census estimates for each age category from Statistics Canada [19]. Statistics Canada inter-censal population estimates for years between census years were used.

Equation 6: Crude incidence of prostate biopsy by age group and year per 100,000 men

$$Crude\ Incidence\ in\ Age\ Group = \left[\frac{Number\ of\ Prostate\ Biopsies\ in\ Age\ Groupd\ in\ Year\ X}{Number\ of\ Men\ in\ Age\ Group\ in\ Population\ in\ Year\ X}\right] * 100{,}000$$

Demographic changes in the underlying population of men who are eligible for prostate cancer screening may impact study results. The relative percent change in the male population of Ontario over time was calculated and expressed by age group and year using **Equation 7**. Values in each cell were derived to show the relative percent change in the population compared to the referent year 1992.

Equation 7: Relative percent change in population in the age group

$$Relative\ Percent\ Change\ in\ Population\ in\ the\ Age\ Group$$
$$= \left[\frac{Population\ in\ age\ group\ in\ year\ X - Population\ in\ age\ group\ in\ 1992}{Population\ in\ age\ group\ in\ 1992}\right] * 100\%$$

7.5.4 Age standardized incidence of prostate biopsy

Age standardized incidences were determined using **direct standardization**. Standardized incidences were determined for each study year from 1992 to 2012 and were stratified by age groups starting at age 40 using 5 year intervals. As before, men aged 90 and above were grouped together.

To calculate age standardized incidences, I first applied the same age group strata to census data for all Ontario men between 1992 and 2012 to create a **standard population**. In this standard population, I determined the proportion of men in each age group strata. This proportion was multiplied by the crude age group specific biopsy incidence rates in the study population in each year (expressed as number of biopsies per 100,000 men) to calculate the age standardized biopsy rate in each study year (**Equation 8**). Rates for all age groups are summed to calculate the overall age standardized biopsy rate for a given study year.

Equation 8: Age standardized incidence of prostate biopsy by age group and year per 100,000 men

$$Age\ Standardized\ Incidence\ in\ Age\ Group$$
$$= [Crude\ Incidence\ in\ Age\ Group * \%\ Standard\ Population\ in\ Age\ Group\ Strata]$$

This value was summed for each year to calculate the age standardized biopsy rate for each year. Crude and age standardized biopsy incidences were summarized in tables and figures. Overall and age- and year- stratified results are reported.

7.5.5 Incidence of prostate biopsy over time

Changes over time in prostate biopsy incidence were examined in two ways using the GENMOD procedure in SAS. The purpose of the first method was to determine the influence of time (study year) and patient age on biopsy incidence using regression models. The purpose of the second method was to identify the optimal model for predicting biopsy incidence using study year and patient age.

7.5.5.1 Method 1: Determine influence of study year and patient age on biopsy incidence

First, Poisson regression models were created that included parameters for study year (expressed as an ordinal **variable)** and patient age group. **Poisson regression** was then used to determine the **influence of year on biopsy incidence adjusting for patient age**. These models accounted for the number of men at risk within each year by including the log of this number (retrieved from Statistics Canada census data of Ontario) as an offset variable; therefore, the dependent variable in this model was the prostate biopsy incidence.

The exponent of the parameter estimate for each year was then compared to the exponent of the parameter estimate of the reference year (1992) to calculate the **incidence density ratio (IDR)** and 95% confidence intervals for each year compared to the referent (**Equation 9**). Here,

the IDR represents the prostate biopsy incidence in the year of interest compared to the biopsy incidence in 1992.

Equation 9: Incident density ratio calculation for year X compared to referent year (1992)

$$Incident\ Density\ Ratio\ (Year\ X\ vs\ 1992) = \left[\frac{Exp^{(Parameter\ Estimate\ of\ Year\ X)}}{Exp^{(Parameter\ Estimate\ of\ 1992)}}\right]$$

As previously mentioned, the log of the number of men at risk in the population (denominator) for each study year was used as the **offset variable**. The offset variable has a co-efficient of 1 and serves to fit the data to a per-person unit (i.e. it provides a unit of measurement for incidence). Count data cannot be negative; therefore the Poisson mean must be positive. The **log link function** was used to relate the expected value of the response variable (prostate biopsy incidence) to the predictor variable (age group and year). The log link function ensures the response variable remains positive and within an appropriate range for all predictors.

Poisson regression models assume that the population mean equals the population variance. When this is not true, a characteristic called 'overdispersion' or 'underdispersion' may be seen (with the former being much more common). In these cases, the population count does not have a Poisson distribution and the standard error estimate in the model will be inaccurate. To determine if the study population conformed to a Poisson distribution, I examined each Poisson model's **value/degree's of freedom (DF)** statistic (generated by GENMOD). The value/DF statistic measures how well the study distribution conforms to the Poisson distribution. If the value/DF statistic significantly exceeds 1, overdispersion is present (i.e. the observed variance is greater than the mean). If overdispersion is present, the risk of making a type 1 error with the model (erroneously rejecting the null hypothesis) is increased.

To deal with the presence of overdispersion, the **negative-binomial distribution** was used. The negative binomial distribution is a generalization of the Poisson distribution that allows the population variance to exceed the population mean, thereby providing more flexibility to the model. The negative binomial distribution assumes a Poisson distribution for the response variable and a gamma distribution for the parameter mean. The negative binomial distribution provides more accurate estimates of the standard error in this scenario (thereby minimizing the risk of a type 1 error).

The **risk of biopsy by age group** was also determined using incident density ratios. Each age group was compared to the 40-44 year age group (referent). These models adjusted for study year.

7.5.5.2 Method 2: Predicting biopsy incidence using study year and patient age

Poisson and / or negative binomial regression was used to model prostate biopsy rates as a function of patient age and study year. This analysis determined the best method to model study year. In these models, study year was expressed as a **continuous variable**. The age group 40-44 was used as the referent category. The log of the number of men at risk (denominator) in each year was used as the **offset variable**. The **log link function** was used to relate the expected value of the response variable.

Prior to performing the regression, I plotted the log-transformed counts of prostate biopsy over time for each age group. Visual inspection of the plot revealed a slight non-linear relationship between prostate biopsy counts and study year within the age groups. I therefore performed exploratory analyses using **fractional polynomial regression** (limited to a single parameter only) to model the data and determine what transformation of the year variable was

the best fit for the data. The study year variable was transformed using 8 different polynomial transformations (**Table 3**). Best fit was determined by minimizing the **Akaike information criterion (AIC) statistic** – which measures the relative quality of a model for a given dataset. Each transformation of the year variable was included individually and in combination with the original year variable in the model. The model that best fit the data (as measured with the AIC statistic) was deemed the best model for estimating biopsy incidence using patient age and study year.

Table 3: Polynomial transformations of year variable used to determine the model that best fit the study data

Mathematical transformation
$Year^2$
$Year^3$
$Year^{0.5}$
$\log(year)$
$Year^{-0.5}$
$Year^{-1}$
$Year^{-2}$
$Year^{-3}$

7.6 Proportion of first prostate biopsies that are malignant (Objective 3)

Patients with no prior history of prostate cancer who had their first prostate biopsy were identified in **Section 7.5**. This cohort was linked to the Ontario Cancer Registry (OCR) to determine if the biopsy resulted in a diagnosis of prostate cancer.

7.6.1 Identifying malignant prostate biopsies

Each prostate biopsy was classified as malignant or benign. A biopsy was classified as **malignant** if the patient receiving the biopsy had a diagnosis of prostate cancer recorded in the OCR 1 week before or after the biopsy date. The 1 week period before and after the biopsy was included to allow for variation in the method and timing used by clinicians for submitting claims to OHIP and variation in the dates recorded by pathologists when attributing the diagnosis date. If a diagnosis of cancer was *not* identified in the OCR in the specified time period the biopsy was classified as **benign**.

7.6.1.1 Sensitivity analyses:

Sensitivity analyses were performed to see if changing the timeframe before and after biopsy during which a diagnosis of cancer could be captured in the OCR would significantly change the number of biopsies that were classified as malignant. Time periods of 14, 21, 28, and 35 days before and after the biopsy date were analyzed. The number of cancer diagnoses for each

timeframe was recorded and compared. If using a longer timeframe increased the absolute number of cancer diagnoses by greater than 1% overall, this was considered significant.

7.6.2 Proportion of malignant prostate biopsies overall and stratified by age group

The proportion of malignant prostate biopsies was determined for each study year from 1992-2012 (**Equation 10**). Overall and age stratified proportions were reported starting at age 40 using 5 year intervals. Men aged 90 and above were grouped together.

The **numerator** was the number of biopsies classified as malignant each year. The **denominator** was the number of patients receiving their first prostate biopsy in the study year.

Equation 10: Proportion of malignant biopsies

$$Proportion\ of\ Malignant\ Biopsies = \left[\frac{Number\ of\ Malignant\ Biopsies\ in\ Study\ Year}{Total\ Number\ of\ Biopsies\ in\ Study\ Year}\right]$$

7.6.3 Proportion of malignant prostate biopsies over time

Changes over time in the proportion of malignant prostate biopsies were examined in two ways using the GENMOD procedure in SAS. The purpose of the first method was to determine the influence of time (study year) and patient age on the proportion of malignancy at biopsy using regression models. The purpose of the second method was to identify the optimal model for predicting malignancy at biopsy using study year and patient age.

7.6.3.1 Method 1: Determine influence of study year and patient age on the proportion of malignant prostate biopsies

First, Poisson regression models were created that included parameters for study year (expressed as an ordinal **variable)** and patient age group. **Poisson regression was** used to determine the influence of year on malignant biopsy rates independent of patient age. These models accounted for the number of men at risk by including the log of the number of biopsies performed (the denominator in incidence calculation) as an offset variable; therefore, the model's dependent variable was the proportion of biopsies that identified malignant disease.

The exponent of the parameter estimate for each year was then compared to the exponent of the parameter estimate of the reference year (1992) to calculate the **incidence density ratio (IDR)** and 95% confidence intervals for each year compared to the referent (**Equation 8**). Here, the IDR represents the risk of malignancy at first prostate biopsy in one year relative to the risk the comparison year.

The same regression methods were used as detailed in **Section 7.5**. The **log link function** was used to relate the expected value of the response variable (proportion of malignant prostate biopsies) to the predictor variables (age group and year).

To determine if the study population conformed to a Poisson distribution, we examined the Poisson model's **value/degree's of freedom (DF)** statistic (generated by GENMOD). To deal with the presence of overdispersion, the **negative-binomial distribution** was used.

7.6.3.2 Method 2: Predicting the incidence of malignancy at biopsy using study year and patient age

Poisson and/or negative binomial regression were used to model prostate biopsy data using age group and study year as predictor variables and malignant prostate biopsy counts as the outcome. This analysis determined the best method to model study year. In these models, study year was expressed as a **continuous variable**. The age group 40-44 was used as the referent category. The log of the number of men at risk (denominator) in each year was used as the **offset variable**. The **log link function** was used to relate the expected value of the response variable.

Prior to performing the regression, I plotted the log-transformed counts of malignant prostate biopsy over time for each age group and identified a non-linear relationship. I therefore performed exploratory analyses using **fractional polynomial regression** (limited to a single parameter only) to model the data and determine what transformation of the year variable was the best fit for the data. The study year variable was transformed using 8 different polynomial transformations (**Table 3**). Best fit was determined by minimizing the **Akaike information criterion (AIC) statistic**. Each transformation of the year variable was included individually and in combination with the original year variable in the model. The model that best fit the data (as measured with the AIC statistic) was deemed the best model for estimating malignant biopsy proportion using patient age and study year.

7.7 Health status of patients at first prostate biopsy (Objective 4)

7.7.1 Determining the health status of patients

The health status of patients receiving prostate biopsies in Ontario was characterized using the **ADG score**. The ADG score is a method of categorizing patients' medical conditions using administrative data. It serves a similar function to other common measures of patient health status such as the Charlson and Elixhauser comorbidity indices [20,21]. An advantage of the ADG score for this study is that is can be applied to both inpatient and outpatient populations using diagnostic codes from both health care environments. Furthermore, the ADG score has been validated in the Ontario administrative datasets I am using [22].

The ADG Score is a diagnosis-based method that classifies diseases using International Classification of Disease (ICD) codes in administrative health databases for physician services, hospital care, and emergency medicine care. ICD codes are obtained from both inpatient and outpatient medical settings. Each ICD code is assigned to 1 of 32 'Aggregate Diagnosis Groups'. Assignment is based on; disease severity, duration, etiology, certainty of diagnosis, and specialty care requirements [22,23]. For this cohort, three administrative health datasets were linked to calculate the ADG score of each patient: National Ambulatory Care Reporting System (NACRS), Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), and Ontario Health Insurance Plan (OHIP).

The ADG score was calculated for each patient at the time of their first prostate biopsy. The ADG score was calculated using encounters from the two years prior to the patients prostate biopsy. Patients with no medical encounters in the datasets in the two years prior to biopsy are assigned an ADG score of zero. The ADG score has previously been shown to have excellent

discrimination (C-stat > 0.91) and calibration for predicting the probability of death within 1-year and has been used successfully with ICES data [22].

7.7.2 The association between patient age and study year with ADG score

Linear regression was performed to determine the association of ADG score with patient age, and study year (including interaction terms). Associations were described using parameter estimates obtained from the regression model in each case. Parameter estimates above 0 indicate a positive linear association between the variable and ADG score. Parameter estimates below 0 indicate a negative linear association between the variable and ADG score. The interaction term was added to the model to determine if associations between age and ADG score and study year and ADG score are independent of each other. A statistical interaction occurs when an independent variable (ex: study year) has a different association with the dependent variable (ADG score) for a given patient age. For example, a change in ADG score over time may have occurred more prominently in one patient age group than another.

7.7.3 The influence of time on patient health status at first prostate biopsy

Changes in the health status of men receiving their first prostate biopsy over time were examined. As patients age, their health status generally decreases. The purpose of this analysis was to determine if the health status of men receiving prostate biopsy changed over time *independent of patient age*.

The **%MFP8 macro program** in SAS was used to determine the optimal prediction model we could derive from the ADG score data of our prostate biopsy cohort. The %MFP8

macro is a program that performs a **function selection procedure** for continuous predictor variables [24]. %MFP8 performs **multiple fractional polynomial transformations** of the independent variables of interest and builds the **multivariable model** that maximizes fit for the given dataset. This model can then be used to provide predictions of the outcome (ADG score) for any combination of the independent variables (patient age and study year).

For this study, three independent variables were included in the %MFP8 macro program: patient age; year of biopsy; and an interaction term of patient age*year of biopsy. The dependent variable (outcome) was the ADG score. %MFP8 requires that each variable in the model have a positive value (this requires a linear transformation if covariates have negative or 0 values). This was accomplished by adding the smallest positive integer, in our case 20, to all ADG scores in the dataset. Once %MFP8 identified the optimal model, the final model equation was adjusted by subtracting 20 to reset expected outcomes to the proper ADG score range.

Using the optimal model derived from the %MFP8 macro, we calculated predicted ADG scores for all patients ages and years of interest in this study. Patient age from 40 to 100 and study years from 1992 to 2012 were included. These data are presented by age group and study year in tabular form. These data were also illustrated using a heatmap. A heatmap is a method for visualizing a continuous variable (the ADG score) as a function of two other continuous variables (year and patient age). The heat map provides the predicted ADG score for any given combination of patient age and year.

Figure 2: ADG score categories and weights

ADG Score: Derived using weights for each of the 32 ADG Categories	
ADG Category	**Weight**
Time Limited: Minor	0
Time Limited: Minor-primary Infections	0
Time Limited: Major	6
Time Limited: Major-primary Infections	4
Allergies	-6
Asthma	0
Likely to Recur: Discrete	0
Likely to Recur: Discrete Infections	0
Likely to Recur: Progressive	8
Chronic Medical: Stable	4
Chronic Medical: Unstable	12
Chronic Specialty: Stable Orthopedic	-3
Chronic Specialty: Stable Ear, Nose, Throat	0
Chronic Specialty: Stable Eye	3
Chronic Specialty: Unstable Orthopedic	-2
Chronic Specialty: Unstable Ear, Nose, Throat	-4
Chronic Specialty: Unstable Eye	1
Dermatologic	-4
Injuries/Adverse Effects: Minor	-1
Injuries/Adverse Effects: Major	2
Psychosocial: Time Limited, Minor	-1
Psychosocial: Recurrent or Persistent, Stable	-3
Psychosocial: Recurrent or Persistent, Unstable	16
Signs/Symptoms: Minor	3
Signs/Symptoms: Uncertain	2
Signs/Symptoms: Major	2
Discretionary	-2
See and Reassure	1
Prevention/Administrative	-2
Malignancy	13
Pregnancy	-19
Dental	-1
ADG = Aggregated Diagnosis Group ***Table derived with permission from authors: Austin PC et al. Medical Care 2011** [22]*	

8 Results:

8.1 Validation of prostate biopsy administrative codes (Objective 1)

8.1.1 Determining the sensitivity of the Ontario Health Insurance Plan prostate biopsy procedure code Z712

I identified 148,674 patients in the Ontario Cancer Registry (OCR) with histologically **confirmed prostate cancer** using the DXCONFIRM variable from 1991-2012. Five records (0.003%) were excluded because they were duplicate diagnoses recorded on the same date for the same patient. The gold standard cohort thus contained 148,669 patients.

I identified 168,787 **prostate biopsy codes (Z712)** in the Ontario Health Insurance Plan (OHIP) database during the study period (1991 – June 2013) of which 1,654 (0.9%) were duplicate codes for the same patient on the same date and were therefore excluded. A cohort of 167,133 unique prostate biopsy procedures was available for linkage.

Overall, 97,369 histologically confirmed prostate cancer cases (65.5%) had a corresponding prostate biopsy code (Z712) within 1 week of the diagnosis and 51,295 (34.5%) did not (**Table 4**). The **crude sensitivity** of the prostate biopsy code improved over time from 33% in 1992 to 75% in 2012. From 1996 onwards, the code's sensitivity was over 50%.

8.1.1.1 Sensitivity analyses

Additional analyses were performed to determine if the sensitivity of the OHIP prostate biopsy code improved by increasing the time interval for linking a prostate biopsy code to a cancer diagnosis. We used intervals of 14 and 21 days around the cancer diagnosis to allow for a

greater delay OHIP code submission, pathologic processing, or data entry. The overall crude sensitivity of the prostate biopsy code improved minimally from 65.5% to 66.8% and 67.5% for 14 and 21 day intervals, respectively.

