# The effect of statin use on the incidence of prostate cancer: a population-based nested case-control study

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## ABSTRACT

**Background:** 5-alpha-reductase inhibitors reduce prostate cancer (PC) risk, but have not been widely used in prevention because of side-effects and cost-effectiveness. Statins are indicated for the primary and secondary prevention of cardiovascular disease and have an excellent benefit to risk profile. They may also reduce the risk of PC.

**Objectives:** 1) Review the biological and epidemiologic rationale about statins to prevent PC; 2) Determine if statin use reduces PC risk; 3) Evaluate the effect of statin dose, duration of use, and lipophilicity on statin impact on PC risk;

**Methods:** We performed a systematic search of Medline (Ovid), EMBASE (Ovid), and PubMed for studies addressing biologic and epidemiologic evidence of PC risk and statin use. To assess the validity of potential screening variables, we measured the bivariate association with PC risk using conditional logistic regression and used logistic regression to evaluate the association with the diagnosis of clinically significant disease. We then completed a nested case-control study investigating the impact of statin use on PC diagnosis and clinically significant PC using data from men aged >=40 years in the Canadian province of Saskatchewan between 1990-2010. Drug exposure histories were derived from a population-based prescription drug database. We used conditional logistic regression to model use of statins as a class and stratified the analyses for groups of statins defined by lipophilicity. Clinically significant PC was defined as: Gleason score of 8, 9 or 10 OR stage C or D or III or IV at diagnosis.

**Results:** There is a compelling pre-clinical rationale for statins as potential chemopreventive agents, as they interfere with five of the ten hallmarks of cancer. However, the epidemiological literature investigating the effect of statin use on PC incidence has reported widely varying results and is often plagued by small sample sizes, short pre-diagnosis information on drug exposure, and potential biases. Screened1 was used to help account for PC screening as it balanced efficacy and allowed separate

interpretation of drugs used for benign prostatic hypertrophy. 12,745 cases of PC were risk-set matched on age and geographic location to 50,979 controls. Greater than 90% of subjects had pre-diagnosis drug exposure histories >15 years. 2064 (16.2%) cases and 7956 (15.6%) controls were dispensed one or more statin prescriptions. In multivariable models, ever prescription of statins was not associated with PC diagnosis (OR 0.97; 95% CI 0.90-1.05). Neither lipophilic statins (OR 0.96,95% CI 0.88-1.04) nor hydrophilic statins (OR 1.06, 95% CI 0.95-1.20) impacted PC diagnosis. There was no effect of the dose or duration of statin use. Diagnosis of clinically significant PC decreased with statin use (OR 0.84, 95% CI 0.73-0.97).

**Conclusion:** Despite a strong pre-clinical rationale, statin use is not associated with change in PC risk, regardless of duration or dose of statin use. Statin use is associated with a decreased risk of clinically significant PC. At this stage, we believe further studies with both long pre-diagnosis drug histories and an ability to adjust directly for PC screening are needed before considering embarking on randomized chemoprevention trials.

## PREFACE

The work described in this thesis represents original research conducted by the candidate. The objective of this work was to investigate the effect of statin use on the incidence of prostate cancer.

The thesis is organized into three chapters. Chapter 1 is a review of the literature that summarizes the existing biologic and epidemiologic evidence investigating if statins prevent prostate cancer. Chapter 2 describes the objectives, main methods, and results of the nested case-control study. Chapter 3 details the construction and choice of a score variable used to account for prostate cancer screening.

**Conflicts of interest:** The candidate reports having attended advisory boards for Merck and AstraZeneca related to non-statin oncology products. These disclosures are not thought to create significant conflicts of interest for this study.

**Disclaimers:** This study is based on de-identified data provided by the Saskatchewan Ministry of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Ministry of Health. The Canadian Institutes of Health Research played no role in the design or conduct of the study and bears no responsibility for the analysis of the data or the interpretation of the results.

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| | |
|---|---|
| 95% CI | 95% Confidence Interval |
| Akt/PKB | Protein Kinase B |
| ASA | Acetylsalicylic Acid |
| ATC | Anatomical Therapeutic Chemical |
| BPH | Benign Prostatic Hypertrophy |
| COX2 | Cyclooxygenase-2 |
| DDD | Defined Daily Dose |
| DRE | Digital Rectal Exam |
| HMG-CoA | 3-hydroxy-3-methylglutaryl coenzyme A |
| ICD-9 | International Classification of Disease, Ninth Revision |
| MEPS | Microscopic Examination of Prostatic Secretions |
| mg | milligram |
| NR | Not Reported |
| NSAID | Non-Steroidal Anti-Inflammatory Drug |
| OR | Odds Ratio |
| PC | Prostate Cancer |
| PPD | Period of Preclinical Detectability |
| PSA | Prostate Specific Antigen |
| Q1 | First Quartile |
| Q3 | Third Quartile |
| Ras/Rho/Rac | protein superfamily of small GTPases |
| RCMP | Royal Canadian Mounted Police |
| RCT | Randomized Controlled Trial |
| ROC | Receiver Operating Curve |
| RR | Risk Ratio |
| SCR | Saskatchewan Cancer Registry |
| SD | Standard Deviation |
| SEER | Surveillance Epidemiology and End Results |
| SPDP | Saskatchewan Prescription Drug Plan |
| TNFα | Tumour Necrosis Factor Alpha |
| TURP | Transurethral Resection of Prostate |
| US | United States of America |
| VEGF | Vascular Endothelial Growth Factor |
| WHO | World Health Organization |

## Introduction

For men living in economically developed nations, prostate cancer (PC) is the most common non-cutaneous cancer and represents the third leading cause of cancer-related death. [1] Prostate Specific Antigen (PSA) screening has led to a substantial increase in PC incidence, but even prior to the era of PSA screening the age-adjusted incidence rates for PC were steadily increasing both worldwide and in Canada.[2] While most PC patients are diagnosed at an early disease stage, 10-15% of patients are diagnosed with metastatic incurable disease and others recur after curative intention treatment.[3] Substantial advances in the treatment of incurable disease have been introduced over the last decade. While these innovations improve patient survival, they've also been associated with increasing treatment costs.[4] The trend of increasing incidence, coupled with an aging population, and increasing treatment costs, suggests that the clinical and economic burden of PC will continue to grow in the future.[5]

Despite the public health problem posed by PC, the only three established risk factors - aging, African-American ethnicity, and family history of PC – are not modifiable.[6-9] With no evident modifiable risk factors, the possibility of chemoprevention becomes a preferred strategy. Randomized controlled trials show that the 5-alpha-reductase inhibitors finasteride and dutasteride reduce the overall risk of developing PC, but may increase the risk of aggressive or advanced PC.[10] While non-steroidal anti-inflammatory drugs may also decrease risk of PC, neither of these classes of drugs have been widely prescribed due to potential side effects and cost effectiveness.[11, 12] Therefore, despite many studies exploring chemopreventive agents for PC, there are no currently accepted and widely used options.

Statins, on the other hand, are indicated for the treatment of hypercholesterolemia and for the primary and secondary prevention of cardiovascular disease, have an excellent benefit-to-risk profile, and can be

taken safely over the long term.[13, 14] Postulated anti-cancer effects of statins are biologically plausible. The enzyme HMG-CoA reductase is upregulated in several cancers, including PC.[15-17] The downstream products of the mevalonate pathway, including cholesterol, retinoids and the isoprene moieties, are involved in steroid hormone production, cell cycle regulation, and numerous signal transduction pathways.[18] Therefore, blocking this pathway could influence the processes leading to tumour initiation, progression and spread.[19] While pre-clinical research provides a good rationale for statins preventing PC, epidemiologic studies of the relationship between statin use and PC risk have reported conflicting results.[20] We therefore undertook a search of the existing literature to synthesize the biological and epidemiological evidence investigating a potential impact of statins on PC incidence.

A 2012 meta-analysis suggested that use of statins may reduce the risk of PC by 7%, but results showed substantial heterogeneity.[20] The discrepancies between these studies may reflect their limitations. Most were limited by exposure data confined to the recent past, limited information on dose, timing and duration of statin use, and by the possibility of uncontrolled detection and recall biases. Very few studies have allowed for the long latency of any potential protective effects; the follow-up periods of most studies may have been too short to detect an impact. Due to these weaknesses in the existing epidemiologic literature, we conducted a nested case-control study to assess the effects of statin use on the risk of developing prostate cancer using data from the Saskatchewan Cancer Registry (SCR) and the Saskatchewan Prescription Drug Plan (SPDP). The SPDP has collected data on all drug prescriptions filled in Saskatchewan since 1975, allowing for long-term data on pre-diagnosis statin exposure and eliminating the risk of recall bias, while providing information on dose and duration of treatment.[21]

However, the SCR does not include information on PC screening, which has a significant impact on PC detection. In epidemiological studies, adjusting for screening is important because screening can increase the risk of selection bias and detection bias.[22] Therefore, we used administrative codes associated with physician visits where PC screening likely occurred to build a variable to help adjust for likelihood of PC screening.

