The Relationship Between Metformin Exposure, Prostate Cancer and Race/ethnicity

By

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Abstract

Relative to those without diabetes, individuals with type 2 diabetes have an increased risk of several cancers, but a decreased risk of prostate cancer. While metformin may reduce the risk of some cancers, it may not reduce the risk of prostate cancer. However, race/ethnicity may modify metformin's effect. Thus, our objective was to investigate the impact of metformin exposure on prostate cancer risk in Western and Asian populations by conducting two studies: 1) a systematic review of published literature and 2) an retrospective cohort study. In our literature review, metformin was not associated with prostate cancer in either population. However, this study was limited by significant heterogeneity across published studies. Despite less heterogeneity, our cohort study further suggested that there is no relationship between metformin exposure, prostate cancer and race/ethnicity.

Preface

CBC was responsible for the statistical analysis, interpretation of the data and preparing all chapters of the of thesis. JAJ, SRM and DTE provided guidance throughout and edited portions of the thesis. Chapter 2 did not require ethnics approval but Chapter 3 required approval from the Health Research Ethics Board of the University of Alberta (Pro00003385_AME5). The data used in Chapter 3 were obtained by Population Data BC. All inferences, opinions, and conclusions drawn in this manuscript are those of the authors, and do not reflect the opinions or policies of the Data Stewards at Population Data BC.

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Table of Contents

List of Figures

List of Tables

Chapter 1. Introduction

1.1Background

1.1.1 Type 2 Diabetes

The current prevalence of type 2 diabetes in Canada is estimated to be 8% and by 2020 it may rise to 11%, while the prevalence of prediabetes may rise to 23%[1,2]. However, about 20% of diabetes cases remain undiagnosed[3]. In 2009, the annual economic burden of diabetes was $12.2 billion and accounted for about 3.5% of Canada's health expenditure. Unfortunately, it is estimated that by 2020, the direct costs of diabetes alone will exceed $16 million annually[4]. Patients with diabetes also have 1.29 times more comorbid conditions than those without and, consequently, 1.42 times the number of physician visits[1]. Thus, providing comprehensive care to a diabetes patient may cost 4.5 times more than treating diabetes alone[5].

Typically, insulin produced by the pancreas maintains glucose homeostasis by initiating the cellular signalling cascade responsible for the influx of glucose into peripheral tissues such as fat and muscle[6]. However, in type 2 diabetes, due to insulin resistance in those peripheral tissues, increasing levels of insulin are required to maintain glucose homeostasis, inducing a state of hyperinsulinemia[6]. Eventually, pancreatic insulin production is no longer capable of regulating glucose metabolism causing one of the hallmark indicators of diabetes, hyperglycemia[6]. Large, long-term epidemiologic studies suggest that this period of hyperinsulinemia may precede the diagnosis of type 2 diabetes by over 10

years[7]. While type 2 diabetes manifests through a combination of insufficient insulin production and insulin resistance, type 1 diabetes is due to insufficient insulin production, secondary to an autoimmune reaction resulting in reduced pancreatic beta-cell mass[6].

Diabetes is often managed with a combination of glucose-lowering agents (oral medications and/or insulin), diet and exercise[8]. In type 2 diabetes, if insufficient results are derived from lifestyle modifications, metformin is typically the first oral medication prescribed[8]. However, if glycemic control is not achieved, a combination of metformin with one or more other hypoglycemic agents may be used[8]. Such agents include acarbose, sulfonylureas, meglitinides, dipeptidyl peptidase inhibitors, glucagon-like peptide 1 receptor agonists and thiazolidinediones[8]. If glycemic control is still not achieved a regimen of insulin is often initiated with or without metformin. Insulin, in some cases, may also be used as initial therapy[8].

These medications aim to achieve glycemic control and reduce the risk of associated microvascular complications, such as retinopathy, nephropathy and neuropathy[8]. There is limited evidence, however, that improved glycemic control reduces the risk of macrovascular complications, once the leading cause of mortality amongst diabetic patients[8]. Nonetheless, individuals with diabetes are three times more likely to be hospitalized with cardiovascular disease, 12 times more likely to be hospitalized with end-stage renal disease and 20 times more likely to be hospitalized for limb amputations[3]. About 37% of patients with

diabetes are also affected by two or more comorbidities such as mental health, cardiovascular or respiratory disease[3]. Thus, while treating diabetes itself is crucial, patients with diabetes are complex and often require additional care. Despite the health and economic burden of diabetes, if managed properly, patients can still maintain a high quality of life. Unfortunately, only 50% of patients meet their glycemic targets, 36% meet their blood pressure targets and 57% their cholesterol targets, while only 13% of patients meet all three targets[9]. Hence, while diabetes can be managed, there is a significant gap in management in Canadian patients, increasing the patient's risk of complications and the economic burden on our healthcare system[9].