I then examined the 51,295 (34.5%) patients with prostate cancer diagnoses who were without corresponding prostate biopsy codes. First I identified all OHIP codes submitted for these patients within 1 week of their prostate cancer diagnosis to determine if some frequently submitted codes might explain how the histologic diagnosis of cancer was obtained and thus explain why some histologic diagnoses were not linked to a prostate biopsy code. The most common code indicating a procedure that might procure prostatic tissue for diagnosis was trans-urethral resection of the prostate (n=26,882) followed by cystoscopy with needle biopsy of the biopsy (n=11,647) (**Table 5**).

I determined the frequency of all identified alternative codes that may be a source of prostate tissue within 1 week of prostate cancer diagnosis. After excluding duplicate records, I identified 35,486 of 51,295 (69.2%) patients without a prostate biopsy code that had a code for an alternative procedure that would have procured prostate tissue within 1 week of their cancer diagnosis, thereby explaining why they did not have a prostate biopsy code (**Table 6**). These patients were removed from the denominator in the **corrected sensitivity** calculation of the prostate biopsy code. The corrected sensitivity was 86.0% overall (**Table 4**).

The proportion of histologically confirmed prostate cancer cases missing biopsy codes per study year was examined to determine if the sensitivity changed over time (**Figure 3**). The **crude sensitivity** ranged from 25.8% in 1991 to 75.4% in 2012. After adjusting the denominator in our sensitivity calculation by removing patients with alternative OHIP codes that explain why they may not have a prostate biopsy code, the **corrected sensitivity** improved to 68% in 1991

and 88% in 2012. The corrected sensitivity of the code gradually increased over time to a high of 91.5% in 2010.

Table 4: Sensitivity of OHIP prostate biopsy code (Z712) using histologically confirmed prostate cancer diagnoses from the OCR as a gold standard reference cohort.

	OCR Prostate Cancer Diagnosis from Histology (n)	OHIP Prostate Biopsy Claim (Z712 code) (n)	Crude sensitivity of Z712 code % (95%CI)	Alternative OHIP Claim that explains lack of biopsy* (n)	Corrected Sensitivity of Z712 code (after removing alternative codes) % (95%CI)
Overall (1991-2012)	**148664**	**97369**	**65.5% (65.3-65.7)**	**35486**	**86.0% (85.6-86.2)**
1991	2311	596	25.8% (24.0-27.6)	1377	63.8% (60.7-66.9)
1992	4971	1656	33.3% (32.0-34.6)	2538	68.1% (66.2-69.9)
1993	5331	2163	40.6% (39.3-41.9)	2370	73.0% (71.5-74.6)
1994	5150	2338	45.4% (44.0-46.8)	2055	75.5% (74.0-77.1)
1995	4765	2292	48.1% (46.7-49.5)	1853	78.7% (77.2-80.2)
1996	5157	2729	52.9% (51.6-54.3)	1750	80.1% (78.8-81.4)
1997	5791	3213	55.5% (54.2-56.8)	1823	81.0% (79.8-82.2)
1998	5792	3341	57.7% (56.4-59.0)	1738	82.4% (81.2-83.6)
1999	6001	3563	59.4% (58.1-60.6)	1641	81.7% (80.6-82.9)
2000	6634	4316	65.1% (63.9-66.2)	1568	85.2% (84.2-86.2)
2001	7445	5002	67.2% (66.1-68.3)	1618	85.8% (84.9-86.7)
2002	7057	4720	66.9% (65.8-68.0)	1531	85.4% (84.5-86.3)
2003	6883	4590	66.7% (65.6-67.8)	1565	86.3% (85.4-87.2)
2004	7765	5305	68.3% (67.3-69.4)	1761	88.4% (87.5-89.2)
2005	8405	5996	71.3% (70.4-72.3)	1681	89.2% (88.4-89.9)
2006	8867	6637	74.9% (73.9-75.8)	1567	90.9% (90.3-91.6)
2007	9062	6948	76.7% (75.8-77.5)	1374	90.4% (89.7-91.0)
2008	8629	6654	77.1% (76.2-78.0)	1289	90.7% (90.0-91.3)
2009	8689	6862	79.0% (78.1-79.8)	1164	91.2% (90.5-91.8)
2010	8712	6891	79.1% (78.2-80.0)	1178	91.5% (90.8-92.1)
2011	9003	6849	76.1% (75.2-77.0)	1159	87.3% (86.6-88.1)
2012	6244	4708	75.4% (74..3-76.5)	886	87.9% (87.0-88.7)

*****For list of alternative claims included see Table 6

Table 5: List of most common OHIP codes recorded within 1 week of prostate cancer diagnosis in the OCR in people who did not have a prostate biopsy coded*

Procedure Name	Fee Code	Frequency
Trans-urethral resection of prostate	S655	26882
Cystoscopy	Z606	22407
Partial assessment (urology)	A354	16291
Electrocardiogram	G313	15257
Physician visit	C352	13262
Electrocardiogram	G310	12775
Physician visit	C002	12305
Physician visit	C132	12193
Cystoscopy with needle biopsy of prostate	E780	11647
Anesthesia assessment	E007	11503
Physician visit	A007	10481
Intracavitary ultrasound (e.g. transrectal)	J138	9696
Ultrasonic guidance of biopsy	J149	9220
Supportive care	C010	8955

*Procedures from Ministry of Health Schedule of Benefits [17].

Figure 3: Corrected sensitivity of OHIP prostate biopsy code (Z712) over time for detecting prostate cancer diagnosed with histology in OCR

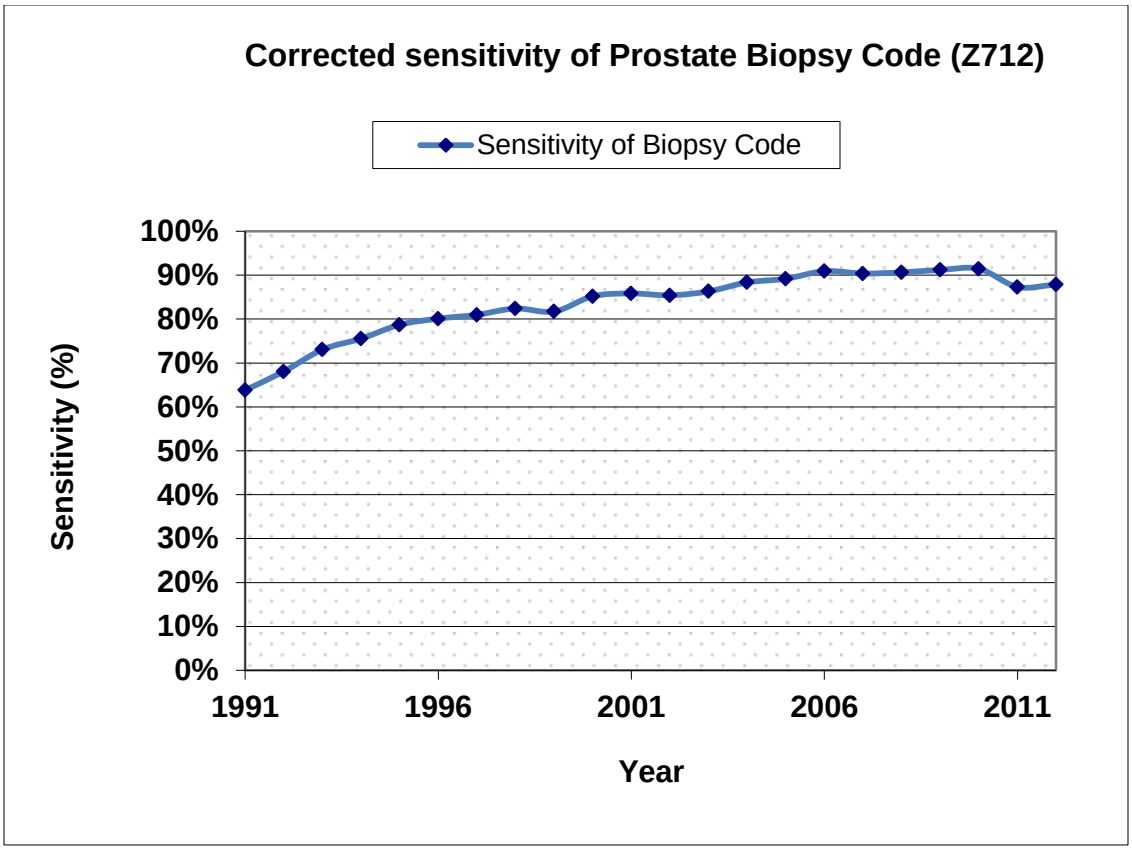


Table 6: Number of patients with alternative OHIP codes recorded within 1 week of cancer diagnosis in patients who did not have a prostate biopsy coded*		
Procedure Name	**OHIP code**	**Patients with code (n)**
Trans-urethral resection of prostate - standard - residual regrowth - drainage of abscess	 S655 S654 S656	14051
Cystoscopy - with needle biopsy of prostate - with bladder neck resection (male)	 E780 E787	11859
Ultrasound - intracavitary - guided biopsy	 J138 J149	8277
Cystectomy - without transplant - with ureterointestinal transplant - with ureteroileal conduit - with continent urinary diversion	 S484 S485 S453 S440	1180
Prostate biopsy - perineal - with abscess drainage	 S644 Z713	39
Prostatectomy - perineal - perineal with vesiculectomy - suprapubic - simple retropubic - radical retropubic - staging pelvic lymph node dissection - laparoscopic radical	 S645 S646 S647 S650 S651 S652 S653	3117
Total	**All alternative codes**	**35,486**

***Footnotes:** Alternative codes were grouped by procedure. The number of patients with any of the group of listed code(s) is presented [17].

8.1.2 Determining the specificity of the Ontario Health Insurance Plan (OHIP) prostate biopsy procedure code (Z712).

Electronic medical records were reviewed for a stratified random sample of 240 prostate biopsy codes (30/year) submitted from The Ottawa Hospital. I reviewed the patient record to determine if a prostate biopsy was performed using procedure reports for each patient. If a prostate biopsy was not performed, I recorded the reason and/or alternative procedure.

Six thousand five hundred and forty-four prostate biopsy procedure codes (Z712) were recorded at The Ottawa Hospital from February 1st 2007 to October 30th 2014 (mean 818 SD +/- 135 biopsies per year) (**Table 7**). Amongst the 240 random cases reviewed, thirty-eight (15.8%) codes were false positives. Amongst these, 34 (89.5%) were needle insertions of fiducial markers around the prostate prior to radiotherapy, 3 (7.9%) were prostate needle biopsies that were abandoned after the procedure started because the patient could not tolerate the procedure, and 1 (2.6%) was a trans-rectal ultrasound guided biopsy of a rectal nodule beside the prostate.

Table 7: Characteristics of OHIP prostate biopsy code (Z712) by year at The Ottawa Hospital.						
Year of biopsy	**Z712 code (n)**	**Sampled records (n)**	**True positive (n)**	**False positive (n)**	**Positive predictive value TP/(TP+FP) % (95%CI)**	**False positive rate FP/(TP+FP) % (95%CI)**
2007	638	30	20	10	66.7%	33.3%
2008	757	30	22	8	73.3%	26.7%
2009	792	30	19	11	63.3%	36.7%
2010	908	30	24	6	80.0%	20.0
2011	1075	30	28	2	93.3%	6.7%
2012	855	30	30	0	100.0%	0.0%
2013	827	30	30	0	100.0%	0.0%
2014	692	30	29	1	96.7%	3.3%
Overall	**6544**	**240**	**202**	**38**	**84.2% (79.5-88.8)**	**15.8% (11.2-20.5)**

All patients who receive needle placement of fiducial markers prior to radiotherapy have a prior diagnosis of prostate cancer. Patients with a prior diagnosis of prostate cancer were excluded from our study cohort because our objective was to characterize *first time* prostate biopsy procedures which reflect prostate cancer screening patterns in the population. Therefore, the **corrected false positive rate** of the prostate biopsy code applied to our study cohort, which excludes patients who received fiducial markers, was 1.9% (**Table 8**).

Table 8: Characteristics of OHIP prostate biopsy code (Z 712) by year excluding patients who received trans-rectal ultrasound guided needle implantation of gold markers around the prostate for radiotherapy

Year	Z712 (n)	Sampled records (n)	Fiducial Implants (n)	True positive (TP) (n)	Corrected false positive (FP) (n)	Positive predictive value TP/(TP+FP) (%)	Corrected false positive rate FP/(TP+FP) (%)
2007	638	30	8	20	2	90.9%	9.1%
2008	757	30	8	22	0	100.0%	0.0%
2009	792	30	10	19	1	95.0%	5.0%
2010	908	30	5	24	1	96.0%	4.0%
2011	1075	30	2	28	0	100.0%	0.0%
2012	855	30	0	30	0	100.0%	0.0%
2013	827	30	0	30	0	100.0%	0.0%
2014	692	30	1	29	0	100.0%	0.0%
Overall	**6544**	**240**	**34**	**202**	**4**	**98.1% (96.2-99.9)**	**1.9% (0.1-3.8)**

*Patients who receive needle implantation of gold markers around the prostate for radiotherapy all have a prior diagnosis of prostate cancer and thus are excluded from our study cohort.

As described in ***Section 7.4.2***, code specificity increases as its false positive rate decreases. This is because the key component of the false positive rate (the B-cell in 2x2 table) is included in the denominator when calculating both the positive predictive value and specificity. Our simulation model shows that a false positive rate of 1.9% implies a specificity that exceeds 95% even if the true negative rate (i.e. 1-positive predictive value) is as low as 50% (**Table 9**).

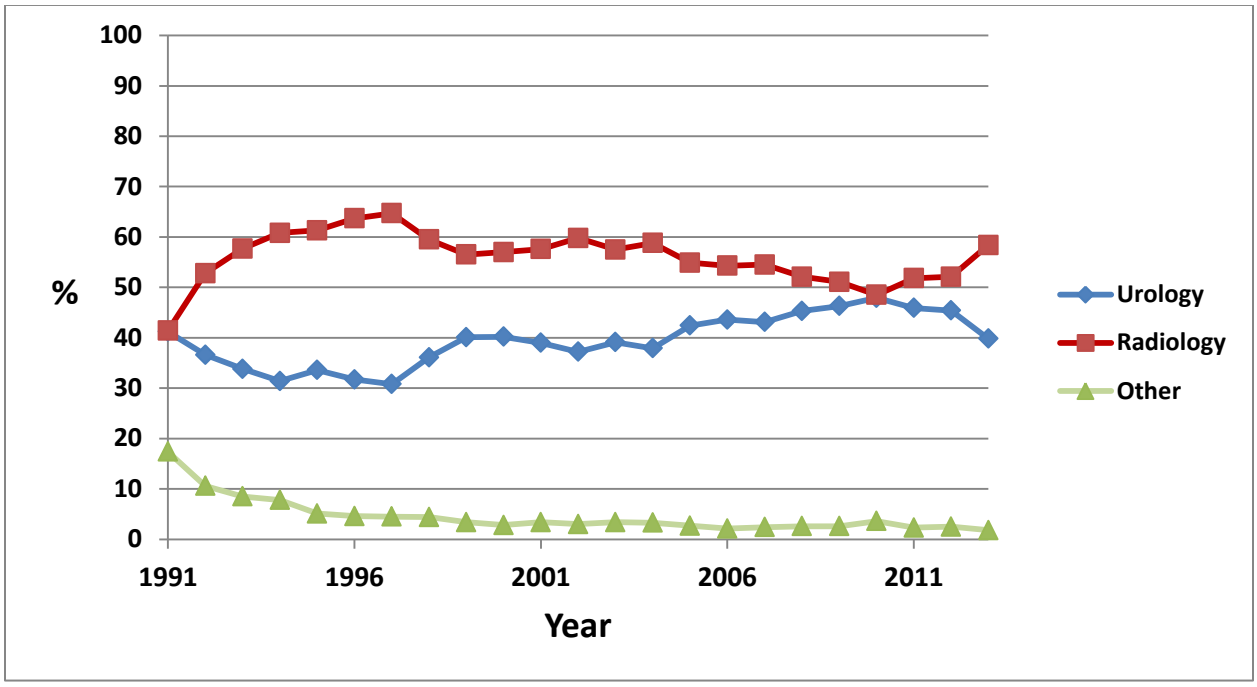
Table 9: Simulation model illustrating the influence of a low false positive rate on code specificity.		
True negative Rate (D/ C+D)	**False positive Rate (B/ A+B)**	**Specificity (D/B+D)**
50%	50%	50.0%
75%	50%	60.0%
99%	50%	66.4%
50%	10%	83.3%
75%	10%	88.2%
99%	10%	90.8%
50%	5%	90.9%
75%	5%	93.8%
99%	5%	95.2%
50%	**2%**	**96.2%**
75%	**2%**	**97.4%**
99%	**2%**	**98.0%**
See Table 2 for visual display of 2x2 table cell locations.		

The proportion of biopsies performed by specialty was determined to assess the applicability of the cohort I used from The Ottawa Hospital (in which all biopsies were done by radiologists) to derive the prostate biopsy code specificity to Ontario population data in OHIP. During the study period, 167,133 prostate biopsy codes were submitted to OHIP, of which 68,246 (40.8%) were submitted by urologists, 92,987 (55.6%) were submitted by radiologist, and 5,900 (3.5%) were submitted by other specialties (**Table 10**). In the 1990's, radiologists were performing many more prostate biopsies than urologists. After the year 2000, the proportion of biopsies performed by radiologists and urologists had become more even, however radiologists still performed the majority of prostate biopsies (**Figure 4**).

Table 10: OHIP prostate biopsy codes recorded stratified by specialty in Ontario from 1991-2013.

Year	Urology (%)	Radiology (%)	Other (%)
1991	41.2	41.4	17.4
1992	36.6	52.8	10.6
1993	33.8	57.7	8.5
1994	31.4	60.8	7.8
1995	33.6	61.3	5.1
1996	31.7	63.7	4.6
1997	30.8	64.7	4.5
1998	36.1	59.5	4.4
1999	40.1	56.5	3.4
2000	40.2	57.0	2.8
2001	39.0	57.6	3.4
2002	37.2	59.8	3.0
2003	39.1	57.5	3.4
2004	37.9	58.8	3.3
2005	42.4	54.9	2.7
2006	43.6	54.3	2.1
2007	43.1	54.5	2.4
2008	45.3	52.1	2.6
2009	46.3	51.1	2.6
2010	47.9	48.5	3.6
2011	45.9	51.8	2.3
2012	45.4	52.1	2.5
2013	39.8	58.4	1.8
Overall	**39.5**	**55.9**	**4.6**

Figure 4: Proportion of prostate biopsy codes submitted by specialty in Ontario from 1991-2013.