Our study is important, because statins are prescribed to many Canadians and even a small decrease (or increase) in cancer risk associated with their use could have significant implications for public health, health expenditures, and resource utilization. Finding no associations with PC risk would also be helpful, as it provides reassurance to the thousands who use these medications on a regular basis. If there appears to be a substantial decrease in PC risk with statin use, then these data would help justify randomized controlled trials.[13, 14]

**Chapter 1 – Biologic and epidemiologic evidence assessing if statins prevent prostate cancer (Paper 1, accepted by The Canadian Journal of Urology)**

## Introduction

Prostate cancer (PC) is a significant public health problem. It is the most common non-cutaneous malignancy in men living in developed countries, with an estimated 758,700 newly diagnosed cases in 2012, and the third leading cause of death from cancer.[1] During their lives, 1 in 8 men will be diagnosed with PC.[23] Even before the advent of Prostate Specific Antigen (PSA) screening, the age-adjusted incidence rates for PC were steadily increasing both worldwide and in Canada.[2] This trend, coupled with an aging population and increasing treatment costs, suggests that the clinical and economic burden of PC will continue to grow in the future.[5]

These burdens emphasize the need for strategies to prevent the development of PC. Several drugs, including the 5-alpha-reductase inhibitors finasteride[24] and dutasteride,[25] were found to reduce the risk of PC. However, using 5-alpha-reductase inhibitors preventatively may increase the risk of aggressive or advanced PC.[10] A protective effect of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs)[26, 27] has been confirmed in a pooled analysis of relevant clinical trials.[28] However, these drugs have not been widely used in PC prevention because of concerns about side-effects and cost-effectiveness.[11, 12]

Evidence from laboratory and animal studies suggests that statins may reduce the risk of PC.[29-31] Statins — inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the mevalonate pathway of cholesterol synthesis— are among the most commonly prescribed medications in North America. Canadian studies demonstrate that statins were used by 8.3%

of adults in 2002 and 46.6% of seniors in 2012.[32, 33] As cholesterol-lowering drugs, statins are indicated for the treatment of hypercholesterolemia and for the primary and secondary prevention of cardiovascular disease.[13, 14, 34] For these indications, they have an excellent benefit-to-risk profile, and can be taken over the long term.[13, 14]

Despite the public health problem posed by PC, little is known about its causes. In a detailed review of the literature,[6] only three established risk factors were found: aging, African-American ethnicity[7, 8], and family history of PC[9]; none of which are modifiable. The search for highly penetrant candidate genes has been largely unsuccessful.[35] Migrant studies show that risk increases among men who move from low risk to high risk areas,[36] but studies of lifestyle factors such as smoking, dietary habits, alcohol intake, and physical activity have produced inconsistent results and failed to validate modifiable risk factors.[37-41]

While no modifiable risk factors have been identified for PC, certain biologic capabilities and conditions are necessary for carcinogenesis. These requirements include: evading growth suppression, avoiding immune destruction, enabling replicative immortality, resisting cell death, sustained proliferative signalling, inducing angiogenesis, genome instability, tumour-promoting inflammation, dysregulated cellular energetics, and the activation of invasion and metastasis.[42] Any potential chemopreventive agent would need to interfere with one or more of these processes to prevent PC.

## Objectives

1) Identify and describe the evidence supporting a biologic rationale for statins impacting the development of PC.

2) Identify and evaluate existing epidemiologic studies investigating the impact of statin use on PC incidence.

## Methods

We performed a systematic search of Medline (Ovid), EMBASE (Ovid), and PubMed from inception to March 7, 2016. The specific search strategy for Medline is outlined in Appendix 1. We planned a narrative review and therefore only included a representative selection of biologic mechanism articles. However, all epidemiologic studies that focused on statin use and PC incidence were included. We excluded studies focused on PC mortality, aggressiveness, or recurrence.

## Results

### Biological rationale

The postulated anti-cancer effects of statins are biologically plausible. The enzyme HMG-CoA reductase is upregulated in several cancers, including PC.[15-17] The downstream products of the mevalonate pathway, including cholesterol, retinoids and the isoprene moieties, are involved in steroid hormone production, cell cycle regulation, and numerous signal transduction pathways.[18] Therefore, blocking this pathway could influence the processes leading to tumour initiation, progression and spread.[19]

Inhibition of HMG-CoA reductase may reduce the risk of cancer via both cholesterol-mediated and cholesterol-independent pathways. Cholesterol is a precursor of androgens,[43] which are required for prostatic carcinogenesis by inducing a sustained proliferative response.[44] While statins were found to

lower serum androgens in some studies,[45, 46] others showed no effect.[47, 48] It has been proposed that lowering blood cholesterol may hinder carcinogenesis by reducing intra-prostatic androgen levels,[49] or by altering cell membrane signaling.[50] However, epidemiologic studies that examined the relationship between serum cholesterol levels and PC risk have found no consistent associations.[51-54]

Numerous animal and experimental studies suggest that statins have potent anti-tumour effects, independent of their cholesterol-lowering effects, including pro-apoptotic, anti-proliferative, anti-inflammatory and anti-angiogenic effects.[19] Statins induced apoptosis (programmed cell death) in several cell lines derived from PC, possibly by activating multiple caspases, [55, 56] and inhibiting pro-survival *Akt*-mediated signalling.[15] These pro-apoptotic effects may be reversed by the addition of mevalonate.[55] Furthermore, there is evidence that statins are more effective in inducing apoptosis in tumour cells than in normal cells.[57] Such effects suggest an ability to circumvent the ability of malignant cells to resist cell death.

Statins, in particular lipophilic statins, were found to decrease the proliferation of PC cells *in vitro* and tumour growth rate *in vivo*, likely due to their ability to block $G_1$-S transition in the cell cycle through stabilization of the cell cycle inhibitor kinases p21 and p27.[58] Also, several small G-proteins in the *Ras*, *Rho*, and *Rac* signalling pathways, essential for cancer cell survival and proliferation, are activated via post-translational modifications involving the geranylgeranyl and farnesyl isoprene units – other downstream products of the mevalonate pathway blocked by statins.[18] Therefore, statins may reduce proliferative signalling both through reduction of androgens and blocking of isoprene moieties.

Like NSAIDs,[26, 27] statins can suppress the production of several inflammatory mediators including interleukins and TNFα.[59] A growing body of evidence implicates inflammation in prostatic carcinogenesis.[6, 60, 61] Therefore, statins could inhibit prostatic carcinogenesis either independently or synergistically with NSAIDs by decreasing inflammation. In one experiment, the combination of aspirin and simvastatin inhibited the growth of early PC but not advanced PC cell lines.[62] However, the combination of atorvastatin and the COX2-selective NSAID celecoxib was found to inhibit the growth of LnCAP cells derived from advanced androgen-sensitive PC both *in vitro* and when implanted in animals.[63]

Statins, especially at higher doses,[64] may also inhibit angiogenesis (the formation of new blood vessels), a process involved in later stages of tumour development and migration.[65] This effect appears to be mediated by activation of the endothelial protein kinase *Akt/PKB*, and suppression of the release of Vascular Endothelial Growth Factor (VEGF) in response to cellular hypoxia.[64] Statins also inhibit tumour invasiveness, likely by blocking the release of matrix metalloproteinases,[66] and by suppressing the expression of endothelial adhesion molecules.[29] Taken together, these observations suggest that statins may reduce the metastatic potential of PC cells.

Overall, statins may help prevent the development of PC through inhibition of sustained proliferative signals (androgen and *Ras/Rho*), sensitizing potentially malignant cells to programmed cell death, minimizing inflammation, reducing angiogenesis, and impeding invasiveness by blocking adhesion molecules. Interfering with five of the ten potential hallmarks of cancer provides a strong biological rationale for testing the chemopreventive potential of statins.

## Epidemiologic evidence

Despite strong and consistent laboratory evidence, epidemiologic studies of the relationship between statin use and PC risk have reported conflicting results (Table 1.1).[43, 52, 58, 67-96] A meta-analysis of three cardiovascular RCTs that included prostate cancer incidence as a safety endpoint, found no evidence of an association with PC incidence (risk ratio [RR]=0.98; 95%CI: 0.83-1.15).[30, 31] These RCTs were limited by small sample size (n=300 patients) and by short follow-up time (which averaged 3 years). Since PCs are generally slow-growing,[38] any potential effects of medication use will likely involve a long latency period (10-15 years).[97] Statin use in the recent past may not be etiologically relevant for PC prevention, because exposure most likely took place after tumour initiation. However, recent statin use could still influence disease progression and aggressiveness.

Initial observational studies examined multiple cancer sites (not just PC) and produced conflicting results.[52, 68, 75, 76, 98] Studies using Canadian[68], Dutch[76], and Danish[75] pharmacy databases reported small, statistically non-significant inverse associations of PC risk with statin use, whereas a study using the British General Practice Research database[52] and a similar US study[98] reported no significant associations. More recently, similar studies from Britain,[96] Finland[58], and the US[89] reported slightly increased risks (< 15%) among statin users. Issues of confounding (e.g., by use of other medications) and bias (e.g., detection bias) were not addressed in any of these studies.

Similarly, the observational studies designed to focus on the association of statins with PC have produced mixed results. Some studies found a reduced incidence of PC among statin users,[69, 70, 84,

99] whereas others found no effect or even increased risks.[74, 83, 94, 100] A systematic review of studies published up to February 2012 included 27 studies – 15 cohort and 12 case-control.[20] While there was heterogeneity among the studies, there did not appear to be any publication bias. Statin use was associated with a 7% reduction in the risk of PC diagnosis (RR 0.93, 95% CI 0.87-0.99). Subgroup analyses suggested similar trends when cohort and case-control studies or those adjusting or not for PSA testing were evaluated separately, but did not reach statistical significance. Heterogeneity of the studies also undermines the strength of these results.

Individual investigations highlight some of the challenges with this data. Breau et al. reported the largest reduction in PC incidence with statin use in a prospective cohort study of 40- to 79-year-old white men with urinary symptoms started in 1990.[70] Drug exposure was ascertained at the baseline interview and biennially thereafter. After a median follow-up time of 16 years, the RR for the effect of statin use on PC was 0.36 (0.25-0.53) and was even stronger for men who used statins for more than 9 years. However, all analyses, including the duration-response analyses, were based on just 38 exposed cases, which limited the investigators' ability to adjust for confounding in multivariate models and increased the risk of chance findings. Furthermore, all statin use data was based on self-reporting, which raises the concern of recall bias. Finally, only 55% of the cohort agreed to participate in completing the exposure questionnaire, increasing the risk of an inadvertent selection bias and jeopardizing generalizability.