1.1.2 Cancer

It is estimated that 40% of Canadians will be diagnosed with cancer in their lifetime[10]. About 200 000 new cases of cancer will be diagnosed in 2015 in Canada, half of which will be lung, breast, colorectal or prostate cancer cases[10]. Women are most likely be diagnosed with breast, lung and colorectal cancer, while men are most likely to be diagnosed with prostate, colorectal and lung cancer[10]. In both sexes, the incidence rates of cancer have been rising, although this may be partially attributed to improved detection[10]. Cancer risk generally increases with age and with an aging population, the absolute number of new cases is expected to rise[11]. In addition to the grave physical and mental burden, the average cancer patient costs the healthcare system $25 000 to treat, thus there is both a social and economic incentive to prevent cancer cases[12].

Unfortunately, cancer is difficult to cure due to the multitude of complex and varying cellular mechanisms capable of causing cancer. These aberrant cellular processes can manifest through genetic factors alone but are also a consequence of DNA damage secondary to environmental exposure to carcinogens, radiation, poor diet or tobacco use. Such DNA damage can lead to escape from apoptosis, unregulated progression through the cell cycle and angiogenesis, which in turn lead to uncontrolled and undifferentiated cellular proliferation and ultimately metastasis and intractable disease[6]. Generally, cancer treatment aims to improve the quality and quantity of life by attenuating cellular proliferation and treating symptoms.

1.1.2.1 Prostate Cancer

One in eight men will develop prostate cancer in their lifetime and the risk increases with age[10]. The Canadian Cancer Society estimates there will be 99 new cases of prostate cancer per 100 000 Canadian men in 2015, about 40 more cases than the second most prevalent cancer in men, colorectal cancer[10]. Fortunately, only 10% of cancer deaths are due to prostate cancer, and only 1 in 27 men with prostate cancer will die from it[10]. However, prostate cancer still has the 3rd highest probability of death of all cancers, yielding 17.4 deaths per 100 000 Canadian men[10]. Moreover, prostate cancer had an estimated economic burden of $10 billion in 2000.[13]

Age, race/ethnicity and family history are the most established risk factors for prostate cancer[14,15]. Increasing age, those of African descent and those with a first-degree relative with prostate cancer have a higher risk of prostate cancer[14]. Conversely, Asian men have a decreased risk of prostate cancer, potentially due to genetics, lifestyle or different rates of screening in Asian countries[16]. However,

the incidence of prostate cancer is rising, possibly influenced by improved detection, economic growth and the subsequent changes in lifestyle[16]. Hence if lifestyle and screening policies explain this discrepancy, the incidence rates of prostate cancer may be similar between Western and Asian men living in Western nations. The risk of prostate cancer is higher in Asian men living in the United States than those living in Asia, but it does not exceed the incidence in non-Hispanic white men, thus the lower risk observed in Asian men is likely influenced by other factors[16,17]. Moreover, the risk profile of prostate cancer at diagnosis is often worse among Asian men and may differ based on nativity[18]. Other possible, but less established, risk factors for prostate cancer include diet and genetics[6].

Screening for prostate cancer has become a controversial matter. Biochemical tests such as the prostate specific antigen (PSA) test are capable of identifying cases of prostate cancer. The risk of prostate cancer generally increases with PSA, but at low levels, the risk of cancer is not negligible, thus false negatives are possible[14,19]. Similarly, higher PSA may not be a definitive test, because higher PSA may be a result of benign prostate hyperplasia, age, prostatitis, urologic procedures and some medications[20]. PSA screening was employed regularly in the past, but because of overdiagnosis, possible overtreatment of clinically insignificant cases and limited evidence supporting reduced mortality with screening programs, PSA is generally not recommended as a screening tool in the general population[14,19]. There are three commonly debated trials exploring the benefits of prostate cancer screening[21–23]. Despite debates regarding the validity of the trials, most trials suggest a mortality benefit of prostate cancer

screening but also debate if these benefits outweigh the potential overtreatment and overdiagnosis associated with screening[22]. The other form of screening is digital rectal exam, which remains a safe, inexpensive test with high specificity but low sensitivity and a positive test likely requires further investigation[6].

While prostate cancer can be fatal, less aggressive forms of prostate cancer are unlikely to be fatal and half of the cases identified are of an indolent nature[24]. But despite prostate cancer's relatively favourable prognosis, the diagnosis is still associated with anxiety, depression, urogenital dysfunction and cardiovascular events[14]. For example, about 30% of patients are affected by anxiety, and patients with prostate cancer may have a 50% increase in fatal cardiovascular events and a 30% increase in non-fatal cardiovascular events[14].

Given that not all cases of prostate cancer require immediate treatment, the decision to initiate treatment can present a clinical dilemma. If low-grade prostate cancer is detected, patients may seek immediate treatment however, active surveillance is also becoming an increasingly popular option in Canada[25]. Because no option is clearly superior and associated with its own risks and benefits, physicians often initiate treatment based on the patient's preferences and a shared definition of treatment success. If offered, treatment is often a combination of radiation, surgery or chemotherapy[14]. However, treatment itself is also associated with short- and long-term side effects. For example anti-androgen medications used to treat prostate cancer may result in gynecomastia, gastrointestinal disturbances or hot flashes[6]. Surgical complications include incontinence and impotence while radiation can cause incontinence, impotence,

cystitis, hematuria and urinary retention[6]. Overall, prostate cancer does not confer the same risk of mortality and morbidity of other cancers but is still plagued by its own complexities such as overdiagnosis, overtreatment and associated sequelae of the cancer itself and the treatment. And because there may be little benefit of screening, prevention is a prudent public health measure.