8.2 Incidence of prostate biopsy in Ontario over time (Objective 2)

8.2.1 Crude incidence of prostate biopsy in Ontario

A total of 328,405 prostate biopsy codes (Z712) were identified in the OHIP database between 1991 and 2013. A total of 115,310 (35.1%) biopsies were excluded for the following reasons: 89,614 (29.6%) biopsies were performed on men who had previously undergone prostate biopsy; 11,304 (3.6%) patients had a diagnosis of prostate cancer in the OCR *prior* to their first biopsy; 10,206 (3.1%) biopsies were from the years 1991 or 2013 (years for which data at the time of this study were incomplete); 3446 (1.1%) were duplicate codes (same patient and date); and finally 700 (0.2%) were in patients <40 years of age. **This left 213,095 Ontario men aged 40 or more with an index prostate biopsy between 1992 and 2012. This is the study cohort for all subsequent analyses**.

The crude number of patients receiving their first prostate biopsy stratified by age-group and year is reported in **Table 11**. A mean of 10,147 biopsies were performed per year during the study period. The greatest number of biopsies was performed in 2007 (13,823). The number remained steady in the 12,000's until 2011 and then dropped in 2012. The age group with the greatest number of biopsies was the 65-69 year group, constituting 21.6% of all biopsies from 1992-2012.

A large drop in biopsy counts was noted in 2012. To ensure that this was not caused by incomplete data in the year 2012 in OHIP, I explored monthly biopsy counts in OHIP for years 2011-2013 to ensure the data was complete. **Table 12** shows that monthly biopsy counts appear to be complete through the first 5 months of 2013. This indicates that the decreased biopsy count observed in 2012 was due to practice change rather than incomplete data collection.

Table 11: Crude number of patients receiving their first prostate biopsy in Ontario from 1992-2012 stratified by age and year.

Age group	Year																					
	1992 (%)	1993 (%)	1994 (%)	1995 (%)	1996 (%)	1997 (%)	1998 (%)	1999 (%)	2000 (%)	2001 (%)	2002 (%)	2003 (%)	2004 (%)	2005 (%)	2006 (%)	2007 (%)	2008 (%)	2009 (%)	2010 (%)	2011 (%)	2012 (%)	Total	% of cohort in age group
40-44	41 (0.7)	40 (0.5)	45 (0.6)	42 (0.6)	45 (0.6)	44 (0.5)	62 (0.7)	55 (0.7)	70 (0.8)	100 (0.9)	76 (0.7)	85 (0.8)	96 (0.9)	118 (0.9)	139 (1.1)	112 (0.8)	133 (1.1)	133 (1.1)	132 (1.1)	107 (0.9)	91 (0.9)	1766	0.8
45-49	95 (1.5)	128 (1.7)	146 (1.9)	147 (2.2)	155 (2.1)	179 (2.0)	188 (2.2)	193 (2.3)	245 (2.6)	287 (2.6)	296 (2.9)	311 (3.0)	321 (2.9)	402 (3.2)	447 (3.4)	456 (3.3)	466 (3.8)	469 (3.7)	441 (3.6)	443 (3.5)	347 (3.4)	6162	2.9
50-54	260 (4.2)	315 (4.2)	365 (4.8)	366 (5.4)	450 (6.0)	548 (6.2)	578 (6.8)	674 (8.0)	685 (7.3)	918 (8.4)	906 (8.7)	969 (9.3)	961 (8.8)	1108 (8.9)	1252 (9.5)	1361 (9.9)	1288 (10.4)	1304 (10.3)	1140 (9.3)	1271 (10.1)	988 (9.7)	17707	8.3
55-59	549 (8.8)	757 (10.2)	823 (10.9)	744 (10.9)	828 (11.1)	1086 (12.2)	1044 (12.3)	1069 (12.7)	1286 (13.7)	1621 (14.8)	1566 (15.1)	1621 (15.6)	1898 (17.4)	2149 (17.2)	2310 (17.4)	2372 (17.2)	2063 (16.7)	2163 (17.1)	2064 (16.9)	2085 (16.5)	1689 (16.6)	31787	14.9
60-64	1096 (17.5)	1316 (17.7)	1405 (18.6)	1300 (19.1)	1459 (19.6)	1577 (17.7)	1490 (17.5)	1562 (18.5)	1680 (17.9)	2001 (18.3)	1985 (19.1)	1968 (18.9)	2018 (18.5)	2450 (19.6)	2675 (20.2)	2908 (21.0)	2652 (21.4)	2786 (22.0)	2724 (22.3)	2817 (22.3)	2185 (21.5)	42054	19.7
65-69	1519 (24.3)	1875 (25.2)	1881 (24.9)	1658 (24.4)	1764 (23.6)	2189 (24.6)	2000 (23.6)	1850 (22.0)	2087 (22.3)	2359 (21.5)	2153 (20.7)	2151 (20.7)	2266 (20.8)	2570 (20.5)	2679 (20.2)	2791 (20.2)	2401 (19.4)	2546 (20.1)	2495 (20.4)	2633 (20.8)	2196 (21.6)	46063	21.6
70-74	1318 (21.0)	1580 (21.2)	1579 (20.9)	1371 (20.2)	1511 (20.3)	1774 (19.9)	1608 (18.9)	1592 (18.9)	1710 (18.2)	1880 (17.2)	1730 (16.6)	1684 (16.2)	1731 (15.9)	1937 (15.5)	1959 (14.8)	2068 (15.0)	1725 (13.9)	1759 (13.9)	1709 (14.0)	1818 (14.4)	1454 (14.3)	35497	16.7
75-79	836 (13.4)	911 (12.2)	796 (10.6)	786 (11.6)	839 (11.2)	1023 (11.5)	983 (11.6)	931 (11.1)	1091 (11.6)	1148 (10.5)	1094 (10.5)	1049 (10.1)	1047 (9.6)	1135 (9.1)	1156 (8.7)	1115 (8.1)	1088 (8.8)	987 (7.8)	988 (8.1)	924 (7.3)	736 (7.3)	20663	9.7
80-84	402 (6.4)	418 (5.6)	374 (5.0)	284 (4.2)	306 (4.1)	369 (4.2)	394 (4.6)	362 (4.3)	390 (4.2)	460 (4.2)	459 (4.4)	444 (4.3)	433 (4.0)	481 (3.8)	493 (3.7)	491 (3.6)	415 (3.4)	408 (3.2)	400 (3.3)	391 (3.1)	346 (3.4)	8520	4.0
85-89	129 (2.1)	98 (1.3)	108 (1.4)	87 (1.3)	94 (1.3)	93 (1.1)	135 (1.6)	105 (1.3)	114 (1.2)	158 (1.4)	118 (1.1)	115 (1.1)	119 (1.1)	145 (1.2)	112 (0.8)	130 (0.9)	137 (1.1)	116 (0.9)	132 (1.1)	138 (1.1)	101 (1.0)	2484	1.2
≥90	18 (0.3)	18 (0.2)	19 (0.3)	16 (0.2)	11 (0.2)	15 (0.2)	12 (0.1)	31 (0.4)	20 (0.2)	23 (0.2)	18 (0.2)	19 (0.2)	19 (0.2)	20 (0.2)	33 (0.3)	19 (0.1)	15 (0.1)	13 (0.1)	14 (0.1)	23 (0.2)	16 (0.2)	392	0.2
Total Column %	6263 100%	7456 100%	7541 100%	6801 100%	7462 100%	8897 100%	8494 100%	8424 100%	9378 100%	10955 100%	10401 100%	10416 100%	10909 100%	12515 100%	13255 100%	13823 100%	12383 100%	12684 100%	12239 100%	12650 100%	10149 100%	213,095	
% of cohort in year	2.9	3.5	3.5	3.2	3.5	4.2	4.0	4.0	4.4	5.1	4.9	4.9	5.1	5.9	6.2	6.5	5.8	6.0	5.7	5.9	4.8	*See Footnotes on next page**	

Table 11 continued:

***Footnotes:**

The proportion of biopsies in each age-group for each year is indicated below the crude number. For example, the left upper most cell indicates 41 patients age 40-44 received a biopsy in 1992 and these represented 0.65% of the biopsies in the year 1992.

The proportion of the overall biopsies for the entire study period performed in each year is indicated in the bottom most row.

The proportion of overall biopsies performed in each age-group for the entire study period is reported in the right-most column.

Table 12: Biopsy count reported by month and year between 2011 and 2013.

	Study Year		
Month	**2011**	**2012**	**2013**
January	1838	1495	1534
February	1580	1352	1201
March	1841	1404	1175
April	1681	1417	1294
May	1730	1558	1092
June	1872	1330	N/A
July	1434	1229	N/A
August	1513	1175	N/A
September	1751	1325	N/A
October	1639	1426	N/A
November	1753	1463	N/A
December	1216	1058	N/A

N/A – data not available in OHIP database at time of data extraction.

Code sensitivity adjusted biopsy counts, calculated using **Equation 5,** revealed the same trends as those observed with the crude data. Code sensitivity adjusted biopsy counts were maximal in 2007, stabilized between 2008 and 2011, and then dropped in 2012 (**Table 13 and Figure 5**). Because adjusted and crude trends were identical for the overall number of prostate biopsies, I do not present code sensitivity adjusted biopsy count data for all tables to avoid redundant information.

Examination of changes over time in the age specific proportions within each study year identified notable trends in age stratified crude prostate biopsy rates (Table 11). The proportion of biopsies in men over 70 years of age decreased steadily over time; for example, men aged 75-79 comprised 13.4% of biopsies in 1992 but only 7.3% of biopsies in 2012. In contrast, the proportion of biopsies in men between 40 and 55 years has increased over time; for example, men aged 50-55 represented 4.2% of biopsies in 1992 but 9.7% of biopsies in 2012. Therefore, the crude proportion of biopsies conducted in older men has decreased over time.

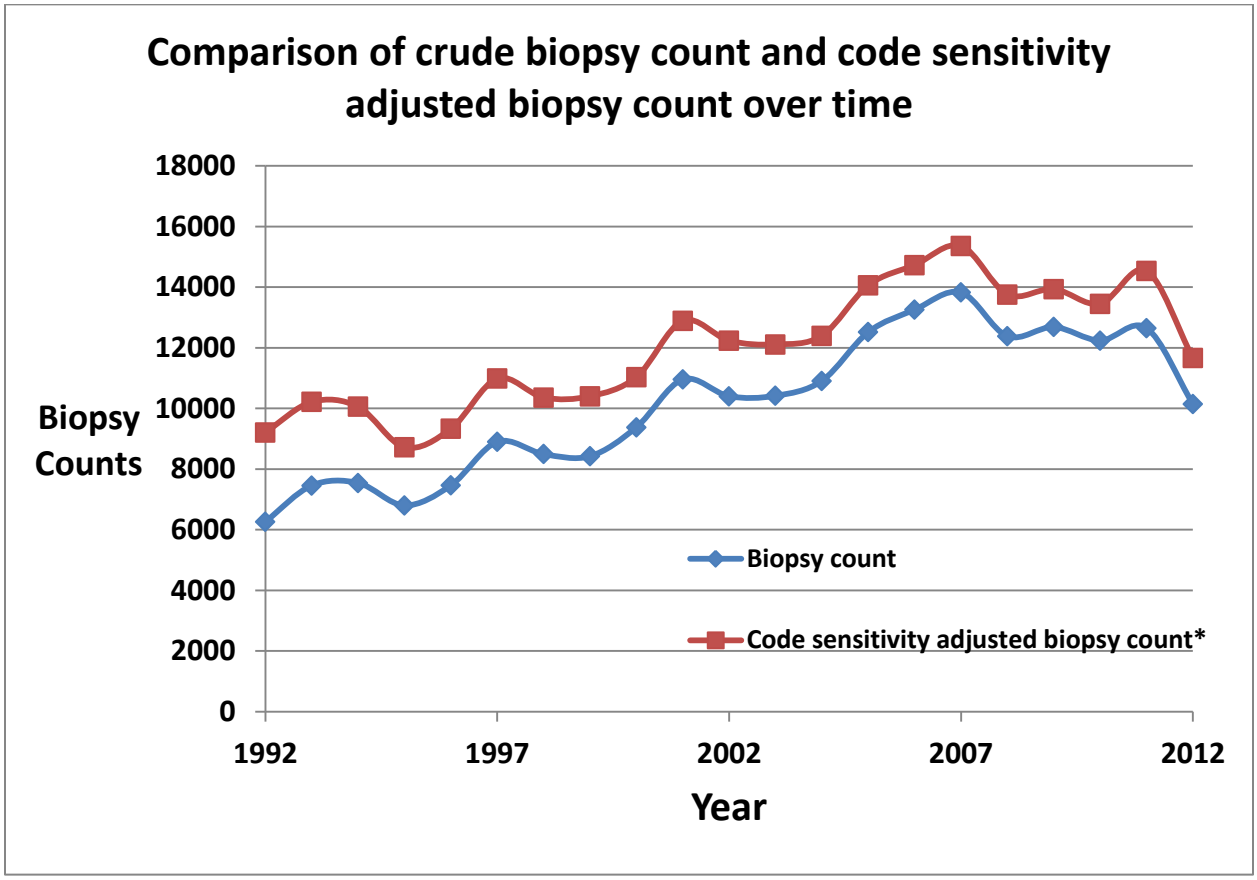
Table 13: Adjusted biopsy count to control for changing sensitivity of biopsy code over time

Study year	Crude biopsy count	Code sensitivity in study year (%)	Code sensitivity adjusted biopsy count*
1992	6263	68	9210
1993	7456	73	10214
1994	7541	75	10055
1995	6801	78	8719
1996	7462	80	9328
1997	8897	81	10984
1998	8494	82	10359
1999	8424	81	10400
2000	9378	85	11033
2001	10955	85	12888
2002	10401	85	12236
2003	10416	86	12112
2004	10909	88	12397
2005	12515	89	14062
2006	13255	90	14728
2007	13823	90	15359
2008	12383	90	13759
2009	12684	91	13938
2010	12239	91	13449
2011	12650	87	14540
2012	10149	87	11666

**** Equation 5:***

$$Code\ Sensitivity\ Adjusted\ Biopsy\ Count = \left[\frac{Biopsy\ Count\ in\ Study\ Year}{Sensitivity\ of\ Biopsy\ Code\ in\ Study\ Year}\right]$$

Figure 5: Crude versus code sensitivity adjusted biopsy count over time.



Footnote: The code sensitivity adjusted biopsy count was calculated using

Equation 5:

$$Code\ Sensitivity\ Adjusted\ Biopsy\ Count = \left[\frac{Biopsy\ Count\ in\ Study\ Year}{Sensitivity\ of\ Biopsy\ Code\ in\ Study\ Year}\right]$$

The number of Ontario men within each age group stratified by study year was obtained from Statistics Canada (**Table 14**). These data were used to determine the number of men at risk of prostate biopsy in Ontario and served as the denominator for calculations of prostate biopsy incidence. The number of Ontario men increased from 1992 to 2013 in each age group. **Table 14** shows the relative change in the male population of Ontario over time within each age group. This table shows that, during the study period, older age groups increased in population relative to 1992 much more than younger age groups. For example, the population in the 40-44 year age group increased by a relative factor of 0.19 (i.e. 19%) in 2012 versus 1992; in contrast, males over 90 increased by a relative factor of 1.64 (i.e. 164%) over the same time period.

Table 14: Number of men in Ontario stratified by study year and age group from Statistics Canada.

	Year																					
Age group	**1992**	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**Total**
40-44	392049	394650	401812	413305	424875	440624	455236	467956	483114	502106	518592	533860	547348	553630	548138	533508	512885	492668	477116	469606	465786	**10028864**
45-49	332058	348918	363734	378691	391260	393371	398689	407895	421348	434974	451957	468164	482917	497933	514456	525992	539483	549290	551560	542438	528854	**9523982**
50-54	260989	271039	280311	289248	301790	326019	345356	361872	378286	392392	394227	399749	410243	424644	438039	453716	469028	483073	496928	512363	523332	**8212644**
55-59	232505	233899	238319	242110	246851	253898	263825	273386	283653	297838	321887	340743	356497	371618	384882	386797	393118	403607	417869	430661	445982	**6819945**
60-64	224083	225163	225857	225455	224784	224877	225969	228972	232006	236857	244993	255727	266538	276710	289387	311810	329849	345477	362009	375219	377010	**5708752**
65-69	193310	196590	198504	201606	205031	208151	209653	210330	209867	209283	209237	210361	213664	216686	222782	231046	241357	251397	261104	273715	296603	**4670277**
70-74	142806	150551	158128	161688	164279	167184	170874	173506	177372	181717	184644	185955	186748	186141	185748	187021	190128	195138	199903	205743	212989	**3768263**
75-79	94859	95002	95340	99253	105321	111993	118844	125416	129395	132691	136201	139957	142804	146212	149891	152717	155088	156866	158678	160429	163255	**2770212**
80-84	53675	56165	58592	61024	62406	63103	63161	63765	67681	73403	79198	85032	90456	94308	97564	100187	103124	105630	109192	113247	116828	**1717741**
85-89	22619	23370	24274	25456	26826	27793	29006	30132	31082	31920	33155	34154	35582	39122	43559	47013	50460	53967	56532	58372	61688	**786082**
≥90	9267	9664	9972	9888	9896	10076	10307	10651	10918	11121	11857	12627	13229	13856	14734	15676	16590	17415	19487	22017	24424	**283672**
Total	**1958220**	**2005011**	**2054843**	**2107724**	**2163319**	**2227089**	**2290920**	**2353881**	**2424722**	**2504302**	**2585948**	**2666329**	**2746026**	**2820860**	**2889180**	**2945483**	**3001110**	**3054528**	**3110378**	**3163810**	**3216751**	**54290434**

Footnotes: The total number of men in all age group per year is indicated in the bottom row. The total number of men in each age group over the entire study period is indicated in the right-most column.

Table 15: Percent change over time in Ontario male population within each age strata relative to 1992.