At the opposite extreme, the study examining a cohort of patients observed after completing RCTs of lovastatin showed a dramatic increase in the risk of PC – (risk ratio 2.94, 0.95-6.86).[67] Interestingly, the investigators compared PC incidence in the cohort receiving lovastatin to the age-adjusted cancer rates from the Surveillance, Epidemiology, and End Results (SEER) registry. The increased number of

cases could be explained by the inclusion of a digital rectal exam in the patient cohort, which was not yet being routinely completed in the community. There were also only 504 men, including 5 cases of prostate cancer in the study increasing the likelihood of a chance finding. In between these two studies, no association between statins and PC risk was reported by Agalliu et al. (odds ratio (OR)=1.0, 0.8-1.2) in their population-based study of 1,001 cases and 942 age-matched controls from King County, Washington.[43] Drug use was self-reported in this study, which raises the possibility of recall bias (cases being more likely to recall drug use) affecting results.

Boudreau et al. eliminated the risk of recall bias by carrying out a retrospective cohort study among 83,372 male subscribers to a non-profit integrated health care plan in western Washington State.[69] Information on statin use, defined as using statins for 1 or more years, was obtained from plan databases. Men were monitored for PC using the SEER tumour registry. Users of lipophilic statins, but not non-lipophilic statins, had lower risk of PC (hazards ratio [HR]=0.8; 0.7-0.9). This study was limited by short duration of follow-up and statin use (3 years) and by limited power to examine the effect of non-lipophilic statins (only 8 cases in about 2400 person-years of follow-up).

None of the studies mentioned above adjusted for PSA screening. The first study to include this important factor used data from the Health Professionals Follow-up Study.[94] A cohort of 34,989 men was followed from 1990 to 2001, and information on drug use and PC diagnosis was collected biennially using self-administered questionnaires. While no significant associations were evident for overall or organ-confined PC (HR=1.0; 0.9-1.1), significant inverse associations between statin use and metastatic or fatal cancers were observed (HR=0.4; 0.2-0.8). Unfortunately, this study had no information on type of statin used, dose, and minimal information on duration.

Murtola et al. linked data from the screening arm of the Finnish Prostate Cancer (PSA) Screening trial to national cancer registration and pharmacy databases to obtain information on PC incidence and use of statins and other cholesterol-lowering drugs.[92] Among men who had at least 1 PSA screen between 1996 and 2004, current statin users had lower risk of overall PC (RR=0.75; 0.6-0.9), especially with longer (≥6 years) duration of use. The associations were much stronger for non-lipophilic than for lipophilic statins. The cases group in this study overlapped with the cases included in a previous case-control study by the same team where no association with overall PC was observed.[83]

Trial populations, which standardize follow-up and frequency of assessment for PC, have informed two other studies.[88, 95] Freedland et al. reported on patients in the REDUCE trial that investigated the chemopreventive potential of dutasteride, evaluating the risk of PC by statin use.[88] There were statistically significant differences in the baseline characteristics of the two groups, including in family history of PC. Multivariate analysis suggested that statin use does not impact risk of PC (OR 1.05, 95% CI 0.89–1.24). Platz et al. completed a similar analysis of the placebo arm of the Prostate Cancer Prevention Trial (PCPT).[95] Statin use again did not impact risk of PC (HR 1.03, 95% CI 0.82-1.30). Both cohorts have the advantage of consistent PC screening practices, but suffer from limited length of follow-up and brief, survey-based ascertainment of drug exposure.

Finally, Jespersen et al. used Danish population-based data to examine the effect of statins in the largest group to date.[78] Statin users had a 6% lower risk of PC (OR 0.94, 95% CI 0.91-0.97), which did not differ by either duration or type of statin used. Conversely, Nordstrom et al. examined men receiving their first prostate biopsy in Sweden and found that statin use increased the risk of PC (OR 1.16; 95% CI 1.04–

1.29).[93] While both were large studies, benefited from population-based case identification, and had reliable exposure assessment during the study, both were only able to look at pre-exposure for 1-2 years.

In summary, epidemiologic data concerning the relationship between statin use and risk of PC are suggestive but inconclusive.[101] The discrepancies between these studies may reflect their limitations. Most studies were limited by exposure data confined to the recent past, limited information on dose, timing and duration of statin use, and by the possibility of uncontrolled detection and recall biases. Very few studies have allowed for the long latency of any potential protective effects; the follow-up periods of most studies may have been too short to detect an impact. None of these studies adjusted simultaneously (in the same model) for possible confounding by use of other drugs such NSAIDs, 5-alpha-reductase inhibitors and non-statin cholesterol-lowering drugs. In most studies, analyses were not stratified by statin type or potency. Finally, many of these studies were carried out in the US where very high levels of PSA screening could complicate the interpretation of their findings. For instance, intensive screening resulted in a paucity of advanced PC cases in most studies limiting their ability to detect clinically meaningful associations with advanced PC.

## Limitations

The limitations of our review include the lack of formal meta-analysis and the risk of publication bias in the literature as we did not seek out unpublished data. However, the intention of this article was to provide a narrative review of the mechanism through which statins may help prevent PC and summarize the existing epidemiologic literature. A meta-analysis would not have further facilitated this goal.

## Conclusion

While the possibility of increased rates of aggressive PC has dampened enthusiasm for dutasteride and finasteride, chemoprevention remains an area of hope for PC. The need to prevent the development of PC has only been increasing due to the aging of the population. There is a compelling pre-clinical rationale for statins as potential chemopreventive agents, as they interfere with five of the ten hallmarks of cancer. However, the epidemiological literature investigating the effect of statin use on PC incidence has reported widely varying results and is often plagued by small sample sizes, short pre-diagnosis information on drug exposure, and potential biases. Large, population-based studies with long pre-diagnosis drug exposure data are needed to investigate the impact of statin use on prostate cancer incidence and determine if a definitive clinical trial is warranted.

TABLE 1.1 – EPIDEMIOLOGIC STUDIES OF THE EFFECT OF STATIN USE ON PROSTATE CANCER INCIDENCE

| Study | Study Period | Cases | Controls | Relative Risk | 95% CI |
|---|---|---|---|---|---|
| **Studies not adjusting for PSA testing** | | | | | |
| Lovastatin groups 1993 [67] | NR | 5 | 499 | 2.94 | 0.95-6.86 |
| Blais 2000 [68] | 1988-1994 | 78 | 780 | 0.74 | 0.36-1.51 |
| Graaf 2004 [76] | 1995-1998 | 186 | 9599 | 0.37 | 0.11-1.25 |
| Kaye 2004 [52] | 1990-2002 | 569 | 7451 | 1.3 | 1.00-1.90 |
| Friis 2005 [75] | 1989-2002 | 1407 | 166726 | 0.87 | 0.61-1.23 |
| Shannon 2005 [84] | 1997-2004 | 100 | 202 | 0.38 | 0.21-0.69 |
| Flick 2007 [74] | 2002-2004 | 888 | 68159 | 0.92 | 0.79-1.07 |
| Murtola 2007 [83] | 1995-2002 | 24723 | 24723 | 1.07 | 1.00-1.16 |
| Boudreau 2008 [69] | 1990-2005 | 2532 | 80840 | 1 | 0.76-1.02 |
| Breau 2010 [70] | 1990-2007 | 224 | 2223 | 0.36 | 0.25-0.53 |
| Haukka 2010 [58] | 1996-2005 | 1051 | 9877 | 1.12 | 1.08-1.17 |
| Hippisley 2010 [77] | 2002-2008 | 7129 | 983366 | 1.02 | 0.96-1.08 |
| Coogan 2010 [73] | 1992-2008 | 1367 | 2007 | 1.1 | 0.90-1.50 |
| Loeb 2010 [79] | 2003-2009 | 1351 | 0 | 0.71 | 0.51-0.98 |
| Tan 2011 [85] | 2000-2010 | 1797 | 2407 | 0.92 | 0.85-0.98 |
| Chang 2011 [72] | 2005-2008 | 388 | 1552 | 1.55 | 1.09-2.19 |
| Mondul 2011 [82] | 1993-2006 | 683 | 1716 | 0.66 | 0.50-0.85 |
| Chan 2012 [71] | 2000-2008 | 298 | 4120 | 1.07 | 0.82-1.40 |
| Marcella 2012 [81] | 1997-2000 | 387 | 380 | 0.37 | 0.23-0.60 |
| Jespersen 2014 [78] | 1997-2010 | 42,480 | 212,400 | 0.94 | 0.91-0.97 |
| Lustman 2014 [80] | 2001-2009 | 1813 | 64928 | 0.26 | 0.22-0.31 |
| | | | | | |
| **Studies adjusting for PSA testing** | | | | | |
| Platz 2006 [94] | 1990-2002 | 2579 | 32410 | 0.96 | 0.85-1.09 |
| Friedman 2008 [89] | 1994-2003 | 1706 | NR | 1.03 | 0.98-1.08 |
| Agalliu 2008 [43] | 2002-2005 | 1001 | 943 | 1 | 0.80-1.20 |
| Smeeth 2009 [96] | 1995-2006 | 3525 | 361150 | 1.06 | 0.86-1.30 |
| Murtola 2010 [92] | 1996-2004 | 1594 | 21614 | 0.75 | 0.63-0.89 |
| Farwell 2011 [86] | 1997-2007 | 546 | 55329 | 0.69 | 0.52-0.90 |
| Jacobs 2011 [90] | 1997-2007 | NR | 3913 | 0.98 | 0.90-1.06 |
| Fowke 2011 [87] | 2002-2010 | 1029 | 1119 | 1.15 | 0.87-1.53 |
| Freedland 2013 [88] | 2003-2005 | 1517 | 5212 | 1.05 | 0.89-1.24 |
| Platz 2014 [95] | 1994-1997 | 574 | 8883 | 1.03 | 0.82-1.30 |
| Kantor 2015 [91] | 2002-2010 | 570 | 31521 | 0.86 | 0.63-1.18 |
| Nordstrom 2015 [93] | 2007-2012 | 7356 | 10144 | 1.16 | 1.04-1.29 |

PSA = prostate specific antigen; CI = confidence interval; NR = not reported

**Chapter 2 – The effect of statin use on the incidence of prostate cancer: a population-based nested case-control study (Paper 2)**

## Introduction

Prostate cancer (PC) is the most common non-cutaneous malignancy diagnosed among men and the third leading cause of cancer-related deaths in North America. [1] Despite being such a common disease, little is known about the causes of PC. Only three risk factors have been clearly established in the literature: increasing age, African-American ethnicity, and family history of PC. [6] None of these risk factors is modifiable. In addition to an aging population, screening with Prostate Specific Antigen (PSA) and increased prostatic procedures have increased diagnosis rates. [2] These trends, along with the aging population and increasing cost of PC treatment, suggest that the burden of PC will continue to escalate and emphasize the need for methods to prevent PC.[5]

With no evident modifiable risk factors, the possibility of chemoprevention becomes even more important. Randomized controlled trials show that the 5-alpha-reductase inhibitors finasteride and dutasteride reduce the overall risk of developing PC, but may increase the risk of aggressive or advanced PC. [10, 24, 25] This risk, along with concerns about side effects and cost effectiveness, has curtailed prescription of these drugs for chemoprevention of PC.