1.1.3 Diabetes and Cancer

In addition to an increased risk of cardiovascular, renal and other diseases, recent evidence suggests that those with type 2 diabetes also have an increased risk of cancer[26]. The most robust association exists between type 2 diabetes and breast, colorectal and endometrial cancer with a 24%, 27% and 97% increase in risk respectively[26]. There are likely many factors involved in this relationship, but increased cancer risk may be secondary to hyperinsulinemia-induced cellular proliferation[27]. Increased circulating insulin may activate insulin and insulin-like growth factor-1 receptors and increase circulating insulin-like growth factors, which regulate cellular metabolism, proliferation, differentiation and apoptosis[28–30]. Because up-regulation of these receptors has been observed in neoplastic cells of the breast, prostate, colorectal and bladder, it is posited that hyperinsulinemia and excessive activation of these receptors may be involved in the pathogenesis of cancer. Alternatively, it has been argued that hyperglycemia may create a metabolic milieu conducive to propagation of cancerous cells[31]. The lack of association between glucose-lowering and reduced risk of cancer in large clinical trials is perhaps the strongest evidence against this argument[32].

Increasing age, race/ethnicity and sex are shared risk factors and likely contribute to the association between type 2 diabetes and cancer. A majority of individuals diagnosed with diabetes and cancer are 45 years or older[11,33]. Men and those of Aboriginal or African descent are also at an increased risk of diabetes and cancer[8,11]. Furthermore, tobacco use, obesity, alcohol use and sedentary lifestyle are also shared but modifiable risk factors[31,34]

If the risk of cancer in those with diabetes is mediated through hyperinsulinemia, glucose-lowering therapies may mitigate the risk of cancer by reducing hyperinsulinemia. Metformin is an inexpensive and well-tolerated first line treatment for patients with type 2 diabetes. Metformin has also been associated with a reduced risk of some cancers, including colorectal, liver and lung[35]. This may be due to a direct effect of metformin to activate AMPK, which in turn inhibits mTOR, causing a decrease in cellular proliferation, or indirectly through its ability to reduce hyperinsulinemia and the associated cellular proliferation[36]. On the contrary, sulfonylureas and the thiazolidinedione pioglitazone have been associated with increased risk of cancer[34,37]

1.1.4 Diabetes, Metformin and Prostate Cancer

While diabetes is usually associated with an increased risk of cancer, it is associated with a 15%-20% relative risk reduction in prostate cancer[29,38]. Hyperinsulinemia and type 2 diabetes have been associated with low testosterone levels. Testosterone levels are positively associated with risk of prostate cancer, hence lower levels may confer a reduced risk of prostate cancer. Treatment of diabetes with glucose-lowering therapies such as metformin will cause a reduction in circulating insulin, which may increase testosterone levels and subsequent proliferation of neoplastic cells in the prostate[39]. However,

metformin's potential direct anti-cancer effects may also reduce the risk of prostate cancer by activating AMPK, which in turn inhibits mTOR, causing a decrease in tumor growth[36].

A number of previous systematic reviews have investigated the effect of metformin on prostate cancer risk. Gandini et al. associated metformin exposure with a 1.06 (0.80,1.41) relative risk and an I^2 of 91%[35]. However they could only pool 12 studies at the time. Franciosi et al. achieved a similar pooled estimate from observational studies, 0.96 (0.87, 1.05) with an I^2 of 60% but pooled certain studies more than once[40]. Noto et al. pooled 7 studies and found a risk estimate of 0.89 (0.66, 1.19) with an I^2 of 66%[41]. Similarly, Soranna et al. found a pooled estimate of 0.92 (0.73, 1.17) with an I^2 of 78%[42]. Wu et al. pooled 10 studies yielding an estimate of 0.92 (0.84, 1.03) with an I^2 of 71%[43]. However, Yu et al. and Deng et al. found a slight statistically significant reductions in prostate cancer risk associated with metformin use, of 9% and 12%, respectively, although with substantial (50-75%) heterogeneity[44,45].

Thus, the literature seems to consistently suggest that there is no association between metformin use and prostate cancer risk, but the available studies have substantial heterogeneity. One of the potential contributors to this heterogeneity is the different level of risk observed in men with different racial/ethnic backgrounds. However, the distinction between race and ethnicity and possible blending of the two present methodological obstacles[46]. Fortunately, adjusting for race or ethnicity to estimate the relationship between two variables or using the race/ethnicity paradigm to describe disparities between racial/ethnic groups can be methodologically robust[46]. The distinction between race and ethnicity is

important to consider, as the former implies some innate biologic predisposition, while ethnicity would encompass broader socio-cultural considerations, including lifestyle behaviours or health care utilization, which may affect disease risk or outcomes.