	Year																			
Age group	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**
40-44	1	2	5	8	12	16	19	23	28	32	36	40	41	40	36	31	26	22	20	19
45-49	5	10	14	18	18	20	23	27	31	36	41	45	50	55	58	62	65	66	63	59
50-54	4	7	11	16	25	32	39	45	50	51	53	57	63	68	74	80	85	90	96	101
55-59	1	3	4	6	9	13	18	22	28	38	47	53	60	66	66	69	74	80	85	92
60-64	0	1	1	0	0	1	2	4	6	9	14	19	23	29	39	47	54	62	67	68
65-69	2	3	4	6	8	8	9	9	8	8	9	11	12	15	20	25	30	35	42	53
70-74	5	11	13	15	17	20	21	24	27	29	30	31	30	30	31	33	37	40	44	49
75-79	0	1	5	11	18	25	32	36	40	44	48	51	54	58	61	63	65	67	69	72
80-84	5	9	14	16	18	18	19	26	37	48	58	69	76	82	87	92	97	103	111	118
85-89	3	7	13	19	23	28	33	37	41	47	51	57	73	93	108	123	139	150	158	173
≥90	4	8	7	7	9	11	15	18	20	28	36	43	50	59	69	79	88	110	138	164

Footnotes: Values in each cell are percentages derived using Equation 7:

$$Relative\ Percent\ Change\ in\ Population\ in\ the\ Age\ Group$$

$$= \left[\frac{Population\ Year\ X\ in\ the\ Age\ Group - Population\ 1992\ in\ the\ Age\ Group}{Population\ 1992\ in\ the\ Age\ Group}\right] * 100\%$$

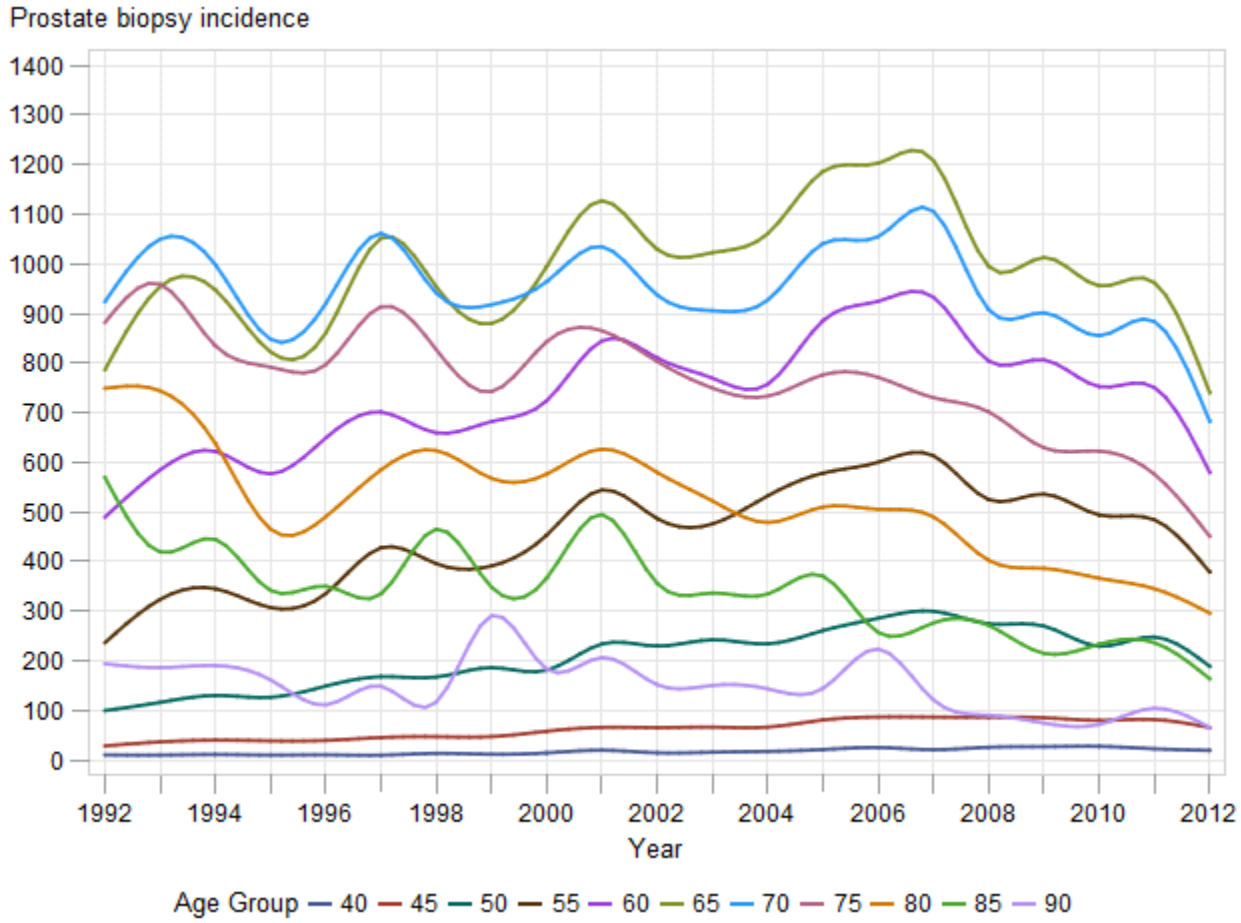
The crude incidence of prostate biopsy for each study year stratified by age group is presented in **Table 16**. Similar to the crude number of biopsies, the incidence of biopsies increased in men aged 40-54 and decreased in men aged 75 and over during the study period. For example, biopsy incidence in men aged 45-49 was 29 per 100,000 men in 1992 and 66 per 100,000 men in 2012. Conversely, the incidence of biopsy in men aged 75-79 was 881 per 100,000 men in 1992 and 451 per 100,000 men in 2012. The crude incidence of prostate biopsy over time by age-group is illustrated in **Figure 5**. This figure shows that biopsy rates in all age groups decreased from 2007 onwards. However, changes in utilization rates between 1992 and 2007 varied by age groups. In men less than 65, biopsy rates tended to increase during this time period. In contrast, biopsy rates during this time period in ages 65-75 were relatively stable and decreasing in ages above 75.

Table 16: Age-stratified crude prostate biopsy incidence per 100,000 males in Ontario from 1992-2012.

Age group	Year																				
	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
40-44	10	10	11	10	11	10	14	12	14	20	15	16	18	21	25	21	26	27	28	23	20
45-49	29	37	40	39	40	46	47	47	58	66	65	66	66	81	87	87	86	85	80	82	66
50-54	100	116	130	127	149	168	167	186	181	234	230	242	234	261	286	300	275	270	229	248	189
55-59	236	324	345	307	335	428	396	391	453	544	487	476	532	578	600	613	525	536	494	484	379
60-64	489	584	622	577	649	701	659	682	724	845	810	770	757	885	924	933	804	806	752	751	580
65-69	786	954	948	822	860	1052	954	880	994	1127	1029	1023	1061	1186	1203	1208	995	1013	956	962	740
70-74	923	1049	999	848	920	1061	941	918	964	1035	937	906	927	1041	1055	1106	907	901	855	884	683
75-79	881	959	835	792	797	913	827	742	843	865	803	750	733	776	771	730	702	629	623	576	451
80-84	749	744	638	465	490	585	624	568	576	627	580	522	479	510	505	490	402	386	366	345	296
85-89	570	419	445	342	350	335	465	348	367	495	356	337	334	371	257	277	272	215	234	236	164
≥90	194	186	191	162	111	149	116	291	183	207	152	150	144	144	224	121	90	75	72	104	66

Footnote: These rates are expressed per 100,000 males.

Figure 6: Crude incidence of prostate biopsy by age group from 1992-2012 in Ontario per 100,000 men.



Footnote: Lines between years were smoothed with spine function.

8.2.2 Age standardized incidence of prostate biopsy in Ontario

Age standardized incidence rates were calculated using direct standardization. The proportion of men in each age strata from 1992-2012 was used as the standard population distribution to calculate age standardized biopsy rates and is reported in **Table 17**. The number of men decreases as the age group increases in years.

Table 17: Number and proportion of men in each age group (strata) in Ontario during study period 1992-2012.

Age group	Count	Percent of population in age group
40-44	10,028,864	18.473
45-49	9,523,982	17.543
50-54	8,212,644	15.127
55-59	6,819,945	12.562
60-64	5,708,752	10.515
65-69	4,670,277	8.602
70-74	3,768,263	6.941
75-79	2,770,212	5.103
80-84	1,717,741	3.164
85-89	786,082	1.448
≥90	283,672	0.523
TOTAL	**54,290,434**	**100.000**

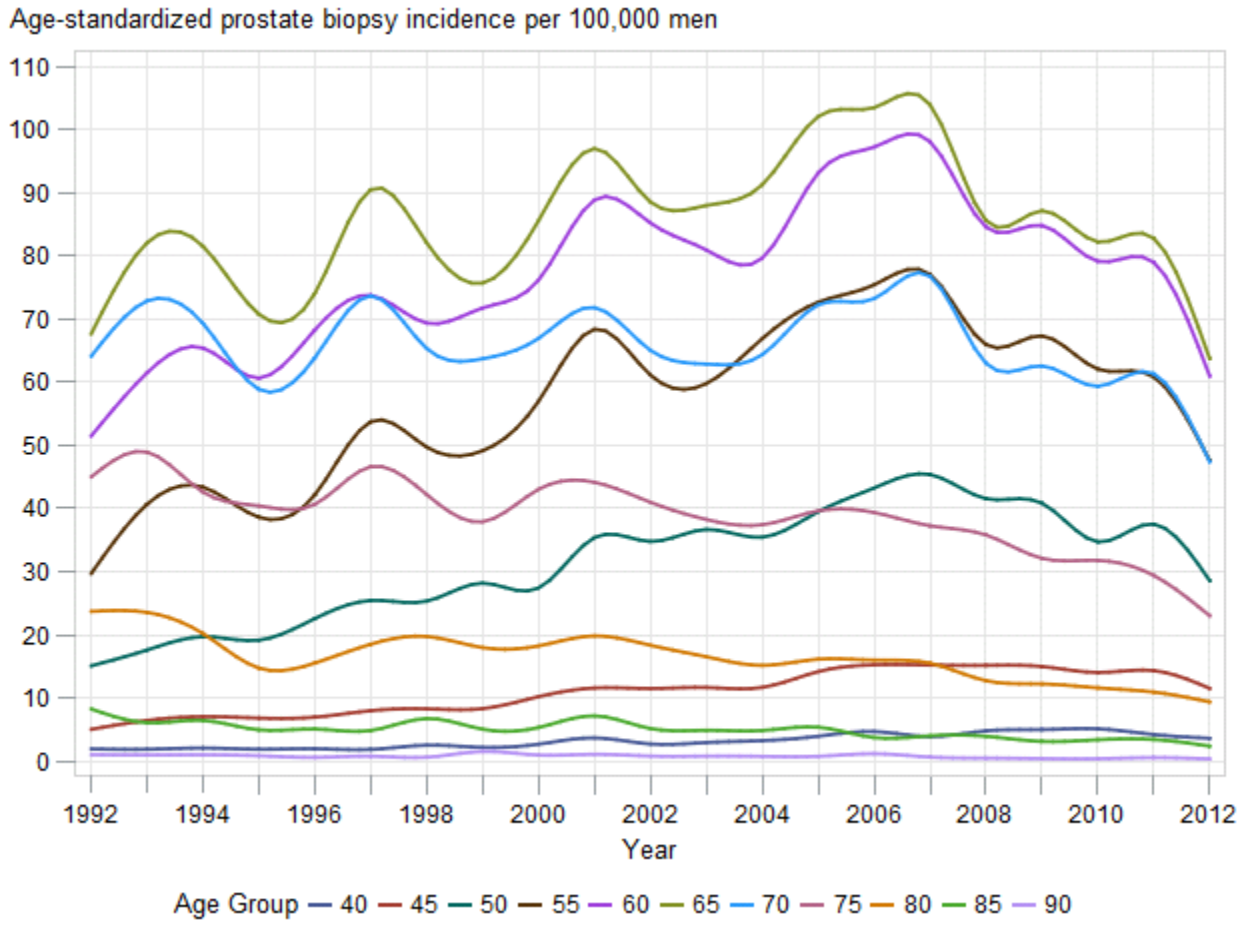
The age standardized incidence of prostate biopsy for each age group in each study year was calculated (**Table 18**). These data account for the changing age structure of the Ontario male

population during the study period (as presented in **Table 16)** and accentuates the age specific changes over time in crude prostate biopsy utilization (**Table 11**). Data from **Table 18** reiterate the themes illustrated in **Figure 5**: i) biopsy rates are highest in men aged 65-69; ii) 2007 was a watershed year after which biopsy rates in all age groups decreased; iii) prior to 2007, biopsy rates were increasing in men younger than 70 but were stable or decreasing in older men. These messages are illustrated in **Figure 7**.

Table 18: Age standardized incidence of prostate biopsy per 100,000 men in Ontario by age group from 1992-2012.

Age group	Year																				
	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
40-44	2	2	2	2	2	2	2	2	3	4	3	3	3	4	5	4	5	5	5	4	4
45-49	5	6	7	7	7	8	8	8	10	11	11	12	12	14	15	15	15	15	14	14	11
50-54	15	18	20	19	23	25	25	28	27	35	35	37	35	39	43	45	42	41	35	38	29
55-59	30	41	44	39	42	54	50	49	57	69	61	60	67	73	76	77	66	68	62	61	48
60-64	52	62	66	61	69	74	70	72	77	90	86	82	80	94	98	99	85	86	80	80	62
65-69	68	83	82	72	75	92	83	77	87	98	90	89	92	103	105	105	87	88	83	84	64
70-74	64	73	69	59	64	74	65	64	67	72	65	63	64	72	73	77	63	63	59	61	47
75-79	45	49	43	40	41	47	42	38	43	44	41	38	37	40	39	37	36	32	32	29	23
80-84	24	24	20	15	16	19	20	18	18	20	18	17	15	16	16	16	13	12	12	11	9
85-89	8	6	7	5	5	5	7	5	5	7	5	5	5	5	4	4	4	3	3	3	2
≥90	1	1	1	1	1	1	1	2	1	1	1	1	1	1	1	1	0	0	0	1	0
Overall	314	365	361	320	345	401	373	363	395	451	416	407	411	461	475	480	416	413	385	386	299

Figure 7 : Age standardized prostate biopsy rates in Ontario from 1992-2012.



Footnote: Lines between years were smoothed with spline function.

8.2.3 Incidence of prostate biopsy over time in Ontario

Poisson regression was used to model prostate biopsy count data. The initial Poisson model had a value/DF statistic of 16, indicating that extensive overdispersion was present in the data. I therefore used the negative-binomial distribution to model the data to account for overdispersion, as shown by the value/degrees of freedom (DF) statistic to 1.25 in the negative binomial regression model. The negative binomial distribution 'K statistic' for dispersion was significant which further supports that overdispersion was present in the Poisson model and that the negative binomial distribution is preferable.

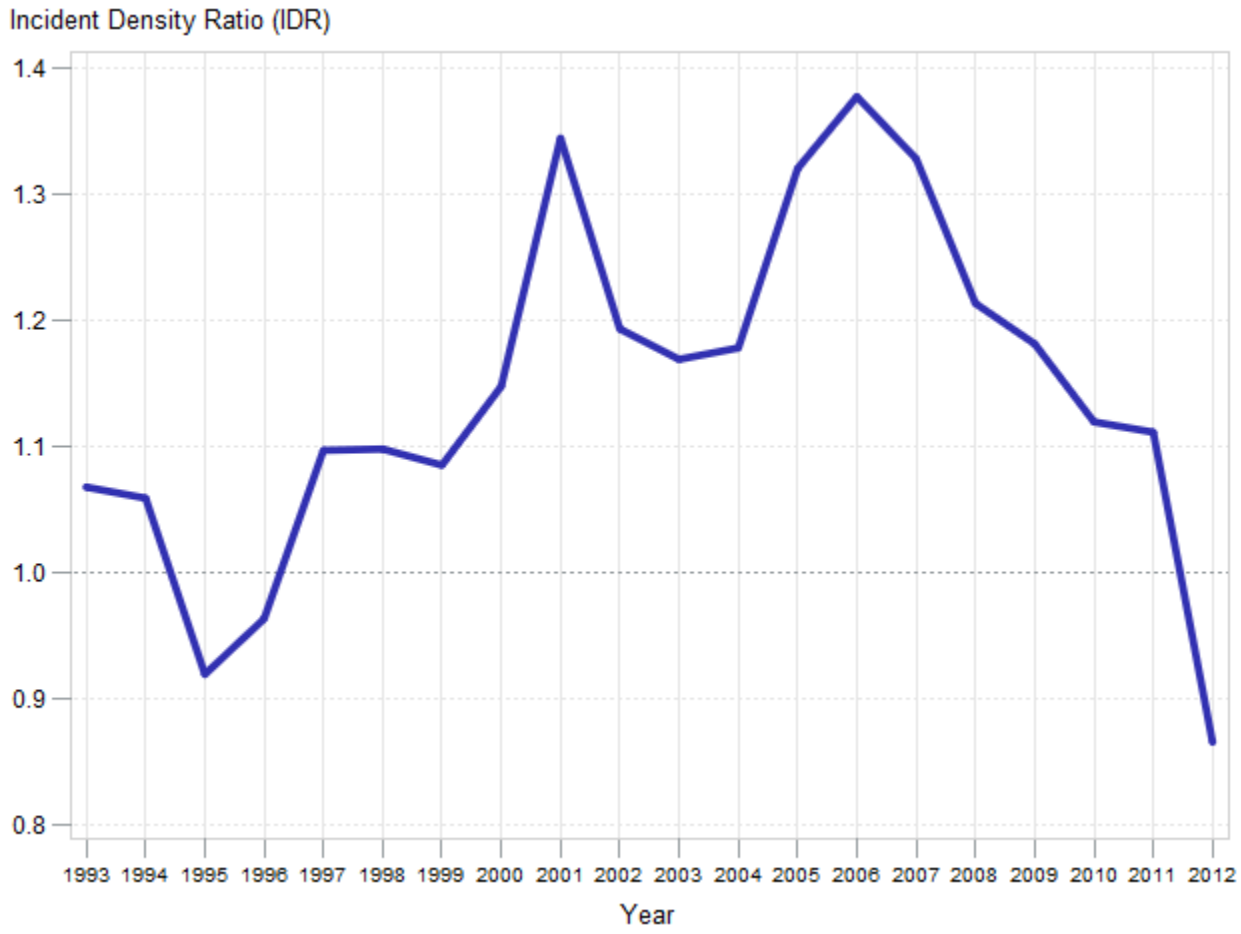
8.2.3.1 Method 1: Determine influence of study year and patient age on biopsy incidence

The incidence density ratio (IDR) for prostate biopsy for each year compared to the reference year (1992) was calculated and is presented in **Table 19**. IDRs above 1 indicate that the prostate biopsy rate was higher that year relative to 1992. IDRs below 1 indicate the incidence of biopsy was lower than the reference year 1992. IDRs with 95% confidence intervals that exclude 1 are significantly distinct from 1992. The data show that the incidence of biopsy was greater than 1992 in almost all years, significantly so and consistently between 2005 and 2008. Notably, in 2012, the IDR was below 1. The change in IDRs over time is illustrated in **Figure 8**.