Laboratory research suggests that statins may help prevent the development of PC through inhibition of sustained proliferative signals (androgen and *Ras/Rho*), sensitizing potentially malignant cells to programmed cell death, minimizing inflammation, reducing angiogenesis, and impeding invasiveness by

blocking adhesion molecules. [15, 18, 29, 59, 63, 64] Interfering with these five hallmarks of cancer provides a strong biological rationale for testing the chemopreventive potential of statins.[42]

Despite strong and consistent laboratory evidence, epidemiologic studies of the relationship between statin use and PC risk have reported conflicting results. A 2012 meta-analysis suggested that use of statins may reduce the risk of PC by 7%, but results showed substantial heterogeneity.[20] The discrepancies between these studies may reflect their limitations. Most were limited by exposure data confined to the recent past, limited information on dose, timing and duration of statin use, and by the possibility of uncontrolled detection and recall biases. Very few studies have allowed for the long latency of any potential protective effects; the follow-up periods of most studies may have been too short to detect an impact.

## Objectives

1) Determine if statin use reduces PC risk
2) Evaluate the effect of statin dose, duration of use, lipophilicity, and patient characteristics on statin impact on PC risk

## Methods

### Study Design

A nested case-control study was performed using health care data from Saskatchewan**.**

## Sources of data

Data was obtained from Saskatchewan's health services databases and the Saskatchewan Cancer Registry (SCR). Saskatchewan Health provides publicly funded health care programs, including hospital and physician services, prescription drugs, and cancer therapy, to the 1.1 million residents of the Canadian province. Coverage is universal; there is no eligibility distinction based on age or income.[102] A unique health services number assigned to all residents enables linkage longitudinally and across databases. Because of the availability of long drug use histories, these databases have been used extensively in pharmacoepidemiologic research.[103, 104]

The Saskatchewan Prescription Drug Plan (SPDP), in operation since 1975, pays for prescription drugs for all residents, except for Registered Indians and RCMP and military personnel whose prescription drug benefits are fully covered by the federal government.[102] The SPDP database captures data from pharmacy claims for formulary drugs dispensed to eligible beneficiaries and accuracy of the prescription information exceeds 99%.[21]

Reporting of cancer cases to SCR is mandated by provincial regulations .[105] Almost all cases are pathologically-confirmed (96%), less than 3% of registrations originate from death certificates, and loss to follow-up is less than 3%.[106, 107] Services provided by hospitals and physicians in Saskatchewan are recorded by the Hospital Services and Medical Services databases. The data collected comprise demographic as well as diagnostic and treatment information including primary diagnosis, coded using the International Classification of Diseases, Ninth Revision (ICD-9) or the ICD-10-CA (after April 2002),[102] [108] and service or procedure codes.

Data extraction for this study from the various databases was carried out by employees of the SCR and Saskatchewan Health. To protect participant privacy, the data delivered for analyses did not include any identifying information and none of the subjects were contacted or interviewed.

### Source population

The source population consisted of all men aged 40 years or older registered with the SPDP 1990-2010, with no prior history of cancer (except for non-melanoma skin cancer). Men entered the source population on January 1, 1990 (statin use was very rare before 1990[109]), their 40th birthday (PC is very rare under 40), or on the date of immigration to Saskatchewan, whichever occurred latest. They left the source population on December 31, 2010, on the date of diagnosis of PC, death, or emigration, whichever occurred first. Registered Indians and other federal beneficiaries were excluded because information about their drug prescriptions is not consistently captured in the SPDP.[103]

### Identification of cases and controls

The case group included all men, diagnosed with primary prostatic carcinoma (ICD-Oncology code 61; behavior code 3) who were registered with the SCR between January 1, 1990 and December 31, 2010. To avoid outcome misclassification, we excluded those diagnosed by death certificate only and restricted the histologically confirmed cases to the following morphology codes: 8140/3, 8010/3, and 8000/3. Risk set (incidence density) sampling was used to select matched controls from Saskatchewan Health's population registry.[110] For each case, a risk set was constructed from all eligible men in the source population who had the same birth date (±1 year), postal code of residence, were registered with Saskatchewan Health for at least as long as the case, and who were alive and free of cancer on the date

of diagnosis of the matching case (the index date). Four controls were randomly sampled without replacement from each risk set. To ensure that the histories of exposure, if any, were of adequate length, we only included men (both cases and controls) who were eligible to benefit from the SPDP for 5 or more years before the index date.

### Comorbidity and Screening

The matched design of the nested case-control study controlled for confounding by age, calendar time, place of residence and duration of registration with Saskatchewan Health. We assessed for potential confounding by indication of statin use (coronary heart disease, and associated conditions such as diabetes and stroke). Previously validated algorithms, based on the frequency of certain ICD codes, were used to identify these conditions from the various administrative databases (Table 1).[111, 112]

Since frequent interactions with physicians may be associated with the use of prescribed statins and with the diagnosis of PC, we included this variable to help control for potential confounding by detection bias. Frequency of medical care up to 10 years before diagnosis was assessed with billing codes for visits and services provided by physicians, which are recorded by the Saskatchewan Medical Services Plan (Table 1). Because we lacked data on PSA testing, we also used these service codes to construct a composite binary variable to help account for likelihood of PSA screening. The screening variable included any physician visit for benign prostatic hypertrophy (BPH), prostatitis, other prostate disorders, and prostatic ablation, resection, or testing of prostatic secretions (Table 1). We describe the development of the screening variable in Chapter 3. We also included variables accounting for visits to a urologist 1-11 years prior to the index date, filling a prescription for 5-alpha reductase inhibitors or

alpha-1-adrenergic receptor blockers, and frequency of visits to a family physician in the multivariable model.

### Exposure assessment

Detailed histories of exposure to prescribed statins (Table 2.1) and 18 other drug classes were obtained from the SPDP for the period between the index date and January 1, 1976, or the coverage initiation date, whichever was later. For each prescription, we had the following information: the date of dispensing, the active ingredient name and strength (mg/pill), and the form and quantity dispensed.

### Statistical analysis

In the primary analysis, we used conditional logistic regression to model exposure to statins as a class rather than individual drugs and repeated the analyses separately for groups of statins defined by lipophilicity.

We divided the time preceding the index date into successive periods: months 1-12, years 2-5, years 6-10, years 11-15, years 16 or more. We then used these periods to analyse the effect of duration of statin use because any potential effects of statins on carcinogenesis are likely to involve a considerable latency period.[97] We excluded the one-year period preceding the index date because drug use shortly before diagnosis could be triggered by symptoms (protopathic bias).[113] While statins are not likely to be prescribed for PC symptoms, they can be prescribed as part of a physician visit associated with symptoms.

Exposure during each period was characterized as the average rate of dispensing statins as a class. The rate of dispensing statins was based on the proportion of the defined daily dose (DDD) of each different statin dispensed ($p_i$ = average mg/day dispensed ÷ DDD for $statin_i$) during each period to account for differences in drug potency within the statin class. The DDD is "the assumed average maintenance dose per day for a drug used for its main indication in adults."[114, 115] The sum of these proportions, i.e. $\Sigma p_i$ for all the different statins (indexed by "i") dispensed during a period, represented the measure of exposure.

We used conditional logistic regression to estimate incidence density ratios (rate ratios) for the effects of drug exposure during each of the study's time periods while adjusting for the potential confounders. Within each period, statin use was represented by categorical indicator variables indicating quartiles of $\Sigma p_i$. These variables were jointly entered into the model to adjust for mutual confounding by exposure in other periods.[116, 117] We assessed for monotonic linear dose-response (and duration-response) relationships between the quintiles of the average annual dose and PC risk, and used the Mantle extension test[118] and its multivariate counterpart (a chi-squared test for ordered categorical variables in the regression analyses[119]) to assess the statistical significance of any trends.

We then limited our data set to PC cases in years where we had PSA test information (excluded 2003-2007 and 2010) and used unconditional logistic regression to evaluate the association between statin use and the diagnosis of clinically significant disease. We defined clinically significant disease as: Gleason score 8-10 OR lymph nodes positive for metastatic PC OR clinical stage Whitmore-Jewett C-D OR clinical stage AJCC III-IV. We included the Whitmore-Jewett staging because it was the stage recorded in the cancer registry in the earlier years of our study.

## Results

Between 1990 and 2010, 12,745 cases of prostate cancer were diagnosed in Saskatchewan and these cases were matched on age, index date, and geographic location to 50,979 controls. Most cases and controls (74.3%) were 65 years or older (Table 2.2). Over 94% of cases were pathologically-confirmed and 12.6% had metastatic disease at diagnosis (Table 2.2). Between 1990 and 2009, the median age of cases decreased from 75 to 68 years old and the proportion of patients diagnosed with clinically significant disease declined from 40.7% to 30.6%, demonstrating the impact of screening over time (Appendix Table A).