1.2 Objective

The aim of this thesis research was to investigate the association between prostate cancer and metformin exposure while also assessing any effect modification by race/ethnicity. This was achieved by 1) synthesizing the existing literature with meta-analytic techniques to explore the association and 2) conducting a population-based retrospective cohort study using administrative health records linked with cancer registry data.

1.3 Summary of Projects

1.3.1 Project #1-Systematic Review

Aim: Metformin is associated with a reduced risk of some cancers but its effect on prostate cancer is unclear. Some studies suggest only Asians derive this benefit. Therefore, we undertook a systematic review with particular attention to race/ethnicity. **Methods:**Medline, Embase, Scopus, Web of Science, and EBM Reviews were searched from inception to 2015. Two reviewers identified and abstracted articles. Studies were pooled using random effects model and stratified by Western- vs Asian-based populations. **Results:** We identified 482 studies; 26 underwent full review. Of Western-based studies (n=23), two were randomized trials and 21 were observational studies. All Asian-based studies (n=3) were observational. There were 1572307 patients, 1171643

Western vs 400664 Asian. Across all studies there was no association between metformin and prostate cancer (RR: 1.01, 95%CI: 0.86-1.18, I^2: 97%), with similar findings in Western-based trials (RR: 1.38, 95%CI: 0.72-2.64 I^2: 15%) and observational studies (RR: 1.03 95%CI: 0.94-1.13, I^2: 88%). Asian-based studies suggested a non-significant reduction (RR: 0.75, 95%CI: 0.42-1.34, I^2: 90%), although these results were highly influenced by one study of almost 400,000 patients (propensity-adjusted RR: 0.47 95%CI 0.45-0.49). Removing this influential study yielded an estimate more congruent with Western-based studies (RR: 0.98 95%CI:0.71-1.36, I^2: 0%). **Conclusion:** There is no association between metformin and risk of prostate cancer, in either Western-based or Asian-based populations, after removing a highly influential Asian-based study.

1.3.2 Project #2-Retrospective Cohort Study

Background: Men with diabetes have a lower risk of developing prostate cancer than men without diabetes. Whether this risk is altered by metformin use or race/ethnicity is not clear.

Objective: To investigate the relationship between metformin exposure, race/ethnicity and prostate cancer among men with diabetes.

Methods: Using British Columbia (Canada) administrative databases, from 1994-2012, adult (age>30 years) men with diabetes were identified. Metformin exposure was defined as a time-dependent variable, stratified first into any use, and secondarily into tertiles of cumulative dose. Validated surname algorithms were used to identify individuals as Chinese, Indian or Other. Multivariable Cox regression models, stratified by age, were used to estimate adjusted risks of prostate cancer, including the interactions between metformin and ethnicities.

Results: The cohort of 106 287 men had mean age of 59 years and median follow-up of 10 years. The incidence of prostate cancer among those exposed vs not exposed to metformin was 105.4 vs 195.1 cases per 1,000 person-years, respectively. Users of metformin aged 40-49 (aHR: 1.14, 0.79-1.63), 60-64 (aHR:0.96,0.82-1.12) and ≥65 (aHR:1.09, 0.98-1.21) years of age had similar risk of prostate cancer as those not exposed to metformin, while those exposed aged 50-59 years had a decreased risk (aHR:0.86, 0.74-1.00). Chinese men were at a decreased risk of prostate cancer across all age strata (aHR ranging from 0.27 to 0.60), but there was no difference in risk between Indian men compared to Other ethnicities.

Conclusion: There was no independent association between metformin exposure and risk of prostate cancer in men with diabetes, and this was true across different ethnicities.

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Chapter 2: Metformin, Asian Race/ethnicity and Risk of Prostate Cancer in Type 2 Diabetes: A Systematic Review and Meta-Analysis

2.1 Introduction

Patients with type 2 diabetes have an increased risk of many cancers including breast, colorectal and endometrial cancer, but a reduced risk of prostate cancer. There are likely many factors involved in the relationship between diabetes and cancer, but increased cancer risk may be secondary to hyperinsulinemia induced cellular proliferation, while hyperinsulinemia may also lead to reduced testosterone levels, yielding a lower prostate cancer risk[1].

Metformin is an inexpensive and well-tolerated first line treatment for patients with type 2 diabetes. Metformin has also been associated with a reduced risk of some cancers, including colorectal, liver and lung[2]. This may be due to a direct effect of metformin to activate AMPK, which in turn inhibits mTOR, causing a decrease in cellular proliferation, or indirectly through its ability to reduce hyperinsulinemia and the associated cellular proliferation[3]. However, because hyperinsulinemia and type 2 diabetes have been associated with low testosterone, a reduction in circulating insulin may lead to increases in testosterone levels and subsequent proliferation of neoplastic cells in the prostate[4].