Table 19: Incident density ratio with 95% confidence interval for each year compared to the year 1992 (reference category) for prostate biopsy in Ontario.

Year	Parameter Estimate	Incidence Density Ratio (IDR)	Lower Confidence Interval	Upper Confidence Interval
1992 (reference)	-	1	1	1
1993	0.065	1.07	0.89	1.28
1994	0.057	1.06	0.89	1.27
1995	-0.084	0.92	0.77	1.10
1996	-0.037	0.96	0.81	1.15
1997	0.092	1.10	0.92	1.31
1998	0.093	1.10	0.92	1.31
1999	0.082	1.08	0.91	1.30
2000	0.138	1.15	0.96	1.37
2001	0.296	1.34	1.13	1.60
2002	0.176	1.19	1.00	1.42
2003	0.156	1.17	0.98	1.39
2004	0.164	1.18	0.99	1.41
2005	0.278	1.32	1.11	1.57
2006	0.320	1.38	1.15	1.64
2007	0.283	1.33	1.11	1.58
2008	0.193	1.21	1.02	1.45
2009	0.166	1.18	0.99	1.41
2010	0.113	1.12	0.94	1.34
2011	0.105	1.11	0.93	1.33
2012	-0.144	0.87	0.73	1.03

Figure 8: Scatter plot of incident density ratio (IDR) over time illustrates the incidence rate of prostate biopsy over time. The IDR is calculated for each study year compared to the referent year (1992) adjusting for age.



The incidence density ratio (IDR) for prostate biopsy for each age group compared to the reference age (40-44) was calculated and is presented in **Table 20**. These data show that the rate of first biopsy was highest in the 65-69 year age group (IDR 57.6, indicating that biopsy rate in this age group was 57.6 times higher than that in men aged 40-44).

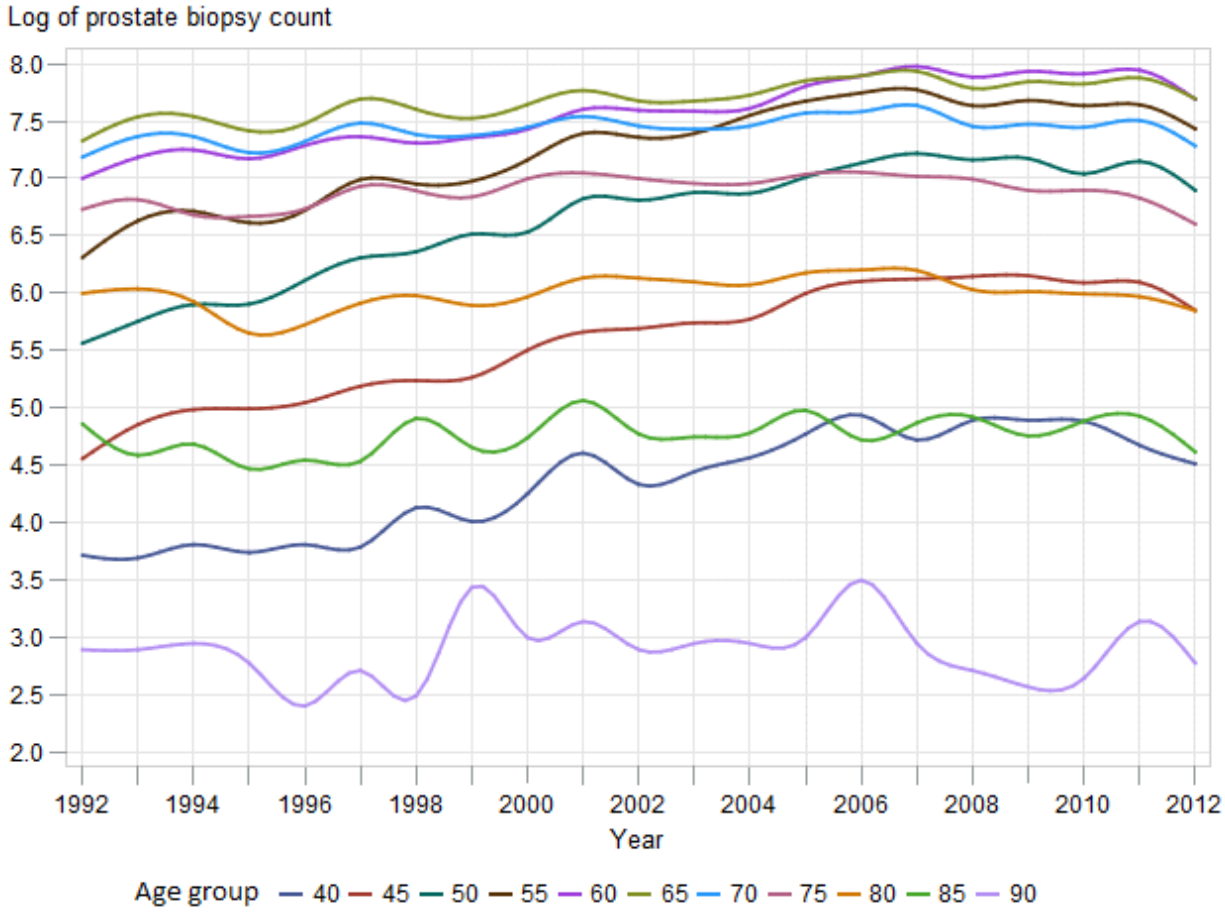
Table 20: Incident density ratio with 95% confidence interval for each age group compared to the age group 40-44 (reference category) for prostate biopsy in Ontario.

Age Group	Parameter Estimate	Incidence Density Ratio (IDR)	Lower Confidence Interval	Upper Confidence Interval
40 (reference)	1	-	-	-
45	1.278	3.59	3.15	4.09
50	2.475	11.88	10.45	13.51
55	3.260	26.05	22.92	29.61
60	3.746	42.35	37.26	48.13
65	4.053	57.58	50.66	65.44
70	4.015	55.43	48.76	63.01
75	3.803	44.83	39.41	50.99
80	3.421	30.60	26.87	34.85
85	2.988	19.85	17.35	22.71
90	2.121	8.34	7.09	9.82

8.2.3.2 Method 2: Predicting biopsy incidence using study year and patient age

Prostate biopsy incidence was also examined with study year as a continuous variable. First, plots of log transformed prostate biopsy counts over time for all age groups revealed a slight non-linear relationship between the log of the number of prostate biopsies performed and time (**Figure 9**). This non-linear relationship was especially prominent in younger age groups. Subsequent fractional polynomial modeling of prostate biopsy counts over time identified a model that included the **study year and study year cubed** as the best fit based on this model having the lowest AIC statistic (2826) compared to other combinations of the year variable in its native and transformed form. The final model for predicting biopsy incidence is presented in **Equation 11**.

Figure 9: Log transformed counts of prostate biopsy over time by age group to determine if prostate biopsy rate should be treated as linear over time in a Poisson model.



Footnote: If the association between log(prostate biopsy count) and time (years) was similar and linear in all age groups one would expect to see relatively straight lines (consistent changes over time) without crossing of lines between age groups.

Equation 11: Optimal model to calculate expected prostate biopsy count using patient age group and study year.

$$Log\ (count) = intercept + B1(X_1) + B2(X_2) + B3(X_3)$$
$$= -86.74 + 1.28(Age\ group\ 45-49) + 0.039(Year) - 0.0001(Year^3)$$

Footnote: *Constant for age group 45-49 displayed in equation. Full model output available in Appendix 1.*

Using parameter estimates obtained from the multivariable Poisson model expressing years using polynomials, we calculated the **expected IDRs** (**Equation 12**) for each study year. We compared these to the **observed IDR**s (**Table 19**) for each study year obtained from the negative binomial regression model (**Table 21 and Figure 10**). **Figure 10** shows that the expected prostate biopsy incidence rate in Ontario increased from 1992 until approximately 2005-2007 and has been decreasing since. The year 2012 has the lowest expected incidence rate over the entire study period.

Equation 12: Derivation of expected and observed incident density ratios for prostate biopsy.

$$\boldsymbol{a)\ Expected\ Incident\ Density\ Ratio}$$
$$= \boldsymbol{e^{(Expected\ Parameter\ Estimate\ from\ Model - Parameter\ Estimate\ of\ Referent\ Year\ in\ Model)}}$$

$$\boldsymbol{Where:\ \ Expected\ Parameter\ Estimate\ from\ Model}$$
$$= [0.039(Year) - 0.0001(Year^3)]$$

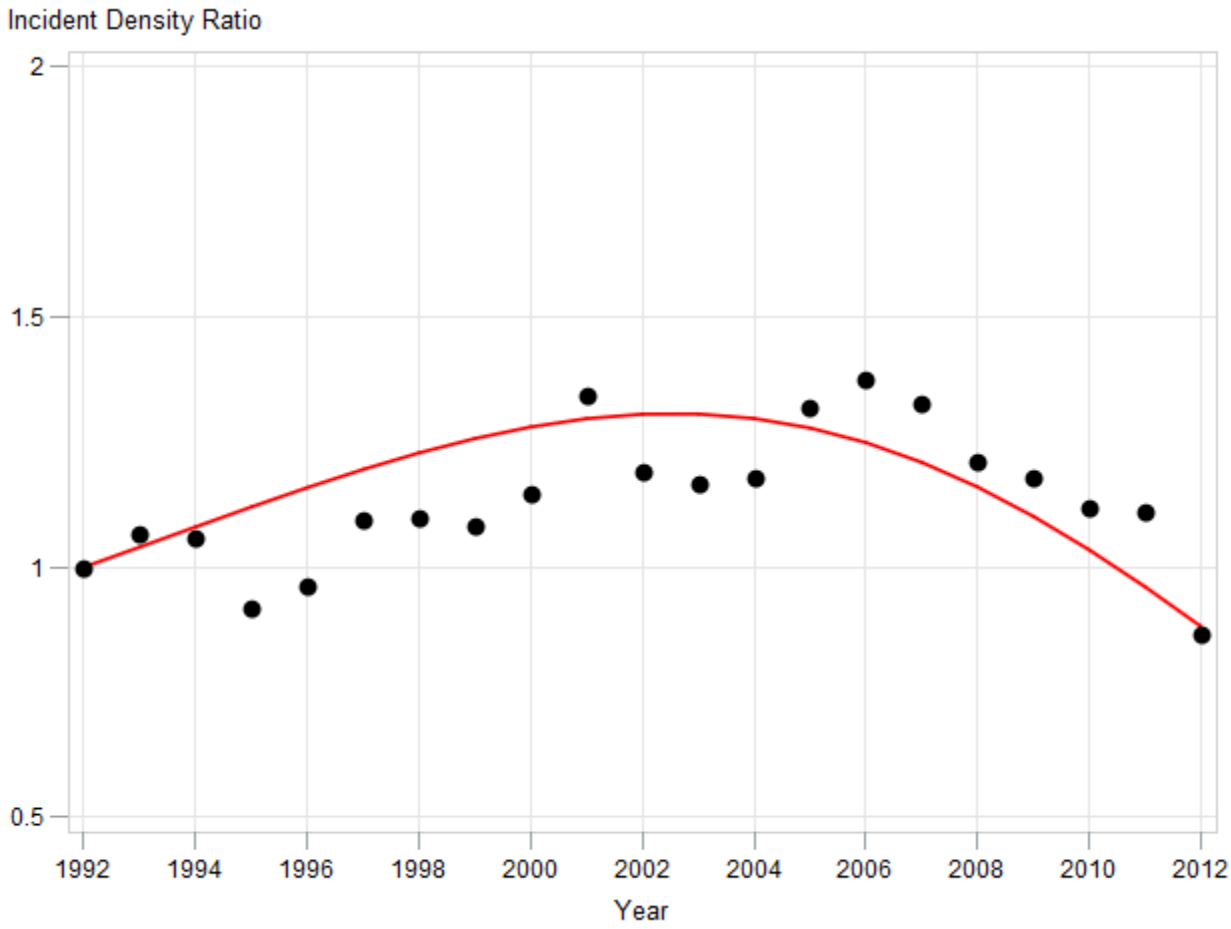
b) $\boldsymbol{Observed\ Incident\ Density\ Ratio}$

$$= \boldsymbol{e^{Parameter\ Estimate\ from\ Negative\ Binomial\ Model\ with\ Year\ as\ Categorical\ Variable\ (Equation\ 9)}}$$

Table 21: Expected and observed incident density ratios for prostate biopsy over time from 1992-2012.

Year	Expected Incident Density Ratio	Observed Incident Density Ratio
1992 (referent)	1.00	1.00
1993	1.04	1.07
1994	1.08	1.06
1995	1.12	0.92
1996	1.16	0.96
1997	1.20	1.10
1998	1.23	1.10
1999	1.26	1.08
2000	1.28	1.15
2001	1.30	1.34
2002	1.31	1.19
2003	1.31	1.17
2004	1.30	1.18
2005	1.28	1.32
2006	1.25	1.38
2007	1.21	1.33
2008	1.16	1.21
2009	1.10	1.18
2010	1.03	1.12
2011	0.96	1.11
2012	0.88	0.87

Figure 10: Plot of expected (red curve) and observed (black dots) prostate biopsy incident density ratios over time in Ontario from 1992-2012.



Footnote: Black dots represent the observed incidence of prostate biopsy in a given year compared to incidence in the reference year (1992). The red curve represents the overall (all age groups) expected incidence of prostate biopsy for any given year and was derived using the optimal fractional polynomial model.

8.3 Proportion of malignant first prostate biopsies over time

8.3.1 Identifying malignant prostate biopsies

Two hundred and thirteen thousand and ninety-five patients had a first prostate biopsy recorded in OHIP and did not have a prior diagnosis of prostate cancer recorded in the OCR. Of the 213,095 biopsies, 84,149 (39%) were classified as malignant and 128,946 (61%) were benign (**Table 22**).

Sensitivity analyses were performed to determine if varying the time period for attributing a malignant diagnosis to a biopsy significantly affected the proportion of biopsies classified as malignant. Extending the time frame from +/- 7 days to +/- 14 days resulted in 684 additional malignant biopsies over the entire study period which translates to an overall absolute increase in the malignant biopsy rate of 0.3% (**Table 23**). The maximum time frame increase examined was +/- 35 days which resulted in an overall increase in the malignant biopsy rate of 0.6%. These changes were not considered to significantly impact the study outcomes therefore the original pre-specified +/- 7 day time frame was used for reporting and additional analyses.

Table 22: Proportion of prostate biopsies that are malignant from 1992-2012 overall.

Biopsy Malignant n (%)	Year																				
	1992	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**Total**
No	4662 (74.4)	5419 (72.7)	5371 (71.2)	4744 (69.8)	5041 (67.6)	6084 (68.4)	5586 (65.8)	5335 (63.3)	5676 (60.5)	6638 (60.6)	6420 (61.7)	6565 (63.0)	6411 (58.8)	7370 (58.9)	7596 (57.3)	7844 (56.8)	6561 (53.0)	6689 (52.7)	6213 (50.8)	6694 (52.9)	6027 (59.4)	**128946**
Yes	1601 (25.6)	2037 (27.3)	2170 (28.8)	2057 (30.3)	2421 (32.4)	2813 (31.6)	2908 (34.2)	3089 (36.7)	3702 (39.5)	4317 (39.4)	3981 (38.3)	3851 (37.0)	4498 (41.2)	5145 (41.1)	5659 (42.7)	5979 (43.3)	5822 (47.0)	5995 (47.3)	6026 (49.2)	5956 (47.1)	4122 (40.6)	**84149**
Total	**6263 (100%)**	**7456 (100%)**	**7541 (100%)**	**6801 (100%)**	**7462 (100%)**	**8897 (100%)**	**8494 (100%)**	**8424 (100%)**	**9378 (100%)**	**10955 (100%)**	**10401 (100%)**	**10416 (100%)**	**10909 (100%)**	**12515 (100%)**	**13255 (100%)**	**13823 (100%)**	**12383 (100%)**	**12684 (100%)**	**12239 (100%)**	**12650 (100%)**	**10149 (100%)**	**213095**

Footnotes: Each cell indicates the number and proportion of biopsies for the study year.

Table 23: Sensitivity analysis to determine effect of extending the time frame for attributing a cancer diagnosis in OCR to a prostate biopsy identified in OHIP.

Days	# Malignant Biopsies	# of Additional Malignant Biopsies	% Absolute Difference in Number of Malignant Biopsies
7	84149	Referent	Referent
14	84833	684	0.32
21	85063	914	0.43
28	85265	1116	0.52
35	85512	1363	0.64

Footnotes: **% Absolute difference in number of malignant biopsies** calculated by dividing the number of additional malignant biopsies by the total number of biopsies (213,095)

8.3.2 Proportion of malignant prostate biopsies overall and stratified by age group

The proportion of first prostate biopsies that were classified malignant increased during the study period from 26% in 1992 to a high of 49% in 2010. The proportion of malignant first biopsies over time is illustrated in **Figure 11**.

The proportion of malignant biopsies was examined by age group. **Figure 12 and Table 24** show that the proportion of malignant biopsies increased for all age groups during the study period until 2010 after which there was a decline.

Figure 11: Proportion of prostate biopsies that are malignant from 1992-2012 overall.