Overall, 2064 (16.2%) cases and 7956 (15.6%) controls filled at least one statin prescription (Table 2.3). Ignoring matching, there were no significant differences in mean or median dose received, as defined by the average annual dose. There were also no significant differences in use of 5-alpha-reductase inhibitors and aspirin between cases and controls. In addition to these drugs exposures to prescribed fibrates, other lipid modifying agents, alpha-1-adrenergic receptor blockers, and non-aspirin NSAIDs, as well as dose distribution outlined in Table 2.3.

In models accounting for matching, but not adjusting for other confounders, ever filling a prescription for a statin was not associated with risk of PC (odds ratio [OR] = 1.05, 95% CI 0.99-1.11). Factors associated with PSA screening were associated with an increased risk of PC diagnosis and a decreased risk of clinically significant PC (Table 2.4). Specifically, accounting for matching but no other confounders, positivity of the composite screening variable was associated with a dramatically increased

risk of PC diagnosis (OR 32.79,95% CI 30.27-35.52) and a noticeable reduction in clinically significant disease (OR 0.77, 95% CI 0.67-0.89).

Multivariable modelling (Table 2.5) demonstrated no statistically significant relationship between ever prescription of statins (OR 0.97, 95% CI 0.90-1.05), fibrates (1.06, 0.94-1.19), or other lipid medications (OR 1.09, 95% CI 0.92-1.29) and PC. PC screening and diabetes mellitus were associated with increased risk of PC diagnosis, while urology visits 1-11 years before diagnosis and prescription of ASA, 5-alpha-reductase inhibitors, NSAIDs, alpha-1-androgen receptor inhibitors and oral hypoglycemic medications were inversely associated with PC diagnosis. Similarly, neither use of lipophilic statins (OR 0.96, 95% CI 0.88-1.04) nor non-lipophilic statins (OR 1.06, 95% CI 0.95-1.20) statistically significantly impacted the likelihood of PC diagnosis in multivariable models. Statin use was not associated with PC risk with either increasing dose or duration of exposure and did not vary with period of use (data not shown).

Finally, using multivariable unconditional regression we found that statin use was inversely associated with clinically significant PC (OR 0.84, 95% CI 0.73-0.97). We used the same variables found to be important in controlling for confounders in the conditional model, but few were as impactful in adjusting for an effect on clinically significant disease.

## Discussion

Our analysis demonstrated no significant effect of statin use on overall PC diagnosis. Specifically, there was no significant impact on PC diagnosis with statin use regardless of dose or duration of exposure and no matter which type of statin was prescribed. However, statin use had an inverse association with clinically significant PC.

The previous epidemiologic literature examining the effect of statin use on overall PC diagnosis has been highly heterogeneous, with relative risks of 0.26 to 2.94. Out of 33 published studies, 5 show an increased risk of PC with statin use, 10 demonstrate a decreased risk, and 18 suggest no effect. (Chapter 1) The difficulty in interpreting these studies has been that almost all of them have had either small sample sizes or significant potential for confounding, recall and selection biases, and were handicapped by short-term data on drug use, short follow-up, or no adjustment for screening.

Examining the two largest cohorts, with the best power to detect an effect of statin use, Murtola et al showed a 7% (0-16%) increase in risk and Jespersen et al showed a 6% (3-9%) decrease in risk. Neither estimate was adjusted for screening, health utilization, or important prescription drugs such as 5-alpha-reductase inhibitors.[78, 83] After adjusting indirectly for screening and directly for health utilization, comorbidities, and other prescription medications, our model showed no impact of statin prescription on PC diagnosis. In addition to the lack of impact from statin use, this analysis suggests that most of these variables are not likely significant confounders of the association. However, our adjustment for PC screening was indirect. Like both of these studies, dosage and duration of use did not influence PC risk.

Data on statin use from the two randomized controlled trials (REDUCE and PCPT) investigating the impact of 5-alpha-reductase inhibitors on PC diagnosis to date use the most consistent approach to PC diagnosis and screening, thereby reducing the likelihood of differences in screening between exposure groups. [88, 95] Evaluation of statin use in the cohorts from these studies suggested no effect of statin use, though both studies had short pre-diagnosis drug exposure histories based on patient recall. Our

study was also consistent with these trials in showing about a 25% reduction in PC incidence among users of 5-alpha-reductase inhibitors.

Overall, our results and the methodologically most robust epidemiological studies detailed above do not support an effect of statin use on overall PC diagnosis. However, the existing literature and our results suggest that statin use may decrease the risk of clinically significant PC.[20, 101] Of 21 studies that examined the effect of statin use on both overall and advanced PC, 8 show a decrease in advanced PC.[101] Out of these eight, three showed no impact of statin use on overall PC.[83, 89, 94] Why might statin use impact development of more advanced disease, but not PC overall? Some have suggested that statins may interfere in tumour progression to more clinically significant disease.[101] One possibility is that our understanding of the biological mechanisms of prostate carcinogenesis is incomplete and that the mechanisms inhibited by statins are more important for the development of aggressive disease.[120] Another possibility is confounding by PC screening. Increased screening uptake among statin users could lead to both increased detection of PC overall and decreased detection of clinically significant disease due to diagnosis at earlier stage. [22] Statin users might be more likely to receive screening because of higher utilization of healthcare services or improved awareness and increased propensity to use preventive measures. Due to lack of information on PSA and digital rectal examination screening, we attempted to adjust for PC screening using several proxy indicators, so we cannot rule out residual confounding as an explanation of our findings. However, it is reassuring that we were able to measure similar effects for 5-alpha-reductase inhibitors to those observed in RCTs, since use of these drugs is also likely subject to the same bias.

The strengths of our study include its large sample size; ours was the largest North American cohort to assess the impact of statin use on PC diagnosis. Our cohort also had the longest and most comprehensive pre-diagnosis drug exposure data, with >90% of patients having 15+ years of data, which given PC long latency permitted the study of statin use during more etiologically relevant periods. By using prescription drug databases and cancer registry data, our study was less susceptible to recall bias and to disease misclassification. We were also able to assess for dose- and duration-response effects.

However, our study also has limitations. In addition to residual confounding by screening, residual confounding may have occurred due to lack of information on other potential risk factors such as physical activity or diet.[22] However, there is no strong evidence supporting a role for these factors in PC carcinogenesis. In addition to age, the only established risk factors for PC are ethnicity and family history which were not available to us. However, the older non-Aboriginal population of Saskatchewan is quite stable and fairly homogeneous (most Aboriginal men are excluded by design, and < 1% of the population in Saskatchewan is of African ancestry[121]) and there is no reason to believe that family history of PC would differ by statin use. We assumed that all prescribed drugs were consumed, which might be a reasonable assumption for men who filled multiple prescriptions of the same drug. However, lack of adherence could have masked beneficial effects due to the ensuring exposure misclassification.

## Conclusion

We found that statin use is not associated with either a protective or detrimental effect on overall PC diagnosis, regardless of duration or dose of exposure. However, statin use was inversely associated with the risk of clinically significant PC. Although we could not rule out confounding by screening as a possible explanation, overall, these results can provide reassurance to the millions who use these

medications with regard to PC risk. At this stage, we believe further studies with both long pre-diagnosis drug histories and an ability to adjust directly for PC screening are needed before considering embarking on randomized chemoprevention trials.

TABLE 2.1 – DEFINITIONS OF VARIABLES TO BE USED IN THE ANALYSIS

| Variable | Definition |
|---|---|
| **Statins (DDD)** | |
| Lipophilic | Simvastatin (30), Lovastatin (45), Fluvastatin (60), Atorvastatin (20), Cerivastatin (0.2), Pitavastatin (2) |
| Non-lipophilic | Pravastatin (30), Rosuvastatin (10) |
| **Screening** | |
| Screening correlates | Binary variable with 1 indicating whether at any point prior to the index date a subject had a physician visit for BPH (ICD-9 code 600.*), prostatitis (601.*) or "other disorders of prostate" (602.*); or any point during the 11 years prior to the index date, or had prostatic ablation or resection, or testing of prostatic secretions. We assume the men who received these services had at least a DRE. |
| Seeing a urologist | Ever seeing a urologist in the 1-11 years prior to the index date (i.e. excluding the year immediately prior to the index date). |
| Frequency of visits to family physicians | Frequency of visits to family physicians in the 5 years prior to the index date. |
| **Medical conditions**‡ | |
| Diabetes | > 1 admission OR > 1 physician claim (ICD-9=250; ICD-10=E10-E14) |
| Hypertension | > 1 admission OR > 1 physician claim (401,405;I10-I15) OR > 1 prescriptions for selective β-blockers; thiazides; CCBs-DH; or centrally acting anti-adrenergics |
| Ischemic Heart diseases | > 1 admission OR > 1 physician claim (410-414; I20-I25) |
| Stroke | > 1 admission OR > 1 physician claim (431,434, 436-438;I61, I63, I64, I69, I67.9) |
| Prostatic hypertrophy | > 1 admission OR > 1 physician claim (600, N40) OR > 1 prescriptions for finasteride or alpha-blockers OR > 1 TURP or ablation |
| Prostatitis | > 1 admission OR > 1 physician claims (601, N41) OR > 1 physician claims for MEPS with |
| **Others** | |
| Income status | Binary variable with 1 indicating ever having a prescription flagged for receiving income security benefits. |
| Vasectomy, TURP, Prostatic biopsy, MEPS | Information on these procedures was extracted from a list of all physician-provided urological services (services for which a physician claimed a fee-for-service code under section R of the Saskatchewan Ministry of Health's "Payment Schedule for Insured Services Provided by a Physician") since January 1, 1975. |
| Classes of medications | Fibrates, Other antilipid medications, Prostatism agents, androgen antagonists, NSAIDS, Angiotensin converting enzyme inhibitors, Angiotensin receptor blockers, alpha- and beta-blockers, Antihypertensive calcium channel blockers, Centrally acting antihypertensives, Vasodilators, Diuretics, DMARDs, Systemic steroids, Anticoagulants, Antiplatelets, Hematopoetic drugs, Hemorrheologic agents, Cholinergic agents, Anticholinergics, Adrenergic agents, Sympatholytic drugs, Skeletal muscle relaxants, Cardiac glycosides, Selective serotonin reuptake inhibitors, Tricyclic antidepressants, Monoamine oxidase inhibitors, other anti-depressants, Benzodiazepines, Biguanides, Insulin, Sulfonylureas, other antidiabetic medications, Proton pump inhibitors, H2-receptor antagonists. All drugs were classified according to the WHO ATC classification. |

‡ Based on the most valid chronic disease identification algorithms (those algorithms with the highest Kappa and Youden's index values) from a comprehensive review of the literature performed by Lix et al[112] and others.
BPH: Benign prostate hypertrophy; DRE: Digital rectal examination; MEPS: Microscopic examination of prostatic secretions; TURP: Transurethral resection of prostate.