Further complicating the issue is potential effect modification by race/ethnicity. Specifically, relative to non-Asian patients with type 2 diabetes, Asian patients appear to have an increased risk of prostate cancer[5,6]. Previous studies have investigated the association between metformin and prostate cancer, but with conflicting results that have not accounted for race/ethnicity. Therefore, we undertook this systematic review to summarize the association between metformin and risk of prostate cancer in Western- and Asian-based populations with type 2 diabetes.

2.2 Methods

2.2.1 Overview

We undertook a systematic review of the literature up to August 2015 using a pre-specified research protocol. Because race/ethnicity was not often explicitly identified, we stratified all analyses by source country, identifying studies as either Western-based (studies using populations based in Europe and North America) or Asian-based (predominantly studies based in Taiwan, no other studies used populations from other Asian countries).

2.2.2 Literature Search

The databases Pubmed/Medline, Scopus, Evidence Based Medicine Reviews (which includes ACP Journal Club, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Methodology Register, Database of Abstracts of Reviews of Effects, Health Technology Assessments and National Health Service Economic Evaluation Database), Web

of Science and Embase were searched from inception until August 2015. We used the search terms metformin, diabetes and cancer. Grey literature such as clinicaltrials.gov and conference abstracts from the American Diabetes Association and the European Association for the Study of Diabetes were also searched.

Manuscript and abstract titles were reviewed and those potentially relevant to our objective were recorded. Two reviewers (CC and ME) then independently analyzed the abstracts and full texts of those recorded. We included observational studies or randomized controlled trials that investigated the incidence of prostate cancer in adult populations, and were comparing those currently exposed to metformin versus those who are not. Additionally, the reference lists were hand searched and experts contacted. Any conflicts regarding study inclusion were reconciled through discussion with the senior author (JAJ) who was the final arbiter of inclusion or exclusion if consensus could not be achieved.

2.2.3 Data Abstraction

Two reviewers (CC and ME) independently abstracted information regarding study design, data source, study region (i.e., Western-or Asian-based), exposure and comparator, number of patients in each exposure group, study period, length of follow up, covariates adjusted for, fully adjusted and crude odds ratios, risk ratios or hazard ratios and confidence intervals. If multiple risk estimates were available, the most completely adjusted value was taken as the primary risk estimate, but we also abstracted unadjusted comparisons where available. Any

discrepancies were reconciled by consensus after referring to the original report. The risk of bias of each study was determined with the Newcastle-Ottawa scale for observational studies and the Cochrane Risk of Bias tool for randomized controlled trials[7,8].

2.2.4 Data Analysis

For observational studies, the adjusted and unadjusted (where available) hazard ratios and confidence intervals were pooled using the random effects model and the inverse variance method. Because randomization balanced measured and unmeasured confounders, we pooled unadjusted risk estimates from the controlled trials using the Mantel-Haenszel method. Heterogeneity was assessed using the I^2 parameter. We stratified our results by study type, study region (i.e., Western-or Asian-based) and risk of bias for observational studies (stratified by the median Newcastle-Ottawa score of 6). Publication bias was assessed with visual inspection of funnel plots. All analyses and calculations were completed in RevMan 5.3 (Copenhagen, Denmark).

2.3 Results

Our initial literature search identified 501 titles of potential interest, once duplicates were removed. After initial review of abstracts and full texts, 22 studies were identified. Two hundred and two (42%) studies were excluded because they lacked metformin exposure and 277 (58%) were excluded because they did not study incident prostate cancer cases. An additional 6 articles were identified from their reference lists, yielding a total of 28 studies that were abstracted,

including two randomized trials and 26 observational studies. There were 2 Western-based randomized trials, 3 Asian-based cohort studies, 1 Asian-based case-control study, 14 Western-based cohort studies and 8 Western-based case-control studies[9–33]. One study (Geraldine et al.) did not have sufficient information to be included in the pooled analyses and Tseng 2014 used a similar cohort to Tseng 2011, hence only Tseng 2014 was included, providing a total of 26 studies included in the quantitative analysis. There were a total of 1572307 patients, 1171643 Western vs 400664 Asian. There was insufficient information to tabulate the crude total number of events. The median Newcastle-Ottawa score was 6; ascertainment of the scores is presented in Tables 2-1 to 2-3.

Across all 26 quantitatively synthesized studies there was no association between metformin use and prostate cancer (RR: 1.01, 95%CI: 0.86-1.18) **(Figure 2-1)**, although there was substantial heterogeneity (I^2: 97%). Similar findings were observed when restricted to Western-based studies, whether observational (RR: 1.03; 0.94-1.13, I^2: 88%) **(Figure 2-2)** or trials (RR: 1.38; 0.72-2.64 I^2: 15%) **(Figure 2-3)**. Asian-based observational studies suggested a non-significant reduction in prostate cancer (RR: 0.75; 0.42-1.34, I^2: 90%) **(Figure 2-4)**, but these results were highly influenced by one single study of almost 400,000 patients, with a propensity-adjusted RR of 0.48 (95%CI: 0.45-0.50)[21]. Removing this one study yielded a much lower heterogeneity estimate more congruent with estimates of effect from Western-based studies (RR: 0.98; 0.71-1.36, I^2: 0%). **Figure 2-5** visually illustrates our search strategy. Finally, visual inspection of funnel plots of the observational studies demonstrated symmetry, suggesting the lack of any substantial publication bias (**Figure 2-6)**.