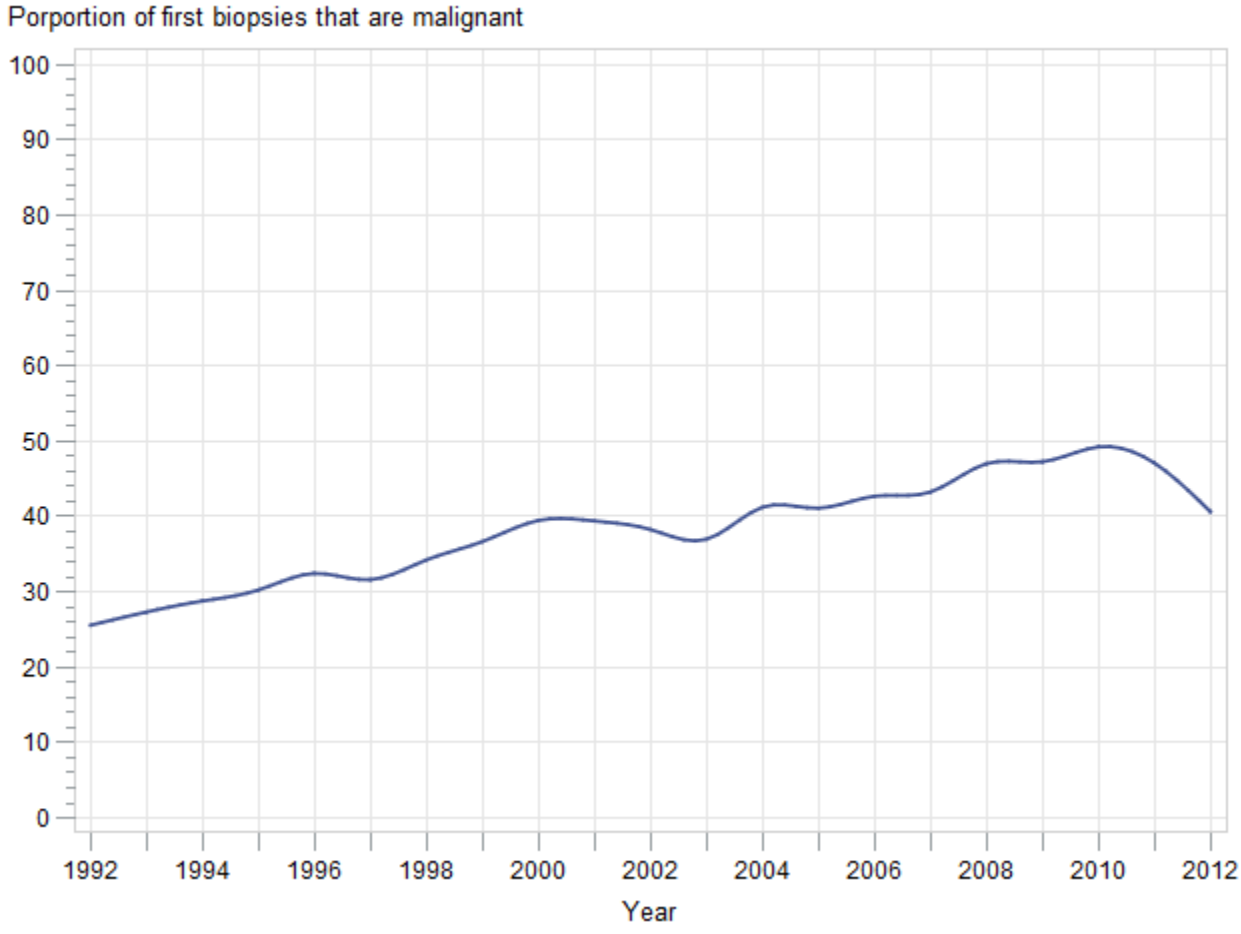


Figure 12: Proportion of prostate biopsies that are malignant from 1992-2012 by age group.

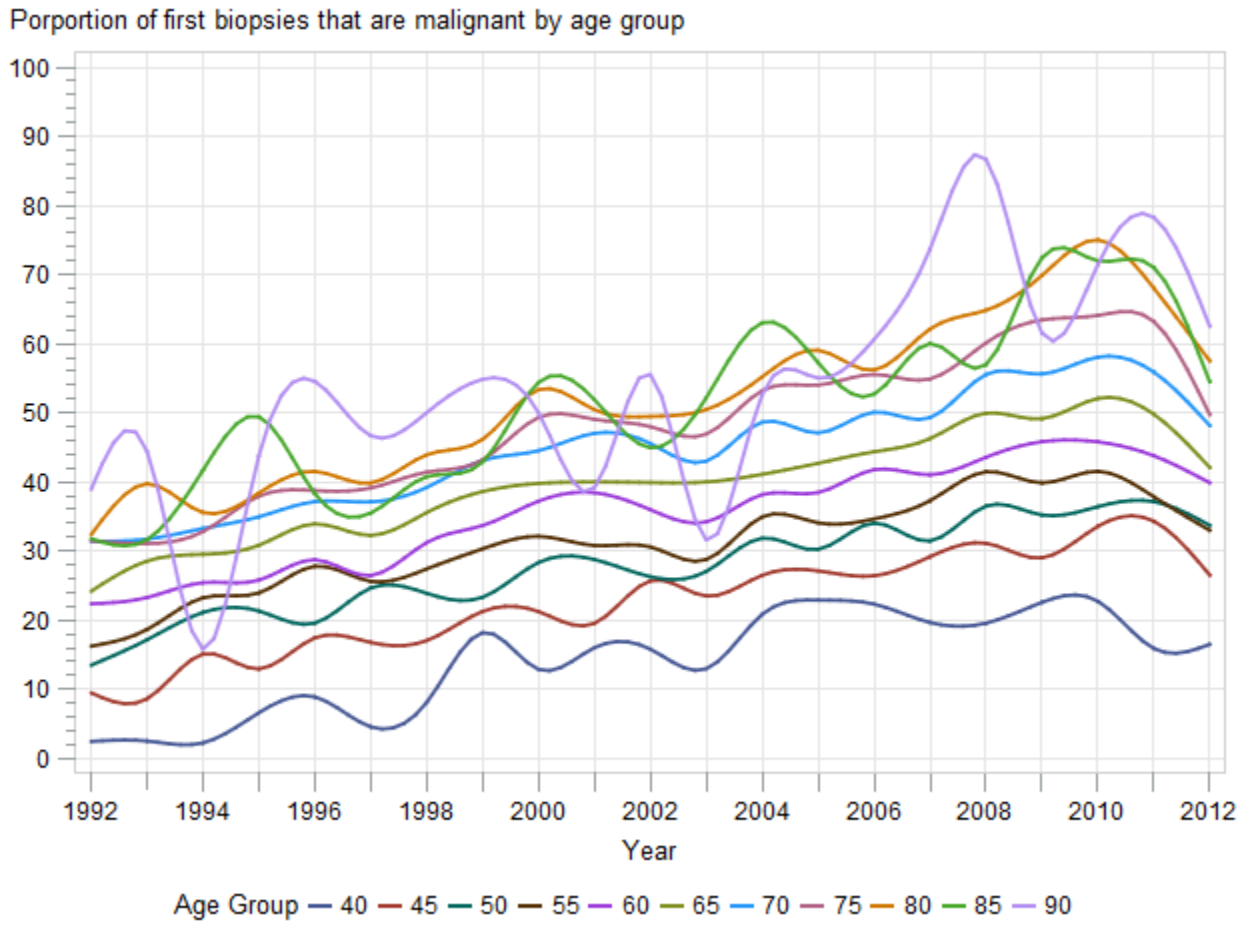


Table 24: Proportion of prostate biopsies that are malignant from 1992-2012 by age group.

Age group	Year																					
	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Mean of Age Group
40	2.4	2.5	2.2	0.0	8.9	4.6	8.1	18.2	12.9	16.0	15.8	12.9	20.8	22.9	22.3	19.6	19.6	22.6	22.7	15.9	16.5	**13.7**
45	9.5	8.6	15.1	12.9	17.4	16.8	17.0	21.2	21.2	19.5	25.7	23.5	26.5	27.1	26.4	29.2	31.1	29.0	33.6	34.3	26.5	**22.5**
50	13.5	17.1	21.1	21.3	19.6	24.6	23.9	23.3	28.3	28.8	26.3	27.0	31.8	30.2	34.0	31.5	36.5	35.2	36.4	37.1	33.7	**27.7**
55	16.2	18.6	23.2	23.9	27.8	25.6	27.4	30.3	32.1	30.8	30.6	28.8	34.9	34.1	34.6	37.3	41.4	39.9	41.5	37.8	33.0	**30.9**
60	22.4	23.3	25.4	25.8	28.7	26.4	31.2	33.7	37.2	38.4	36.0	34.2	38.2	38.5	41.8	41.0	43.6	45.8	45.8	43.8	39.9	**35.3**
65	24.2	28.5	29.5	30.8	33.9	32.3	35.6	38.6	39.8	40.0	39.9	40.0	41.1	42.7	44.3	46.3	49.9	49.1	52.1	49.8	42.1	**39.5**
70	31.4	31.7	33.3	34.9	37.1	37.1	39.2	43.1	44.5	47.0	45.6	43.0	48.6	47.1	50.1	49.3	55.5	55.6	58.1	55.9	48.1	**44.6**
75	31.5	31.1	32.8	37.9	38.7	39.1	41.4	43.2	49.3	49.0	48.0	46.9	53.2	54.0	55.5	54.9	60.1	63.4	64.1	63.2	49.7	**48.0**
80	32.3	39.7	35.6	38.4	41.5	39.8	43.9	46.1	53.3	50.4	49.5	50.5	55.2	59.0	56.2	62.1	64.8	69.9	75.0	68.0	57.5	**51.8**
85	31.8	31.6	41.7	49.4	38.3	35.5	40.7	42.9	54.4	51.9	44.9	52.2	63.0	57.2	52.7	60.0	56.9	72.4	72.0	71.0	54.5	**51.2**
90	38.9	44.4	15.8	43.8	54.6	46.7	50.0	54.8	50.0	39.1	55.6	31.6	52.6	55.0	60.6	73.7	86.7	61.5	71.4	78.3	62.5	**53.7**
Mean of Year	**23.1**	**25.2**	**25.1**	**29.0**	**31.5**	**29.9**	**32.6**	**35.9**	**38.5**	**37.4**	**38.0**	**35.5**	**42.4**	**42.5**	**43.5**	**45.9**	**49.6**	**49.5**	**52.1**	**50.5**	**42.2**	**38.1**
																						Overall Mean

Footnote: The crude number of prostate biopsies performed in each age group and year is presented in Table 11.

8.3.3 Proportion of malignant prostate biopsies over time

The negative binomial distribution was used to model changes in the proportion of malignant prostate biopsies over time. The outcome was the number of biopsies classified as malignant each year. The offset variable was the number of patients receiving their first prostate biopsy in the study year.

8.3.3.1 Method 1: Determine influence of study year and patient age on malignant biopsy incidence

The incidence density ratio (IDR) for malignant prostate biopsy for each year compared to the reference year (1992) was calculated and is presented in **Table 25**. The IDR is the proportion of malignant biopsies in the year of interest compared to the reference year 1992. IDRs above 1 indicate the proportion of malignant prostate biopsies was higher in the year of interest compared to the reference year 1992. IDRs below 1 indicate the proportion of malignant biopsies was lower than the reference year 1992. IDRs with 95% confidence intervals that exclude 1 are significantly distinct from 1992.

The data show that the incidence of malignant biopsies was significantly greater in all study years than the incidence in 1992 (**Table 25**). The peak IDR was 2.094 (95% confidence interval 1.982-2.213) noted in 2010. Notably, the IDR in 2012 (1.726 95% confidence interval 1.629-1.828) was the lowest value since 2005.

Table 25: Incident density ratio for incidence of malignant prostate biopsies by year compared to the year 1992 (referent).

Year	Estimate	Incident Density Ratio (IDR)	Lower Confidence Limit	Upper Confidence Limit
1992 (ref)	--	1	1	1
1993	0.077	1.080	1.012	1.153
1994	0.140	1.150	1.078	1.227
1995	0.197	1.218	1.141	1.300
1996	0.268	1.308	1.228	1.393
1997	0.243	1.275	1.199	1.355
1998	0.325	1.383	1.301	1.470
1999	0.401	1.493	1.406	1.586
2000	0.477	1.611	1.519	1.708
2001	0.485	1.624	1.534	1.720
2002	0.459	1.583	1.494	1.677
2003	0.431	1.538	1.451	1.631
2004	0.545	1.724	1.628	1.825
2005	0.546	1.726	1.632	1.826
2006	0.591	1.806	1.708	1.909
2007	0.606	1.832	1.734	1.936
2008	0.694	2.001	1.893	2.115
2009	0.703	2.020	1.911	2.135
2010	0.739	2.094	1.982	2.213
2011	0.695	2.004	1.897	2.118
2012	0.546	1.726	1.629	1.828

The incidence density ratio (IDR) for malignant prostate biopsy for each age group compared to the reference age group (40-44) was calculated and is presented in **Table 26**. These data show the rate of malignant diagnosis on first biopsy consistently increases with increasing age group. Men over 80 were 3-4 times more likely to be diagnosed with prostate cancer than men aged 40-44.

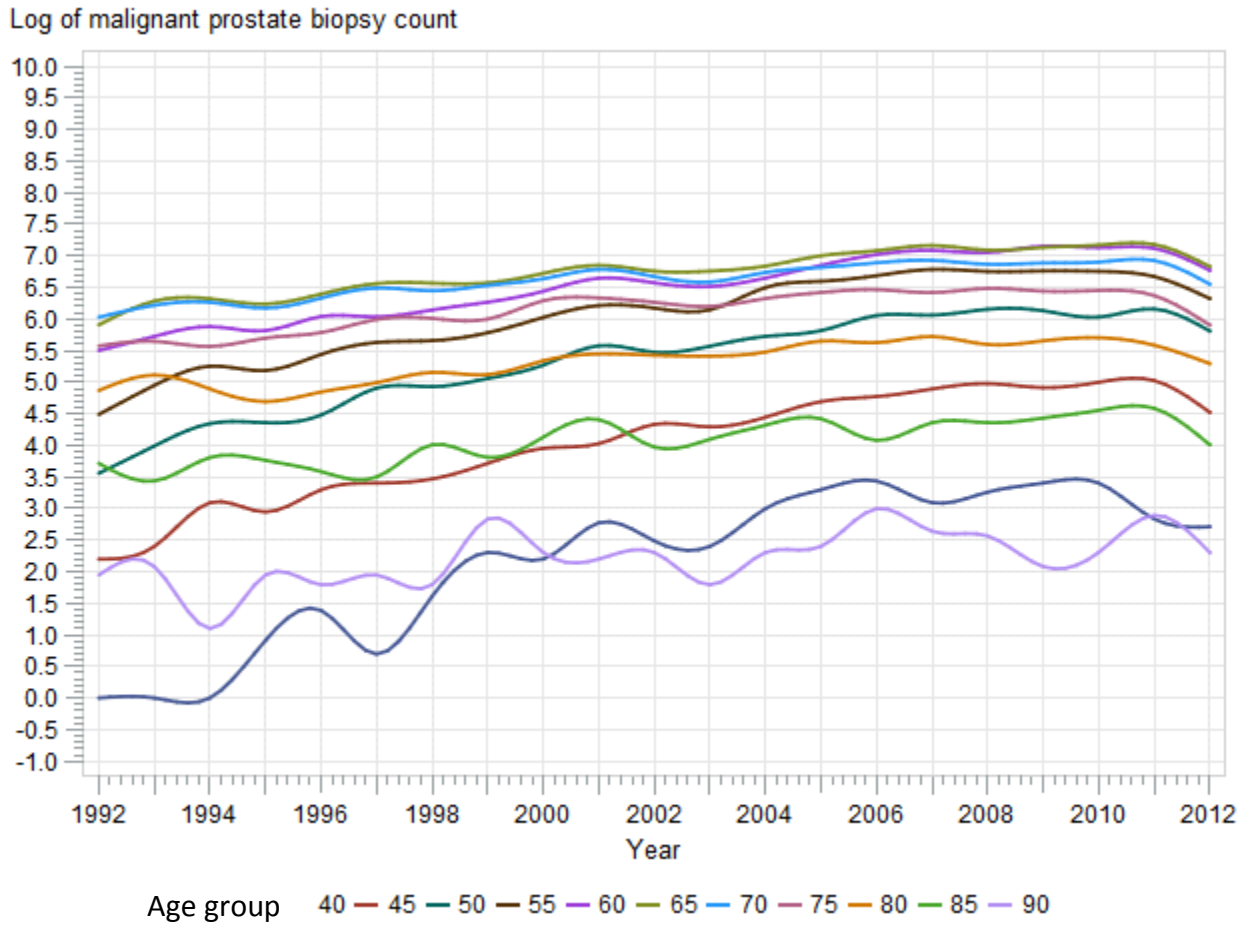
Table 26 : Incident density ratio for incidence of malignant prostate biopsies by age group compared to the 40-45 year age group (referent).

Age group	Estimate	Incident Density Ratio (IDR)	Lower Confidence Limit	Upper Confidence Limit
40 (reference)	-	1	1	1
45	0.41	1.51	1.33	1.71
50	0.59	1.81	1.60	2.03
55	0.69	2.00	1.78	2.25
60	0.82	2.27	2.03	2.56
65	0.93	2.54	2.26	2.86
70	1.05	2.87	2.55	3.22
75	1.13	3.09	2.75	3.48
80	1.21	3.34	2.97	3.76
85	1.19	3.30	2.90	3.75
90	1.23	3.43	2.87	4.10

8.3.3.2 Method 2: Predicting malignant biopsy proportion using study year and patient age

The proportion of malignant prostate biopsies was also examined with study year as a continuous variable. Plots of log transformed malignant biopsy counts over time for all age groups **revealed a slight non-linear relationship** between the log of the number of malignant prostate biopsies and time (**Figure 13**). Subsequent **fractional polynomial modeling** of prostate biopsy counts over time identified a model including the **study year and study year cubed (Equation 13)** as the best fit based on this model having the lowest AIC statistic compared to other combinations of the year variable in its native and transformed form.

Figure 13: Plot of the log of malignant biopsy count per year by year.