TABLE 2.2 – DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF ENROLLED CASES AND CONTROLS

| | Cases | | Controls | |
|---|---|---|---|---|
| | N | % | N | % |
| Total | 12745 | | 50979 | |
| **Age group** | | | | |
| 40-65 | 3273 | 25.7 | 13092 | 25.7 |
| 66-70 | 2432 | 19.1 | 9728 | 19.1 |
| 71-75 | 2740 | 21.5 | 10960 | 21.5 |
| 76-80 | 2217 | 17.4 | 8868 | 17.4 |
| 81+ | 2083 | 16.3 | 8331 | 16.3 |
| **Calendar year of diagnosis** | | | | |
| 1990-1994 | 2861 | 22.4 | 11444 | 22.4 |
| 1995-1999 | 2783 | 21.8 | 11132 | 21.8 |
| 2000-2004 | 3395 | 26.6 | 13579 | 26.6 |
| 2005-2010 | 3706 | 29.1 | 14824 | 29.1 |
| **Duration of exposure data (years)** | | | | |
| 5-14.9 | 917 | 7.2 | 228 | 0.4 |
| 15-19.9 | 3009 | 23.6 | 11620 | 22.8 |
| 20-24.9 | 2877 | 22.6 | 11484 | 22.5 |
| 25-29.9 | 3119 | 24.5 | 13786 | 27.0 |
| 30+ | 2823 | 22.1 | 13861 | 27.2 |
| **Proven method of diagnosis** | | | | |
| Pathology | 12036 | 94.4 | | |
| Cytology | 7 | 0.1 | | |
| Radiology | 184 | 1.4 | | |
| Exploratory surgery | 22 | 0.2 | | |
| Clinical | 276 | 2.2 | | |
| Biochemical | 218 | 1.7 | | |
| Unknown | 1 | 0.0 | | |
| **Composite Gleason Score** | | | | |
| 2,3,4 | 1670 | 13.1 | | |
| 5,6,7 | 5785 | 45.4 | | |
| 8,9,10 | 1386 | 10.9 | | |
| Missing | 3904 | 30.6 | | |
| **Clinical Stage** | | | | |
| Stage I | 2049 | 16.1 | | |
| Stage II | 6806 | 53.4 | | |
| Stage III/C | 1183 | 9.3 | | |
| Stage IV/D | 1611 | 12.6 | | |
| Missing | 1096 | 8.6 | | |

TABLE 2.3 – USE OF IMPORTANT PRESCRIPTION MEDICATIONS AND OVERALL AVERAGE ANNUAL DOSE (IN DDD/YEAR) AMONG EVER-USERS BY CASE-CONTROL STATUS AND DRUG CATEGORY

| | Ever use | Average annual dose (DDDs/year) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Drug category** | **Yes** | **Mean** | **SD** | **Min** | **Q1** | **Median** | **Q3** | **Max** |
| Statins | | | | | | | | |
| Controls | 7956(15.6) | 44.5 | 54.6 | 0.1 | 7.4 | 25.5 | 61.9 | 729.4 |
| Cases | 2064(16.2) | 47.9 | 60.8 | 0.2 | 7.5 | 25.8 | 68.6 | 694.9 |
| Fibrates | | | | | | | | |
| Controls | 2576(5.1) | 45.1 | 919.8 | 0.1 | 2.1 | 7.9 | 29.4 | 46172.5 |
| Cases | 666(5.2) | 36.1 | 260.1 | 0.3 | 2.8 | 8.8 | 32.9 | 6657.2 |
| Other lipid modifying agents | | | | | | | | |
| Controls | 1208(2.4) | 10.0 | 22.4 | 0.0 | 0.2 | 1.7 | 10.1 | 299.5 |
| Cases | 316(2.5) | 11.3 | 31.5 | 0.0 | 0.2 | 2.0 | 9.1 | 409.3 |
| Alpha-1-adrenergic receptor blockers | | | | | | | | |
| Controls | 4023(7.9) | 17.0 | 26.0 | 0.0 | 1.2 | 5.3 | 22.8 | 257.2 |
| Cases | 1293(10.1) | 19.5 | 32.0 | 0.0 | 1.5 | 7.0 | 24.1 | 333.0 |
| 5-alpha-reductase inhibitor | | | | | | | | |
| Controls | 826(1.6) | 15.1 | 19.8 | 0.3 | 2.8 | 7.7 | 19.7 | 131.4 |
| Cases | 260(2.0) | 14.7 | 22.1 | 0.7 | 2.8 | 7.1 | 14.5 | 137.1 |
| Aspirin | | | | | | | | |
| Controls | 21805(42.8) | 3.3 | 11.6 | 0.0 | 0.0 | 0.3 | 1.8 | 244.4 |
| Cases | 5277(41.4) | 3.5 | 12.1 | 0.0 | 0.0 | 0.4 | 1.9 | 318.6 |
| NA-NSAIDs | | | | | | | | |
| Controls | 39806(78.1) | 11.8 | 20.8 | 1.0 | 2.0 | 5.0 | 11.0 | 284.0 |
| Cases | 10037(78.8) | 11.6 | 19.8 | 1.0 | 2.0 | 5.0 | 12.0 | 291.0 |

SD = standard deviation; DDD = defined daily doses

TABLE 2.4 – ASSOCIATION BETWEEN INCIDENCE OF PROSTATE CANCER OR CLINICALLY SIGNIFICANT PROSTATE CANCER AND POTENTIAL SCREENING VARIABLES ADJUSTED ONLY FOR MATCHING

| Variable | Any PC OR (95%CI) | Clinically significant PC OR (95%CI) |
|---|---|---|
| 5-alpha-reductase inhibitor | 1.27 (1.10-1.46) | 0.77 (0.58-1.03) |
| A1-adrenergic receptor blockers | 1.36 (1.27-1.46) | 0.69 (0.60-0.79) |
| Visited a urologist 0-1 year prior | 76.24 (69.53-83.60) | 0.94 (0.84-1.06) |
| Visited a urologist 1-11 years prior | 1.55 (1.49-1.62) | 0.72 (0.66-0.78) |
| 29+ family physician visits in last 5 years | 1.37 (1.31-1.43) | 0.89 (0.82-0.96) |
| Likely screened 0-11 years prior | 32.79 (30.27-35.52) | 0.77 (0.67-0.89) |

PC = prostate cancer; Clinically significant disease = Had Gleason score (in initial biopsy or in surgical specimen) of 8,9 or 10 or stage C or D or III or IV at diagnosis;

TABLE 2.5 – MULTIVARIABLE MODEL TO ESTIMATE IMPACT OF STATIN PRESCRIPTION ON PROSTATE CANCER DIAGNOSIS

| | Any PC | | Clinically significant PC | |
|---|---|---|---|---|
| Parameter | Odds Ratio | 95% CI | Odds Ratio | 95% CI |
| Statins | 0.97 | 0.90-1.05 | 0.84 | 0.73-0.97 |
| Fibrates | 1.06 | 0.94-1.19 | 0.88 | 0.71-1.09 |
| Other lipid drugs | 1.09 | 0.92-1.29 | 1.06 | 0.78-1.45 |
| Screening | 50.75 | 46.56-55.32 | 0.96 | 0.81-1.14 |
| Urology visit 1-11 years prior to diagnosis | 0.44 | 0.41-0.46 | 0.77 | 0.70-0.85 |
| 28+ family physician visits in 5 years pre-dx | 1.00 | 0.94-1.06 | 1.02 | 0.93-1.12 |
| Diabetes | 1.16 | 1.03-1.29 | 1.13 | 0.93-1.36 |
| 5-alpha-reductase inhibitors | 0.73 | 0.62-0.86 | 0.70 | 0.47-1.05 |
| Alpha-1-adrenergic receptor inhibitors | 0.62 | 0.57-0.68 | 0.80 | 0.66-0.96 |
| ASA | 0.89 | 0.84-0.94 | 0.92 | 0.84-1.01 |
| Non-ASA-NSAIDs | 0.83 | 0.78-0.89 | 0.79 | 0.71-0.88 |
| Oral hypoglycemic | 0.82 | 0.72-0.93 | 0.94 | 0.75-1.17 |

PC = prostate cancer; Clinically significant disease = Had Gleason score (in initial biopsy or in surgical specimen) of 8,9 or 10 OR stage C or D or III or IV at diagnosis; 95% CI = 95% confidence interval

# Chapter 3 – Accounting for Screening Bias

## Introduction

Screening programs for cervical, breast, and colon cancers have helped shift the stage distribution of these cancers, with the goal of leading to the detection of disease while it remains curable and reducing disease-specific mortality.[3] Most Canadian provinces now have formal population-based cervical, colorectal, and breast cancer screening programs.[122] While these programs aim to decrease cancer-related mortality, they also increase incidence and the risk of finding and treating preclinical disease that previously would have gone undiagnosed prior to death from another cause.[3] In epidemiological studies, adjusting for screening is important because it can increase the risk of selection bias and detection bias.[22] In a study with cancer incidence as the primary outcome, an exposure that happens to be associated with increased likelihood of screening may appear to increase the risk of cancer due solely to these factors.