Stratification by study design and risk of bias provided similar results. The pooled risk estimates of adjusted data comparing current metformin use against no current metformin use in all cohort studies, Western-based and Asian-based cohort studies were: 1.01 (0.80, 1.28; I^2: 98%), 1.07 (0.93, 1.23; I^2: 91%) and 0.68 (0.32, 1.44; I^2: 790%), respectively **(Figures 2-7 to 2-9)**. In all case-control studies, Western-based and Asian-based case-control studies, the pooled risk estimates were: 0.95 (0.85, 1.07; I^2: 73%), 0.96 (0.84, 1.08; I^2: 76%) and 0.94 (0.61, 1.46; I^2: not calculable), respectively **(Figures 2-10 to 2-12)**. Similar risk estimates, with substantial heterogeneity, were found when observational studies were stratified by median score of 6 on the Newcastle-Ottawa Scale **(Figures 2-13 to 2-20)**.

The pooled risk ratio of crude data comparing current metformin use against no current metformin use in all observational studies was 0.83 (0.65,1.07) with an I^2 of 98% **(Figures 2-21 to 2-23)**. The risk ratio for Western-based observational studies was 0.86 (0.69, 1.07) with an I^2 of 95% and for Asian-based observational studies was 0.66 (0.43,1.03) with an I^2 of 74%, which again, was heavily influenced by the larger Tseng 2014 study with an extreme HR **(Figures 2-21 to 2-23)**.

2.4 Discussion

Our synthesis of the available evidence suggests no association between metformin exposure and prostate cancer risk, a finding which is congruent in observational studies whether Western-based or Asian-based. A non-significantly

lower risk of prostate cancer with metformin exposure was evident in Asian-based studies, although statistically insignificant, and heavily influenced by a single, large study from Taiwan[21]. Removing this study returns this association to the null, and removes substantial heterogeneity. Overall, our findings were robust to various sensitivity analyses and there was no evidence of publication bias.

Previous systematic reviews on the topic have found similar results, with no statistically significant association between metformin exposure and prostate cancer risk. Gandini et al. associated metformin exposure with a 1.06 (0.80,1.41) relative risk and an I^2 of 91%[2]. However they could only pool 12 studies at the time. Franciosi et al. achieved a similar pooled estimate from observational studies, 0.96 (0.87, 1.05) with an I^2 of 60% but pooled certain studies more than once[34]. Noto et al. pooled 7 studies and found a risk estimate of 0.89 (0.66, 1.19) with an I^2 of 66% [35]. Similarly, Soranna et al. found a pooled estimate of 0.92 (0.73, 1.17) with an I^2 of 78%[36]. Wu et al. pooled 10 studies yielding an estimate of 0.92 (0.84, 1.03) with an I^2 of 71%[37]. However, Yu et al. and Deng et al. found a slight statistically significant reductions in prostate cancer risk associated with metformin use, of 9% and 12%, respectively, although with substantial (50-75% heterogenetity[38,39]. Thus, our results agree with most previous systematic reviews, which were also limited by significant heterogeneity, while including more recent studies. Moreover, our specific focus on the stratification by race/ethnicity has specifically addressed one potential source of heterogeneity.

Despite some strengths, the review possesses some limitations. The first and most significant limitation is the lack of individual patient data, thus we were relegated to stratifying by race/ethnicity based on the origin of the database. These databases may contain patients of several ethnicities and any potential ensuing misclassification may have biased our results. Furthermore, despite stratification by race/ethnicity, study design and risk of bias, significant heterogeneity was observed. Because analysis using crude values yielded I^2 ranging from 74% to 98%, the observed heterogeneity may not be solely due to disparate methods of statistical adjustment. Instead it may be a result of different patient populations or methodological heterogeneity. Regardless, pooling may not be the most accurate depiction of the association between metformin exposure and prostate cancer risk.

What may also be considered a major limitation is the inconsistent drug exposure definitions used in each study, which may have also contributed to the observed heterogeneity. While some studies defined metformin exposure using an ever/never definition or metformin use/no use definitions, other studies compared metformin use against sulfonylurea use or diet. Ideally, the association between metformin exposure and cancer risk would account for time-varying and accumulated drug exposure[40]. Van Staa et al., Azoulay et al., Preston et al. and Margel et al. evaluated the association between prostate cancer risk and cumulative metformin exposure[9,18,23,26]. Among these studies, higher metformin doses were associated with increased, decreased and no association with any prostate cancer risk. Preston et al. did not associate higher doses of metformin exposure with any prostate cancer but with a reduced risk of localized prostate

cancer[23]. On the contrary, Margel et al. found no association between cumulative metformin exposure and low- or high-grade prostate cancer[18]. This presents another potential factor in to our research questions, suggesting that definition, cumulative dose or duration of metformin exposure, as well as prostate cancer grade, may influence the association between metformin and prostate cancer risk.