Equation 13: Optimal model for estimating the number of malignant biopsies for a given study year and patient age group.

$$\boldsymbol{Log}\ (\boldsymbol{Malignant\ Biopsy\ Count\ in\ Year})$$

$$= \boldsymbol{Log}\ (\#\ \boldsymbol{Malignant\ Biopsies\ in\ Age\ Group}) + \boldsymbol{Intercept} + \boldsymbol{B1}(\boldsymbol{X1}) + \boldsymbol{B2}(\boldsymbol{X2}) + \boldsymbol{B3}(\boldsymbol{X3})$$

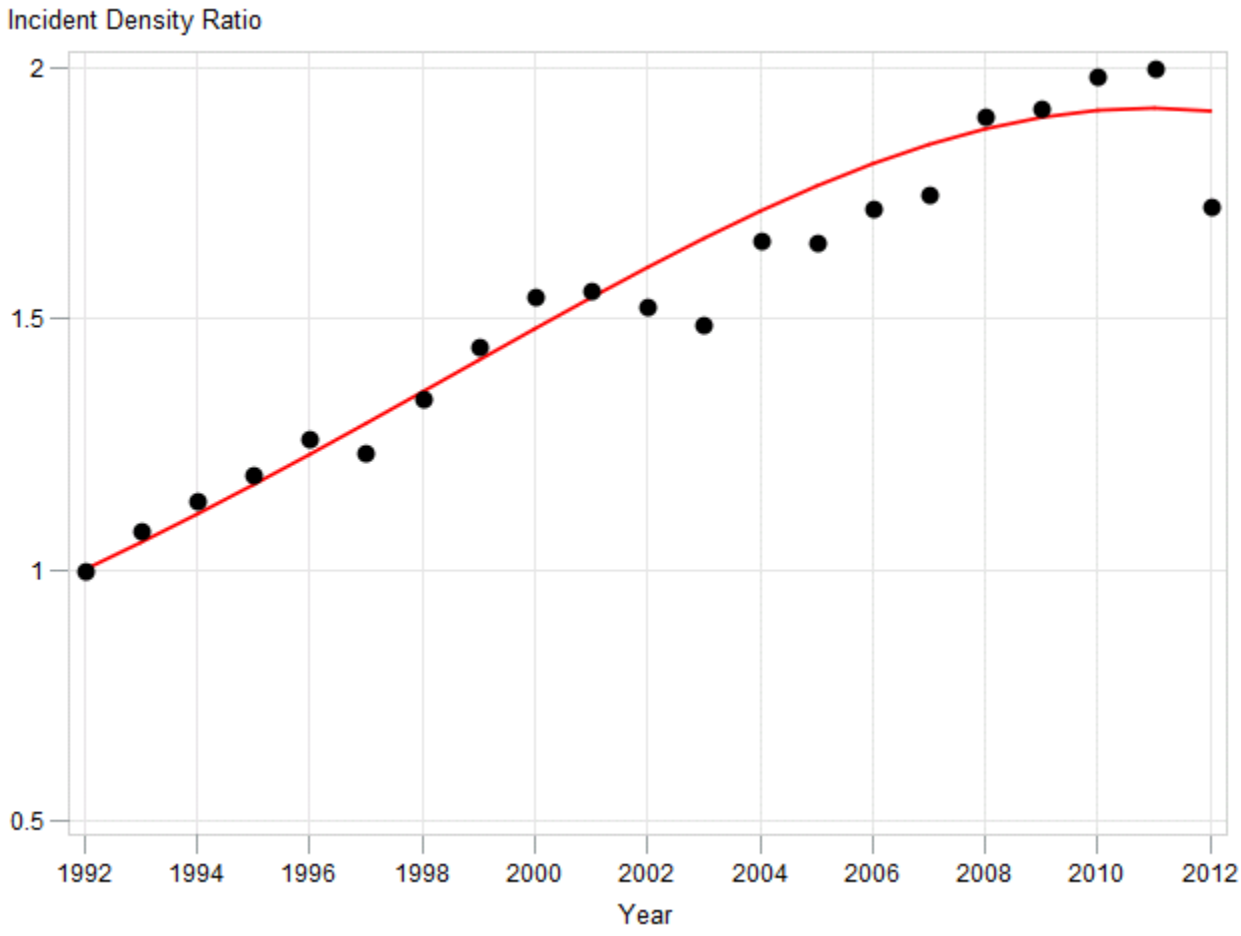
$$= \boldsymbol{Log}\ (\#\boldsymbol{Malignant\ Biopsies\ in\ Age\ Group}) - \mathbf{107.9} + \mathbf{0.41}(\boldsymbol{Age\ group}\ \mathbf{45-49}) + \mathbf{0.053}(\boldsymbol{Year}) - \mathbf{0.000044}(\boldsymbol{Year^3})$$

I calculated the **expected IDRs** (**Equation 12**) for each study year using the optimal model identified from the polynomial transformations (**Equation 13**). These were compared to the **observed IDR**s (**Table 25**) for each study year obtained from the negative binomial regression model (**Table 27 and Figure 14**). **Figure 14** shows that the malignant biopsy incidence in Ontario increased from 1992 until approximately 2010. The observed incidence (black dots on figure) shows a sharp decline in the proportion of biopsies that are malignant in 2012. The expected incidence, red curve derived from the polynomial model shows that the incidence of malignant biopsies levels off in 2012.

Table 27: Expected (from model) and observed proportion of biopsies that are malignant by year from 1992-2012

Year	Expected Incident Density Ratio (IDR)	Observed Incident Density Ratio (IDR)
1992	1.00	1.00
1993	1.05	1.08
1994	1.11	1.15
1995	1.17	1.22
1996	1.23	1.31
1997	1.29	1.27
1998	1.35	1.38
1999	1.42	1.49
2000	1.48	1.61
2001	1.54	1.62
2002	1.60	1.58
2003	1.66	1.54
2004	1.71	1.72
2005	1.76	1.73
2006	1.81	1.81
2007	1.85	1.83
2008	1.88	2.00
2009	1.90	2.02
2010	1.91	2.09
2011	1.92	2.00
2012	1.91	1.73

Figure 14: Expected (from model) and observed incident density ratio for malignant biopsies by year from 1992-2012



8.4 Health status of patients receiving biopsy over time

The ADG score was calculated for all 213,095 patients that received their first prostate biopsy during the study period. The mean ADG score was 4.5 (standard deviation 7.8). Scores ranged from -19 to 72. An ADG score of zero was obtained for 100,560 (47%) patients, indicating that the majority of patients receiving biopsy in Ontario are reasonably healthy because they had no major health care encounters recorded in the 2 years prior to biopsy.

8.4.1 The association between patient age and study year with ADG score

Multivariable linear regression was performed to determine the association between patient age and ADG score, study year and ADG score, and the interaction of patient age and study year with ADG score. I found that as patient age increases the ADG score increases (parameter estimate = 2.07), indicating worse health status. As the study year increased from 1992-2012 the ADG score increased (parameter estimate = 0.02). The interaction term of age and study year was associated with a decrease in ADG (parameter estimate = -0.0009) indicating that the effect of study year varied with patient age.

8.4.2 The influence of time on patient health status at first prostate biopsy

The %MFP8 macro program identified the optimal regression model for predicting the ADG score of patients incorporating fractional polynomial transformations and interactions of the age and year variables (r^2 = 5.4%) (**Equation 14**).

Equation 14: Optimal regression model identified by %MFP8 macro program for using polynomial transformations and interaction terms of the patient age and year to predict ADG score.

$$
\begin{aligned}
\boldsymbol{Expected\ ADG} = \\
&\mathbf{21.57102} \\
&\mathbf{+0.00001} * (\boldsymbol{age} - \mathbf{39})^{\mathbf{3}} \\
&\mathbf{+0.00002} * \left((\boldsymbol{age} - \mathbf{39})^{\mathbf{3}} * \boldsymbol{log}(\boldsymbol{age} - \mathbf{39})\right) \\
&\mathbf{+0.00153} * (\mathbf{age} - \mathbf{39}) * (\mathbf{year} - \mathbf{1991}) \\
&\mathbf{-4.96439} * (\mathbf{year} - \mathbf{1991})^{\mathbf{-2}} \\
&\mathbf{+7.34297} * (\mathbf{year} - \mathbf{1991})^{\mathbf{-1}} \\
&\mathbf{-20}
\end{aligned}
$$

Using **Equation 14** the expected (predicted) ADG score was calculated for each age group and year of interest in our study (**Table 28**). Examination of the table across rows shows that for most age groups of men receiving prostate biopsy in Ontario from 1992 and 2012, the ADG score has decreased slightly. This implies a slightly healthier population of men is being selected for prostate biopsy over time.

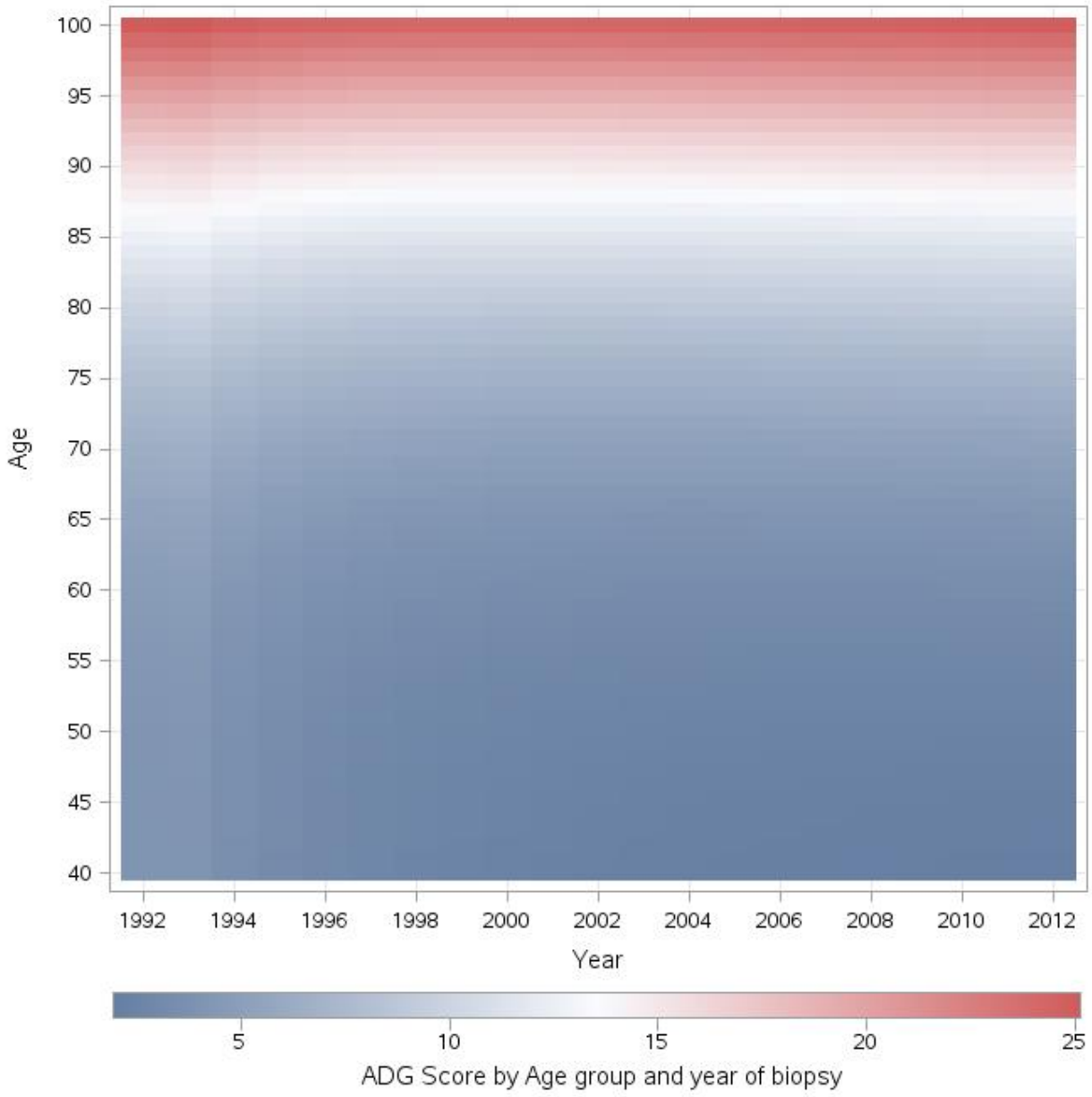
The optimal regression model was used to create a heat map to visually illustrate the expected ADG score using any patient age and year of interest in our study (**Figure 15**). The heat map can be used by identifying the study year and patient age of interest on the x- and y- axes respectively and using the intersection of these points to locate a color on the heatmap to indicate the expected ADG score. This is indicated by the color scale in the legend below the heat map with the lowest ADG scores (indicating a better health status) corresponds to dark blue colors and the highest ADG scores (indicating a worse health status) corresponds to dark red colors. Expected ADG scores ranged from 0 to 25. Visual inspection of the heatmap shows that the expected ADG

decreased slightly for all ages as the study year increased, indicating that the health of men undergoing prostate biopsy appeared to improve over time within all age groups.

Table 28: Expected ADG score by age group and year from 1992-2012.

Age group	Year																				
	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
40	4.0	4.0	3.5	3.1	2.9	2.7	2.5	2.4	2.3	2.3	2.2	2.2	2.1	2.1	2.1	2.0	2.0	2.0	2.0	2.0	1.9
45	4.0	4.0	3.5	3.1	2.9	2.7	2.6	2.5	2.4	2.4	2.3	2.3	2.2	2.2	2.2	2.2	2.2	2.1	2.1	2.1	2.1
50	4.0	4.1	3.6	3.2	3.0	2.8	2.7	2.6	2.6	2.5	2.5	2.4	2.4	2.4	2.4	2.4	2.4	2.3	2.3	2.3	2.3
55	4.2	4.3	3.8	3.5	3.2	3.1	3.0	2.9	2.8	2.8	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7
60	4.6	4.7	4.2	3.9	3.7	3.5	3.4	3.3	3.3	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2
65	5.3	5.4	4.9	4.6	4.4	4.2	4.1	4.1	4.0	4.0	4.0	4.0	3.9	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.1
70	6.3	6.4	6.0	5.6	5.4	5.3	5.2	5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.2	5.2	5.2	5.3
75	7.8	7.9	7.4	7.1	6.9	6.8	6.7	6.7	6.6	6.6	6.6	6.6	6.6	6.7	6.7	6.7	6.7	6.8	6.8	6.8	6.9
80	9.8	9.9	9.5	9.2	9.0	8.8	8.8	8.7	8.7	8.7	8.7	8.7	8.7	8.8	8.8	8.8	8.9	8.9	8.9	9.0	9.0
85	12.5	12.6	12.1	11.8	11.6	11.5	11.4	11.4	11.4	11.4	11.4	11.4	11.5	11.5	11.5	11.6	11.6	11.7	11.7	11.8	11.8
90	15.8	15.9	15.5	15.2	15.0	14.9	14.8	14.8	14.8	14.8	14.8	14.8	14.9	14.9	15.0	15.0	15.1	15.1	15.2	15.2	15.3
95	19.9	20.1	19.6	19.3	19.2	19.1	19.0	19.0	19.0	19.0	19.0	19.1	19.1	19.2	19.2	19.3	19.3	19.4	19.5	19.5	19.6
100	25.0	25.1	24.7	24.4	24.2	24.2	24.1	24.1	24.1	24.1	24.2	24.2	24.3	24.3	24.4	24.4	24.5	24.6	24.7	24.7	24.8

Figure 15: Heatmap of study year, patient age and ADG score. The ADG score can be predicted using study year (x-axis) and patient age (y-axis) to identify the color signal which is associated with a specific ADG score (z-axis below main figure).



9 Discussion:

9.1 Thesis accomplishments

To the best of my knowledge, this is the first study to formally **characterize the prostate biopsy procedure code (Z712)** used in the Ontario Health Insurance Plan administrative dataset. Once I validated the prostate biopsy code, I was able to use it to describe the use of prostate biopsy in Ontario from 1992-2012. Specifically, I determined the crude and age standardized incidence of prostate biopsy in the Ontario population. Population-based, methodologically sound descriptions of prostate biopsy practice patterns in Ontario are of particular interest to the medical community today. In recent years, several randomized trials have been published and have triggered changes in guideline recommendations and possibly changes to clinical practice around prostate cancer screening and detection [8].

I also determined the proportion of prostate biopsies that resulted in a cancer diagnosis, expressed as the proportion of malignant prostate biopsies over time. Knowledge of malignancy status allows us to infer if clinicians have changed the way they are selecting men for biopsy. Along the same theme, I characterized if the health status of patients receiving biopsy by calculating each patient's ADG score. This allowed me to examine if clinicians have altered their practice in response to data showing that older men with comorbidities are not likely to benefit from prostate cancer screening or interventions for localized prostate cancer [25,26].

9.2 Validation of prostate biopsy code

Administrative datasets are not primarily created for research purposes [27]. Therefore, it is essential to define how well the administrative code represents the disease/procedure/patient/outcome you are trying to measure. In other words, is the code a valid

surrogate measure? It is worth pointing out that code validation is not routinely performed by investigators using administrative datasets and this can have important consequences for researchers and clinicians who rely on study data to guide their practice. Indeed, a recent audit of PSA data in the Surveillance, Epidemiology, and End Results (SEER) database revealed that these data had frequent errors and their use in SEER was not currently recommended [28]. The consequences of discovering that PSA data in SEER are not valid are far-reaching. As outlined in a recent editorial, all previous studies using these data need to be questioned for their validity, and ongoing studies using these data need to be re-designed or should omit PSA data altogether [29].

The first step in this study was therefore to determine if the prostate biopsy code (Z712) in OHIP was a valid measure of prostate biopsy procedures performed in Ontario. I **calculated the sensitivity of the prostate biopsy code** using OHIP and OCR datasets. I found that the corrected sensitivity of the code improved over time from 63.8% in 1991 to a high 87.9% in 2012.

It is reasonable to believe the prostate biopsy code provides at sensitivity of greater than 80% for several reasons. First, the code is a physician services claim code which is captured in the OHIP database in one step (claim submission). The least number of steps required to enter a code in a database the more complete it is likely to be. Furthermore, because it is a service claim code, physicians should be motivated to completely submit these codes. Second, there is no alternative procedure code that clinicians would reasonably submit when performing a prostate biopsy. I did explore one possible alternative code (*Z713 – prostate biopsy with drainage of abscess*). I identified only 287 Z713 codes in OHIP compared to 167,133 Z712 codes in the same time period. This proves Z713 is not used as an alternative to Z712 to a meaningful degree. Third, the gold standard (denominator) I used for calculating the sensitivity of the Z712 code was histologic diagnoses of prostate cancer in the OCR. The OCR is a regulated registry which has been shown previously to be highly accurate. We used the OCR as a gold standard however it is possible that

the OCR may capture histologic diagnoses of prostate cancer by some other (non-biopsy) means. For example, pathologic reports from other health care jurisdictions and tissue sampled from other body sites would falsely increase the denominator in the sensitivity calculation and thus falsely decrease the sensitivity of the code. I adjusted the denominator by identifying non-prostate biopsy procedures that may have produced histologic diagnoses (ex: trans-urethral resection of the prostate) in the OCR, however I cannot determine if this adjustment was complete.

Reasons for this improvement of the sensitivity of the biopsy code over time may include: more complete claims submissions by physicians, improvements in electronic data capture and transfer, and a greater proportion of gold standard diagnoses being made by biopsy as opposed to un-adjusted for alternative codes. Given that the code's sensitivity changed over time, I explored if the change in code sensitivity could affect biopsy counts in a clinically meaningful way. I calculated code sensitivity adjusted biopsy counts and found identical trends in biopsy use over time compared to the crude counts. For this reason, crude counts were reported throughout the manuscript to avoid redundancy.