For prostate cancer (PC), a great deal of controversy surrounds the use of the serological prostate specific antigen (PSA) test because randomized trials have demonstrated mixed results regarding its effect on PC-related mortality.[123, 124] Most organizations are now discouraging formal, population-based screening with PSA testing due to concerns about overdiagnosis, overtreatment, and adverse events.[125-128] Despite these concerns, many physicians and patients still pursue PSA-based screening in the hopes that PC will be diagnosed at an earlier stage. While Saskatchewan does not have a formal PC screening program with PSA, opportunistic screening for PC using PSA increased substantially after its introduction in 1990.[107] Therefore, screening was identified *a priori* as an important source of bias in our study.

## Objectives

1) Construct and assess variables to adjust for PC screening
2) Choose one variable to use in the primary analysis

## Methods

To account for impact of screening during the analysis phase, two possible strategies include accounting for screening as a confounding variable or evaluating the impact of an exposure only in patients with clinically significant disease. In this study, we chose to primarily use the approach of adjusting for screening as a confounding variable because there is no broad agreement on what constitutes clinically significant PC.

The first step in adjusting for screening involves determining the period of preclinical detectability (PPD), which is the time during which a cancer can be detected using a particular screening test, but during which the cancer will not cause symptoms.[129] One way to calculate PPD is to double a cancer's lead time, which is based on the assumption that the average of individual lead times must lie somewhere in the middle of the PPD.[130, 131] The existing literature provides a wide variety of estimates of lead time for PC (from 2.5 to 7.8 years) due to different methods and data sets being used.[130-134] These estimates would convert into average PPDs ranging from 5 to almost 16 years. We therefore used an intermediate estimate of 11 years, especially since this period was incorporated for prior pharmacoepidemiology studies using Saskatchewan data.[135]

The second step in adjusting for screening was to identify individuals who may have had testing within the PPD (0-11 years prior to the index date). Unfortunately, there is no administrative code for PSA testing in Saskatchewan. Therefore, we only had data on the PSA test closest to diagnosis for cases between 1990-2002 (previous chart review) and 2007-2009 (included in the cancer registry). However, we had information on medical interventions and diagnoses that are known to be strongly correlated with screening.[136, 137] We therefore examined a variety of combinations of this information to create a variable designed to account for screening.

The screening variables examined used the following components:

1) Any physician visit prior to the index date resulting in one of the following ICD-9 codes:
    a. 600.* - "hyperplasia of the prostate", includes "enlarged prostate"
    b. 601.* - "inflammatory diseases of the prostate"
    c. 602.* - "other disorders of the prostate"

    Because these conditions relate to the prostate, tend to be chronic, and require routine follow-up with a physician, we assumed that most physicians would pursue a digital rectal exam (DRE) and possibly a PSA test. Either DRE or PSA would constitute screening.
2) Any prescription for finasteride, dutasteride, or an alpha-blocker during the 11 years prior to the index date. These medications are almost exclusively used to treat symptoms of benign prostatic hypertrophy, a diagnosis that can only be made after ruling out prostate cancer.[138]
3) Any urological fee for service code within 11 years prior to the index date indicating prostatic ablation, prostatic resection, or testing of prostatic excretions as it again seemed reasonable to assume that these men would have had either a DRE or PSA test.

4) Physician visit code consistent with seeing a urologist from 1-11 years prior to the index date as most urologists will perform a DRE. We excluded the year prior to the index date to avoid protopathic bias caused by tests and physician visits that may have been caused by cancer-related symptoms.
5) More than 28 visits to a family physician in the 5 years prior to the index date as frequent family physician visits are believed to be associated with an increased likelihood of screening.

As outlined below, we tested seven different combinations of these variables to account for screening:

Screened = prescription of a 5-alpha-reductase inhibitor or an alpha-1-adrenergic receptor inhibitor, prostatic secretions, ablation, biopsy, benign prostatic hypertrophy, prostatitis, or other prostatic disorders (categorical – any present = 1, all absent = 0)

Screened1 = Screened minus prescription drug exposures (categorical)

Screened2 = Screened1 + >=28 family physician visits (categorical)

Screened3 = Screened2 + Urology visit 1-11 years prior to index (categorical)

Screened4 = Screened3 variables (continuous – each occurrence summed)

Screened5 = Screened1 variables (continuous)

Screened6 = Screened1 variables + alpha-1-adrenergic receptor inhibitor prescriptions (categorical)

Most of the variables had a binary, categorical outcome because the slow-growing nature of PC means that even infrequent screening is likely sufficient to detect cancer.[129] Despite this assumption, we tested two continuous variables to ensure that they would not provide greater discriminative ability.

To assess the validity of these potential screening variables and choose the most appropriate, we measured the bivariate association between each variable and PC risk using a conditional logistic regression model. We compared the odds ratios (ORs) from these models to bivariate models for the individual components that are believed to be associated with a greater likelihood of screening.[136, 137] We then limited our data set to PC cases in years where we had PSA test information (excluded 2003-2007 and 2010) and used unconditional logistic regression and creation of a receiver-operating characteristic curve to evaluate the association between each screening variable and completion of a PSA test. Finally, we used the same cases and method to evaluate the association between each screening variable and the diagnosis of clinically significant disease. We defined clinically significant disease as: Gleason score 8-10 OR lymph nodes positive for metastatic PC or clinical stage Whitmore-Jewett C-D or clinical stage AJCC III-IV.

## Results

We first examined variables potentially linked to PC diagnosis or screening individually using conditional logistic regression (Table 3.1). This revealed that seeing a urologist 0-1 years prior to diagnosis was associated with a very high risk of prostate cancer (OR 76.24 [95% CI 69.53-83.60]), but this variable was dropped from further consideration as it was most likely a surrogate for the process of diagnosis and/or treatment, not screening. Similarly, urologist visits 0-11 years prior to diagnosis (OR 23.02 [95% CI 21.37-24.80]) also included the year prior to diagnosis prone to protopathic bias. Conditional logistic regression of the screening variables detailed above revealed that they were all positively associated with PC (Table 3.2). Screened, Screened1, and Screened6 had the strongest associations and had the log-likelihood values closest to zero.

When examining each variable's association with having a recorded PSA test using unconditional regression analysis (Table 3.3), all performed near equivalently. Screened, Screened1, and Screened6 had slightly higher odds ratios (OR), but log-likelihood measures and the area under the ROC curve were nearly equivalent. Finally, we examined the association of each screening variable with clinically significant PC (Table 3.4). As one might expect, all were negatively associated with a diagnosis of clinically significant PC, with very similar ORs, log-likelihoods, and areas under the ROC curve.

## Discussion

Taken together, the above evaluations show that variables Screened, Screened1, and Screened6 are superior to the other tested variables in the strength of their association with PC diagnosis and are near equivalent to the others in their association with PSA testing and the development of clinically significant disease. Superiority in predicting PC diagnosis was determined both by higher ORs and log-likelihoods closer to zero. Values of log-likelihood closer to zero indicate that the model better fits the data.[139]

These three variables were therefore, the leading options for inclusion in the remainder of the analysis of statin use impacting PC incidence. All three of these variables behaved similarly in all evaluations and the choice came down to clarity of the final planned analysis. Randomized controlled trials have previously demonstrated that use of the 5-alpha-reductase inhibitors dutasteride or finasteride reduces the risk of PC.[10, 24, 25] Because randomized trials are so strong methodologically, we wanted to have a distinct value for the association in our dataset between 5-alpha-reductase inhibitors and PC. If we had included this exposure both separately and as part of the screening variable, we would have risked too much collinearity.[139] Similarly, we felt it was clearest to include use of alpha-1-adrenergic receptor

inhibitors as a separate variable in our planned multivariable model. While there is no randomized trial evidence of alpha-1-adrenergic receptor inhibitors decreasing PC incidence, some preclinical studies suggest they may impair PC growth.[140-144]

While continuous variables often help improve the power of a planned multivariable model,[139] in this case the continuous screening variables did not improve on the predictive performance of categorical variables. They were inferior in model fit by log-likelihood values in association with PC diagnosis.

## Conclusion

We chose Screened1 as the variable used in our primary analysis to help account for the likelihood of PC screening as it appeared to balance efficacy and allow separate interpretation of the effect of drugs used for benign prostatic hypertrophy.