Moreover, body mass index (BMI) has been associated with increased prostate cancer risk, which may be particularly important in our study. Non-Asian-Americans with normal BMIs possess lower mean prostate specific antigen levels than Asian-Americans with normal BMIs while non-Asian-Americans who are overweight or obese have higher levels than overweight or obese Asian-Americans. Thus BMI introduces an additional variable that may affect the potential association between metformin exposure, race/ethnicity and prostate cancer incidence. Further, most studies lacked adjustment for other prognostic clinical variables such as family history of cancer. Unfortunately, these could not be adequately explored in our review because not all studies adjusted for BMI or other clinical covariates and individual level data was not available.

2.5 Conclusion

In summary, we found no association between metformin and risk of prostate cancer, and this lack of association was present irrespective of race/ethnicity. While research with more robust methods and analysis such as a more accurate classification of race/ethnicity, consistent adjustment for BMI and more accurate definitions of metformin exposure (i.e., individual patient data) would be

welcomed, our results should temper the previous enthusiasm around the potential benefits of metformin on the risk of developing prostate cancer. However, because users and non-users of metformin do not have disparate risks of prostate cancer, it may be possible that metformin negates the reduced risk of prostate cancer between patients with and without diabetes.

Figure 2-1. Current Metformin Use Vs No Current Metformin Use in Western- and Asian- Based Observational Studies

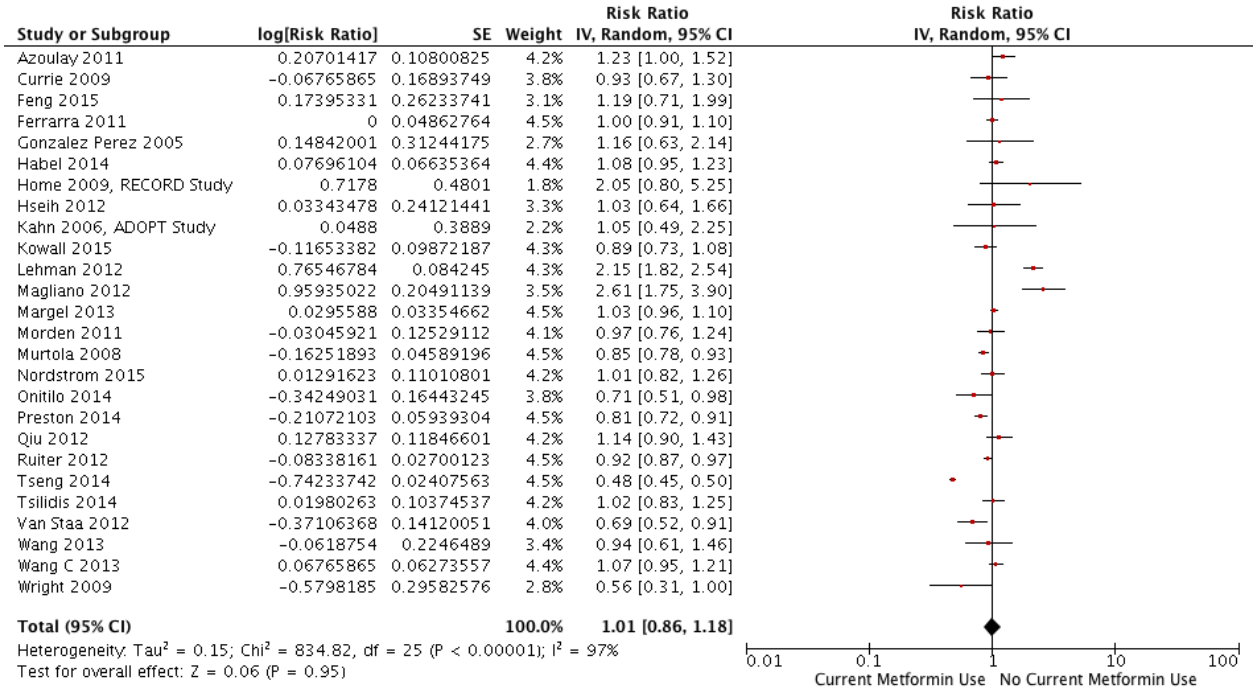


Figure 2-2. Current Metformin Use Vs. No Current Metformin Use in Western-Based Observational Studies