I estimated the **specificity of the prostate biopsy code** using a random sample of prostate biopsy codes from a dataset from the Department of Medical Imaging at The Ottawa Hospital. The Ottawa Hospital is a large tertiary referral cancer center in Ottawa, Ontario, Canada. I found an initial false positive rate of 15.8%. However, the majority of false positives were due to the Z712 code being used for trans-rectal ultrasound guided needle placement of fiducial markers around the prostate prior to prostate cancer radiotherapy treatments. Fiducial marker placements cause an overestimation of the false positive rate for this study for several reasons. First fiducial markers are requested by radiation oncologists. Thus they are predominantly placed in large cancer centers where radiation oncologists work. Therefore, fiducial marker placement will only produce false positive code at these centers. Second, fiducial markers are mostly (or solely) placed by radiologist

(not urologists). In OHIP we found that approximately 40% of Z712 codes are submitted by urologist and none of these are likely to include fiducial marker placement procedure. Furthermore no Z712 codes were submitted by radiation oncologists. Third, requests for fiducial marker placement by radiation oncologists has decreased significantly in recent years because they have better methods for targeting prostate tissue during treatments (ex: intensity-modulated radiation therapy (IMRT)) and thus do not use fiducial markers as frequently. Indeed, I observed only 3 (2.5%) fiducial marker placements since 2011 in the sample. Finally, the most important reason why fiducial markers have little if any influence on this study is because markers for radiotherapy targeting are only placed after a diagnosis of cancer is made by a prostate biopsy. The study population was limited to patient's **first biopsies**, therefore codes I captured in OHIP should not contain any fiducial marker placement procedures. For these reasons I adjusted the false positive rate by removing false positives due to fiducial markers and calculated a corrected **false positive rate of 1.9%** for first time biopsy codes in this study. It is likely the false positive rate in recent years is even lower than 1.9% given the decrease in fiducial marker use noted. I showed in **Table 9** that a false positive rate of 1.9% equates to a specificity of >95% for a corresponding sensitivity of 50% and over 97% for a sensitivity of 75%.

In summary, **this is the first study to show that prostate biopsy Z712 codes in OHIP appear valid for identifying the first prostate biopsy a patient receives**. The code may be less valid for identifying secondary biopsy procedures because some of these codes may actually represent transrectal ultrasound guided needle placements of fiducial markers around the prostate or other procedures. These findings have implications for studies using prostate biopsy codes in OHIP. For example, side effects occurring in patients after these codes are recorded may be secondary to radiotherapy treatments rather than a biopsy procedure [10].

9.3 Incidence of prostate biopsy in Ontario from 1992-2012

The use of prostate biopsy in recent years is of interest to the medical community because recent prostate cancer screening trials triggered changes in guideline recommendations and the impact of these guidelines has yet to be assessed in the Ontario population [6,30–32]. I identified several notable statistics when examining prostate biopsy incidence in Ontario from 1992-2012. Prior to the study I hypothesized that the incidence of prostate biopsy in Ontario would be decreasing over the last 10 years. I found the annual crude rate of biopsy increased from 1992 to 2007 and decreased thereafter. Significant decreases were observed in men over age 70 around 2008, corresponding with the 2008 USPSTF guideline recommendation against PSA screening in older men [33]. A decrease in all age groups was observed in the year 2012 corresponding with the 2012 USPSTF guideline against screening in all men [8]. Because 2012 is the last complete year available in the OHIP dataset, it is unclear if these changes are transient or the first sign of a shift in practice amongst Canadian physicians. However given similar observations in other cohorts it is likely a practice change has occurred [34–36].

In 2009-10, three large randomized trials from the United-States and Europe reported results at 7, 9 and 14 years follow-up respectively. The United-States Prostate, Lung, Colorectal and Ovarian (PLCO) trial reported no benefit to prostate cancer screening with prostate specific antigen [37]. The European Randomized Study for Screening of Prostate Cancer (ERSPC) trial reported a modest 20% reduction in prostate cancer specific mortality [31]. The Goteborg study reported a 44% reduction in prostate cancer specific mortality at 14 years [6]. Each of these trials also highlighted risks of prostate cancer screening, most importantly, over-diagnosis and over-treatment. The number needed to screen to prevent 1 prostate cancer death was 293 in the Goteborg study and 1,055 in the ERSPC study. The results of these trials incited considerable debate in the medical community about the value of population-based PSA screening. In 2008 the

United States Preventive Services Taskforce (USPSTF) recommended against prostate cancer screening in men over 75 years of age [33]. This was followed by revised publication in 2012 in which they gave a Grade D recommendation to prostate cancer screening in all age groups, concluding that the harms outweigh the benefits [8].

These data on prostate biopsy incidence provide indirect evidence that PSA screening rates have decreased in Ontario. However because PSA is not available in ICES dataset I was not able to confirm that prostate cancer screening has also decreased. It is likely that the changes I observed in prostate biopsy use are associated with a change in screening. Prostate cancer screening was widely adopted in Canada when the PSA biomarker was made available in the 1990's. Prostate biopsies are the end result of prostate cancer screening, therefore trends in prostate biopsy are likely be indicative of prostate cancer screening practices. Indeed a previous study of over 300,000 men in Denmark reported that men in the highest quartile of PSA screening intensity were 76% more likely to receive a prostate biopsy than men in the lowest quartile of PSA testing [38]. The association between PSA screening intensity and prostate biopsy incidence is also supported by comparing these biopsy results with studies that reported decreased use of PSA screening in other cohorts following the USPSTF recommendation [32,34–36]. In one study Bhindi et al. examined changes in PSA screening and biopsy use at a large tertiary care center in Toronto, Ontario, Canada [39]. They reported changes in prostate biopsy rates using a time series analysis from October 2008 to June 2013. They found that the median number of patients receiving their first biopsy almost halved from a median of 42.5 (IQR 37.5-45.5) to 24 (IQR 19.0-32.5) in the time period before and after the USPSTF recommendation in 2012. These authors concluded that the decrease in biopsies they observed were likely due to decreased use of PSA screening in their catchment area.

A second finding of interest in these data was that decreases in biopsy rates over the entire study period were most prominent in men over the age of 70. As a result, over time younger men represented a larger proportion of patients receiving biopsy. For example men aged 50-55 represented 4% of biopsies in 1992 and 10% of biopsies in 2012. Similar trends were noted in previous studies examining PSA screening trends and biopsy use [39,40]. These changes were expected as a plethora of evidence has merged over the last decade showing that older men with comorbid medical conditions are unlikely to benefit from screening and interventions for localized prostate cancer [25,26].

It remains too early to tell if physician practice has changed for the long term or if trial results and taskforce recommendations caused only a transient change in practice. Repeat analyses of population-based dataset from Ontario and other health care jurisdictions are needed to answer this question. None the less, to the best of my knowledge this is the first study to report a decrease in the incidence of prostate biopsy use on a population-wide scale.

9.4 Proportion of malignant prostate biopsies in Ontario from 1992-2012

Selecting men for prostate biopsy after PSA screening may be challenging. In the PSA screening era many men screen positive and receive a consultation with a urologist who has to decide if a prostate biopsy is indicated. Men receiving biopsies should have a sufficiently high risk of malignancy to warrant the potential side effects of the biopsy [10]. Previous studies have identified clinical factors that increase a patients risk of malignancy on biopsy [13,41]. Factors associated with malignancy include; patient age, family history of prostate cancer, ethnicity, suspicious digital rectal exam, lower urinary tract symptoms, and various PSA

measurements/kinetics. Validated nomograms have been constructed to aid clinicians and patients in the difficult decision of proceeding with a biopsy or not. Clinical application of these nomograms should decrease over-diagnosis of prostate cancer.

I sought to determine if physicians in Ontario have improved over time at selecting men for biopsy based on the risk of malignancy. To do so, I determined the proportion of biopsies that were malignant at first prostate biopsy in Ontario for each year from 1992-2012. Overall, I identified 84,149 (39%) malignant biopsies. The incidence of malignant biopsies increased during the study period from 26% in 1992 to 49% in 2010. After 2010, there was a sharp decline to 40% in 2012. Because 2012 is the last year of data in this study, it is unclear if this decline is a chance statistical finding or the first sign of a change in practice, therefore additional years need to be examined in future studies. These results from Ontario are consistent with trends observed in other population-based datasets after the 2012 USPSTF recommendation against PSA screening [34]. Malignant biopsy trends over time were similar in all age groups.

These results suggest that physicians are doing a better job of selecting men for prostate biopsy based on their risk of malignancy. The increase in malignant biopsy rate is noteworthy for three additional reasons. First, the increased incidence of malignant first biopsies occurred in conjunction with increasing biopsy rates in the population. This provides some reassurance that increasing biopsy rates are not exposing more men without cancer to the risks of biopsy. Second, the increased proportion of malignant first biopsies occurred while prostate cancer rates in the United-States decreased in the population [42]. Thus, although more men are receiving prostate biopsies in Ontario the number of potentially unnecessary biopsies (screen positive patients that receive a biopsy despite low risk of malignancy) is not increasing. Third, malignant biopsies increased at the same time I observed decreased biopsy rates in older men. One alternative explanation for increased positive biopsy rates during the study period is a change in the

procurement and pathological processing of biopsy tissue. More sampling (more core biopsies) and use of separate specimen vials for each core has been shown to increase cancer detection [43].

Overall these findings suggest that physicians in Ontario are judiciously selecting men for prostate biopsy. However, it remains likely that many men who were diagnosed with cancer in this cohort have indolent disease. Further assessment with pathologic grade and stage information is required.

9.5 Health status of patients receiving prostate biopsy in Ontario from 1992-2012

Over-diagnosis and subsequent over-treatment are the principle reasons why the USPSTF and Canadian Taskforce on Preventive Health Care recommended *against* PSA screening [7,8]. Physicians should select men for screening and biopsy that are healthy enough to derive benefit from the detection of clinically localized cancer. Patients over 70 and those with significant medical comorbidities are unlikely to benefit from screening related biopsies and thus should generally not be screened.

I characterized the health status of patients receiving their first prostate biopsy in Ontario from 1992 to 2012 using the ADG score. I then examined if the health status (ADG score) of patients receiving biopsy was changing over time. The ADG score is a diagnosis based scoring system applied to inpatient and outpatient health care settings that has been validated for use with Ontario administrative health care databases [22]. A low ADG score (approaching 0) indicates a lower probability of mortality.

I calculated the ADG score for all 213,095 patients in our cohort and found that 100,560 (47%) had ADG scores of 0, indicating they were quite healthy in the two years leading up to their

prostate biopsy. I also found that patients receiving biopsy were healthier over time independent of patient age. This suggests that physicians are selecting healthier men for prostate biopsy, and likely prostate cancer screening. These findings are reassuring because previous studies have not consistently shown that health status is associated with screening choices. One study using United-States Department of Veterans Affairs Medicare claims showed that elderly men in poor health were just as likely to receive PSA testing as men in good health [44]. Another study using data from the National Health Interview Survey in the United-States before and after the 2012 USPSTF recommendation against PSA screening showed that although men in poorer health were less likely to be screened than their healthy peers over 30% of men with high (>52%) risk of mortality at 9 years received screening [45]. My findings are consistent with a previous study I published indicating that urologist in Ontario select men with greater than 10 year life expectancy to receive curative treatment via radical prostatectomy [14].

9.6 Study strengths

This study has several strengths. Most importantly, the first step of the study validated use of the OHIP prostate biopsy code (Z712) for identifying the first prostate biopsy procedure a patient receives in Ontario by comparing it to a gold standard measure of prostate biopsy (OCR histologic diagnoses). Furthermore, I reported the estimated sensitivity and specificity of the code because these measures vary less with changes in disease prevalence [46]. Validated codes are the foundation of administrative database studies, without them it is impossible to interpret this study or others that use these codes. Second, I used sensitivity analyses when measuring biopsy code validity and malignant biopsy rates making these results more rigorous. Third, the population-based nature of this study makes the results more meaningful. Most studies examining prostate biopsy trends over time have cohorts that were derived from one or a few large academic hospital

centers making their results difficult to generalize. My data include all biopsy procedures performed in Ontario by urologists and radiologists. They should be reflective of broad medical practice and are more likely to be correlated with population-based prostate cancer screening trends. To the best of my knowledge this is the first study to report age standardized biopsy rates for an entire population, allowing future studies to compare rates in other jurisdictions to those in Ontario. I observed a long time period spanning the introduction of PSA to the recommendation against PSA screening. I exploited the long time frame by using fractional polynomial models to examine changes in biopsy trends allowing for different trends in each era. Finally, I used a previously validated highly accurate measure of patient health status, the ADG score, to characterize the health status of patients in our cohort making these results more believable than the majority of studies that are limited in their capture of comorbid status.

9.7 Study limitations

The sensitivity of our prostate biopsy code for identifying histologically confirmed prostate cancers in the OCR (gold standard) was modest at approximately 80-90%. Explanation for this could be that our gold standard cases may include histologic prostate cancer diagnoses made from procedures outside of Ontario, were prostate biopsies performed in Ontario with no claim submission, or were derived from procedures that procure tissue but are not prostate biopsies (ex: biopsy of metastatic deposit). I removed cases from the OCR cohort that had alternative explanations for their tissues histology however I am not able to explain why a proportion 10-20% of patients have histologic diagnoses and no biopsy. I estimated the specificity of the prostate biopsy code to be greater than 95%, however this calculation was performed using procedure reports from one large academic center.

This study reports changing rates of prostate biopsy over time which I believe are partially explained by changes in prostate cancer screening however this is a hypothesis. Thus I cannot conclude that the decline in biopsy rates observed in 2008 and 2012 are a result of decreases in PSA screening. PSA data is becoming available in Ontario administrative datasets currently, however these data will not be able to provide insight into past practice trends.

I am unable to comment on the clinical significance of detected cancers as I do not have cancer grade and stage available in our dataset. Although I interpreted the increase in malignant biopsy rate to suggest physicians are doing a better job of selecting patients for biopsy, it is possible that the increase was caused by more indolent tumor detection. Furthermore although I found increasing malignant biopsy rates and healthier patients receiving biopsies we did not investigate what treatments these patients are receiving nor if they benefit from treatment, therefor I cannot comment on rates of over-diagnosis and over-treatment.

Finally, prior to starting this study I hypothesized that biopsy rates would be decreasing since the USPSTF recommended against prostate cancer screening. I did observe a corresponding decline in biopsy rates in men over 70 years of age in 2008 and in all men in 2012 however at the time of analyses, data beyond 2012 was not available so I do not know if the observed decrease persisted in subsequent years. This will require further exploration as data become available.

10 Conclusions

This is the first study to report crude and age standardized prostate biopsy incidence at a population level. I found that biopsy rates decreased in 2008 and 2012 in conjunction with changes to the USPSTF recommendations for prostate cancer screening. More years of follow up are required to determine if these changes were transient or the start of broad practice changes.

Physicians have changed the way they select patients for biopsy over time. Patients receiving biopsy in more recent years were more likely to have a malignancy detected and be in good health.

11 Thesis supervision and structure

11.1 Supervisors and their Roles

Dr. Carl van Walraven:

Dr. van Walraven is a physician in the Department of Medicine, Professor at the University of Ottawa, Senior Scientist at the Ottawa Hospital Research Institute (OHRI), and Scientist at the Institute for Clinical Evaluative Sciences (ICES). Dr. van Walraven has provided mentorship and guidance for all elements of this thesis. Specifically, he has provided methodological expertise for using large administrative databases including the OHDW and ICES.

Dr. Rodney H Breau:

Dr. Breau is a surgeon in the Division of Urology (Surgical Oncology), an Assistant Professor at the University of Ottawa, and Associate Scientist at the OHRI. Dr. Breau has provided mentorship and guidance for all elements of this thesis. Specifically, he has provided content expertise for all elements related to urological oncology.

11.2 Thesis advisory committee (TAC)

Dr. Carl van Walraven

Dr. Rodney H Breau

Dr. Dean Fergusson

Dr. Dean Fergusson:

Dr. Fergusson is a Senior Scientist at the OHRI and Associate Professor at the University of Ottawa. Dr. Fergusson has provided mentorship and guidance as a member of the thesis advisory committee.

11.3 Category of Thesis

Completion of this thesis will required:

- Secondary analyses of large datasets including the Institute for Clinical Evaluative Sciences.
- Complex methodological techniques for building search algorithms for identifying the study cohort from large datasets and analyzing these datasets.

The design of this thesis best fits the category of *complete research project* and *secondary analysis of existing datasets*.

11.4 Publication of study results

Study results will be published in peer-reviewed journals after completion of the thesis. All supervisors will be authors on study related publications provided they have contributed in a significant manner to the manuscript in question. Additional authors will be permitted on study related manuscripts if they contribute in a significant fashion to the production of the manuscript in question.

11.5 Candidate signature:

1. Candidate:

_____ _____

Luke T. Lavallée **Date:**

Luke T. Lavallée MDCM FRCSC
Master's Degree Candidate
Urologic Oncology
Division of Urology
The University of Ottawa
501 ch. Smyth Rd.
Box / C.P. 222
Ottawa, ON
K1H 8L6
Phone 613-737-8899 ext 73019
Fax 613-739-6842
lulavallee@toh.on.ca

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13 Appendix

13.1 Full model output from Equation 11: Estimating the expected prostate biopsy count using patient age group and study year in a negative binomial model.

Parameter	Parameter Estimate	95% Confidence Limits	
Intercept	-86.7422	-111.256	-62.2287
Year	0.0391	0.0268	0.0514
Year3	-0.0001	-0.0001	-0.0001
Age 45-49	1.2757	1.1375	1.4139
Age 50-54	2.4726	2.3359	2.6093
Age 55-59	3.2581	3.1217	3.3945
Age 60-64	3.7432	3.6069	3.8795
Age 65-69	4.0514	3.9151	4.1878
Age 70-74	4.0133	3.8768	4.1499
Age 75-79	3.8001	3.6630	3.9372
Age 80-84	3.4213	3.2830	3.5596
Age 85-89	2.9889	2.8463	3.1315
Age ≥90	2.1232	1.9537	2.2927

13.2 Full model output from Equation 13: Estimating the expected number of malignant prostate biopsies using patient age group and study year in a negative binomial model.

Parameter	Parameter Estimate	95% Confidence Limits	
Intercept	-107.934	-116.987	-98.8803
Year	0.0530	0.0485	0.0576
Year3	-0.0000	-0.0001	-0.0000
Age 45-49	0.4096	0.2810	0.5382
Age 50-54	0.5873	0.4658	0.7089
Age 55-59	0.6922	0.5721	0.8122
Age 60-64	0.8221	0.7026	0.9416
Age 65-69	0.9370	0.8177	1.0563
Age 70-74	1.0580	0.9385	1.1774
Age 75-79	1.1295	1.0094	1.2495
Age 80-84	1.2059	1.0839	1.3279
Age 85-89	1.1953	1.0649	1.3257
Age ≥90	1.2323	1.0524	1.4121