TABLE 3.1 – POSSIBLE COMPONENTS OF SCREENING VARIABLES

| Variable | OR (95%CI) | P-value |
|---|---|---|
| 5-alpha-reductase inhibitor | 1.27 (1.10-1.46) | <0.001 |
| A1-adrenergic receptor blockers | 1.36 (1.27-1.46) | <0.001 |
| Visited a urologist 0-1 year prior | 76.24 (69.53-83.60) | <0.001 |
| Visited a urologist 0-11 years prior | 23.02 (21.37-24.80) | <0.001 |
| Visited a urologist 1-11 years prior | 1.55 (1.49-1.62) | <0.001 |
| Benign prostatic hyperplasia | 14.92 (14.12-15.77) | <0.001 |
| Ever had a prostatic ablation | 0.88 (0.83-0.93) | <0.001 |
| Ever had a prostatic biopsy | 19.68 (18.34-21.12) | <0.001 |
| 29+ family physician visits in last 5 years | 1.37 (1.31-1.43) | <0.001 |
| Prostatitis | 4.39 (4.20-4.59) | <0.001 |
| Other prostatic condition | 6.89 (6.08-7.81) | <0.001 |

OR = odds ratio, 95% CI = 95% confidence interval

TABLE 3.2 – ASSESSMENT WITH PROSTATE CANCER DIAGNOSIS AS OUTCOME

| Variable | OR | 95% CI | Log Likelihood |
|---|---|---|---|
| Screened | 33.96 | 31.23-36.92 | -12087.56 |
| Screened1 | 32.79 | 30.27-35.52 | -11815.85 |
| Screened2 | 19.61 | 17.85-21.55 | -16221.59 |
| Screened3 | 18.02 | 16.31-19.91 | -16869.42 |
| Screened4 | 1.26 | 1.24-1.26 | -17368.53 |
| Screened5 | 1.31 | 1.30-1.32 | -17076.38 |
| Screened6 | 33.94 | 31.23-36.89 | -12064.05 |

OR = odds ratio, 95% CI = 95% confidence interval

TABLE 3.3 – OUTCOMES WITH PSA TESTING AS OUTCOME

| Variable | OR | 95% CI | Log Likelihood | ROC area |
|---|---|---|---|---|
| Screened | 2.10 | 1.77-2.49 | -5294.61 | 0.5248 |
| Screened1 | 1.92 | 1.63-2.27 | -5300.18 | 0.5235 |
| Screened2 | 1.37 | 1.09-1.73 | -5324.95 | 0.5061 |
| Screened3 | 1.38 | 1.07-1.77 | -5325.41 | 0.5052 |
| Screened4 | 1.02 | 1.01-1.04 | -5321.76 | 0.5189 |
| Screened5 | 1.04 | 1.02-1.05 | -5314.98 | 0.5383 |
| Screened6 | 2.08 | 1.75-2.46 | -5295.52 | 0.5245 |

OR = odds ratio, 95% CI = 95% confidence interval, ROC = receiver-operating characteristic curve

TABLE 3.4 – OUTCOMES WITH CLINICALLY SIGNIFICANT DISEASE AS OUTCOME

| Variable | OR | 95% CI | Log Likelihood | ROC area |
|---|---|---|---|---|
| Screened | 0.82 | 0.69-0.98 | -5917.00 | 0.4942 |
| Screened1 | 0.88 | 0.74-1.03 | -5918.15 | 0.4957 |
| Screened2 | 0.87 | 0.69-1.08 | -5918.55 | 0.4974 |
| Screened3 | 0.84 | 0.66-1.07 | -5918.31 | 0.4972 |
| Screened4 | 0.96 | 0.95-0.97 | -5893.77 | 0.4535 |
| Screened5 | 0.96 | 0.95-0.97 | -5898.21 | 0.4612 |
| Screened6 | 0.81 | 0.68-0.97 | -5916.67 | 0.4938 |

OR = odds ratio, 95% CI = 95% confidence interval, ROC = receiver-operating characteristic curve

## Appendix

TABLE A – TIME TRENDS IN AGE, GLEASON SCORE, STAGE, AND CLINICALLY SIGNIFICANT DISEASE AMONG CASES

| Year | Age | | Gleason score | | Stage (%) | | | Clinically significant disease |
|---|---|---|---|---|---|---|---|---|
| | Mean | Median | Mean | Median | Early | Late | Missing | % |
| 1990 | 74.4 | 75.0 | 5.4 | 5.0 | 62.9 | 32.9 | 4.2 | 40.7 |
| 1991 | 73.4 | 73.0 | 5.5 | 6.0 | 60.0 | 36.1 | 3.9 | 42.7 |
| 1992 | 73.1 | 73.0 | 5.4 | 5.0 | 67.2 | 29.5 | 3.3 | 36.0 |
| 1993 | 72.9 | 73.0 | 5.5 | 6.0 | 68.1 | 28.7 | 3.2 | 34.3 |
| 1994 | 72.5 | 73.0 | 5.5 | 6.0 | 68.4 | 28.7 | 2.9 | 35.1 |
| 1995 | 72.3 | 72.0 | 5.6 | 6.0 | 69.0 | 23.6 | 7.3 | 31.5 |
| 1996 | 72.4 | 72.5 | 5.6 | 6.0 | 63.3 | 28.1 | 8.6 | 36.5 |
| 1997 | 73.1 | 73.0 | 5.7 | 6.0 | 66.4 | 25.3 | 8.3 | 31.3 |
| 1998 | 72.9 | 73.0 | 5.9 | 6.0 | 65.2 | 23.6 | 11.2 | 33.0 |
| 1999 | 72.2 | 72.0 | 5.8 | 6.0 | 71.6 | 16.1 | 12.4 | 25.3 |
| 2000 | 72.2 | 73.0 | 6.0 | 6.0 | 73.7 | 17.8 | 8.5 | 25.9 |
| 2001 | 71.5 | 72.0 | 6.3 | 6.0 | 78.6 | 17.2 | 4.2 | 25.0 |
| 2002 | 70.9 | 71.0 | 6.6 | 6.0 | 79.0 | 16.2 | 4.8 | 27.4 |
| 2003 | 70.9 | 71.0 | 8.0 | 8.0 | 28.3 | 14.4 | 57.3 | 17.1 |
| 2004 | 70.7 | 71.0 | 5.5 | 6.0 | 80.3 | 13.4 | 6.3 | 14.3 |
| 2005 | 70.5 | 70.0 | 6.0 | 6.0 | 76.2 | 17.9 | 5.9 | 19.8 |
| 2006 | 69.8 | 69.0 | 5.5 | 7.0 | 76.2 | 17.9 | 5.9 | 19.9 |
| 2007 | 68.9 | 69.0 | 6.5 | 7.0 | 79.1 | 16.6 | 4.2 | 29.1 |
| 2008 | 69.6 | 69.0 | 6.6 | 7.0 | 74.7 | 20.7 | 4.5 | 32.4 |
| 2009 | 69.0 | 68.0 | 6.6 | 7.0 | 74.0 | 21.5 | 4.4 | 30.6 |
| 2010 | 69.2 | 68.0 | . | . | 68.3 | 26.3 | 5.4 | 27.9 |

Clinically significant disease = Had Gleason score (in initial biopsy or in surgical specimen) of 8,9 or 10 OR stage C or D or III or IV at diagnosis – Note: Gleason scores were mostly missing in years 2003-2007.

## Conclusion

We found a compelling pre-clinical rationale for statins as potential chemopreventive agents, as they interfere with five of the ten hallmarks of cancer. Statins may help prevent the development of PC through inhibition of sustained proliferative signals (androgen and *Ras/Rho*), sensitizing potentially malignant cells to programmed cell death, minimizing inflammation, reducing angiogenesis, and impeding invasiveness by blocking adhesion molecules. However, the epidemiological literature investigating the effect of statin use on PC incidence has reported widely varying results and is often plagued by small sample sizes, short pre-diagnosis information on drug exposure, and potential biases. While meta-analyses of the pooled data indicate a small reduction in PC risk with statin use, these studies similarly revealed substantial heterogeneity. Overall, the previous epidemiologic data is suggestive of a reduction in PC risk with statin use, but inconclusive.

Despite the strong pre-clinical rationale for statins as chemopreventive agents for PC, our nested case control study showed that statin use is not associated with either a protective or detrimental effect on overall PC diagnosis, regardless of duration or dose of exposure. This result does not support the hypothesis that statin use decreases PC risk. Specifically, multivariable modelling demonstrated no statistically significant relationship between ever prescription of statins (OR 0.97, 95% CI 0.90-1.05). Similarly, neither restricting the evaluation to use of lipophilic statins (OR 0.96, 95% CI 0.88-1.04) nor non-lipophilic statins (OR 1.06, 95% CI 0.95-1.20) statistically significantly impacted the likelihood of PC diagnosis in multivariable models. However, using multivariable unconditional regression we found that statin use was inversely associated with clinically significant PC (OR 0.84, 95% CI 0.73-0.97).

The strengths of our study include its large sample size; ours was the largest North American cohort to assess the impact of statin use on PC diagnosis. Our cohort also had the longest and most comprehensive pre-diagnosis drug exposure data, with >90% of patients having 15+ years of data, which given PC long latency permitted the study of statin use during more etiologically relevant periods. By using prescription drug databases and cancer registry data, our study was less susceptible to recall bias and to disease misclassification. We were also able to assess for dose- and duration-response effects.

However, our results need to be interpreted within the context of the limitations of this observational study. As a retrospective study, we were only able to assess and adjust for variables that had been routinely recorded. Therefore, we assumed that all prescribed drugs were consumed, which might be a reasonable assumption for men who filled multiple prescriptions of the same drug. However, lack of adherence could have masked beneficial effects due to the ensuring exposure misclassification. Residual confounding by unmeasured or mismeasured confounders (especially screening) remains a possible alternative explanation for our findings.

However, we did create a variable to indirectly adjust for PC screening. We created the variable by assessing different combinations of medical interventions and diagnoses that are known to be strongly correlated with screening. Specifically, we assessed prescription of 5-alpha reductase inhibitors, prescription of alpha-1-adrenergic receptor blockers, visits to a urologist, diagnosis of benign prostatic hyperplasia, prostatitis, or other prostatic conditions, prostate ablation, prostate biopsy, and frequent visits to a family physician. The chosen variable influenced PC risk as we would expect for screened individuals and allowed separate interpretation of the effect of drugs used for benign prostatic

hypertrophy. It is also reassuring that we were able to measure similar effects for 5-alpha-reductase inhibitors to those observed in RCTs, since use of these drugs is also likely subject to the same bias.

This thesis synthesizes the existing research on the effect of statin use on PC risk and contributes some of the least potentially biased data to this question. Overall, our results and the other methodologically most robust epidemiological studies do not support an effect of statin use on overall PC diagnosis. However, there remains the possibility that the mechanisms inhibited by statins are more important for the development of aggressive disease. Although we could not rule out confounding by screening as a possible explanation, overall, these results can provide reassurance to the millions who use these medications that they do not appear to increase PC risk. Our study also provides an approach to indirectly adjusting for PC screening and using administrative data that can be adapted for other jurisdictions. At this stage, we believe further studies with both long pre-diagnosis drug histories and an ability to adjust directly for PC screening are needed before considering embarking on randomized chemoprevention trials.

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