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Azoulay 2011	0.20701417	0.10800825	5.0%	1.23 [1.00, 1.52]
Currie 2009	-0.06765865	0.16893749	3.7%	0.93 [0.67, 1.30]
Feng 2015	0.17395331	0.26233741	2.3%	1.19 [0.71, 1.99]
Ferrarra 2011	0	0.04862764	6.3%	1.00 [0.91, 1.10]
Gonzalez Perez 2005	0.14842001	0.31244175	1.8%	1.16 [0.63, 2.14]
Habel 2014	0.07696104	0.06635364	6.0%	1.08 [0.95, 1.23]
Kowall 2015	-0.11653382	0.09872187	5.3%	0.89 [0.73, 1.08]
Lehman 2012	0.76546784	0.084245	5.6%	2.15 [1.82, 2.54]
Magliano 2012	0.95935022	0.20491139	3.1%	2.61 [1.75, 3.90]
Margel 2013	0.0295588	0.03354662	6.5%	1.03 [0.96, 1.10]
Morden 2011	-0.03045921	0.12529112	4.7%	0.97 [0.76, 1.24]
Murtola 2008	-0.16251893	0.04589196	6.3%	0.85 [0.78, 0.93]
Nordstrom 2015	0.01291623	0.11010801	5.0%	1.01 [0.82, 1.26]
Onitilo 2014	-0.34249031	0.16443245	3.8%	0.71 [0.51, 0.98]
Preston 2014	-0.21072103	0.05939304	6.1%	0.81 [0.72, 0.91]
Qiu 2012	0.12783337	0.12783337	4.6%	1.14 [0.88, 1.46]
Ruiter 2012	-0.08338161	0.02700123	6.6%	0.92 [0.87, 0.97]
Tsilidis 2014	0.01980263	0.10374537	5.1%	1.02 [0.83, 1.25]
Van Staa 2012	-0.37106368	0.14120051	4.3%	0.69 [0.52, 0.91]
Wang C 2013	0.06765865	0.06273557	6.0%	1.07 [0.95, 1.21]
Wright 2009	-0.5798185	0.29582576	1.9%	0.56 [0.31, 1.00]
Total (95% CI)			**100.0%**	**1.03 [0.94, 1.13]**

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 163.12$, df = 20 ($P < 0.00001$); $I^2 = 88\%$
Test for overall effect: Z = 0.59 (P = 0.56)

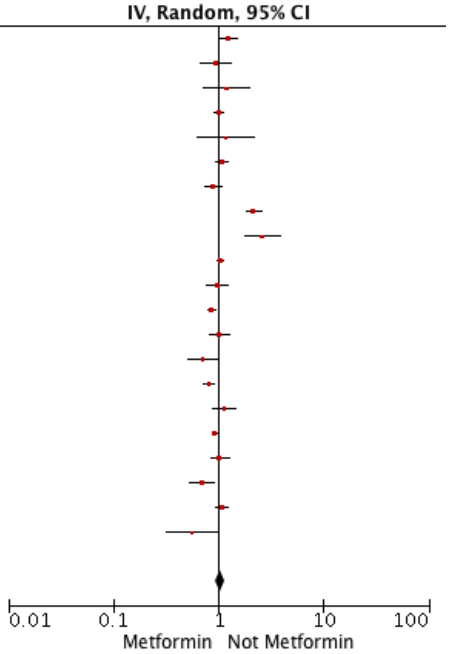


Figure 2-3. Current Metformin Use Vs. No Current Metformin Use in Western-Based Randomized Trials

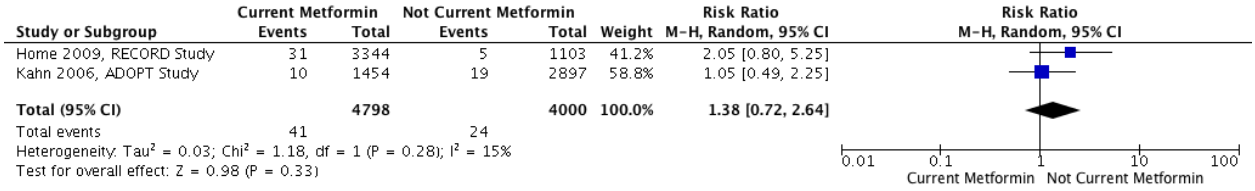


Figure 2-4. Current Metformin Use Vs. No Current Metformin Use in Asian-Based Observational Studies

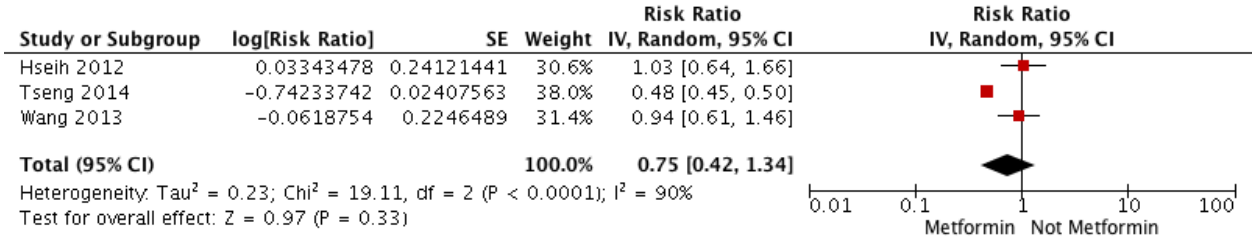


Figure 2-5. Summary of Literature Search and Selection

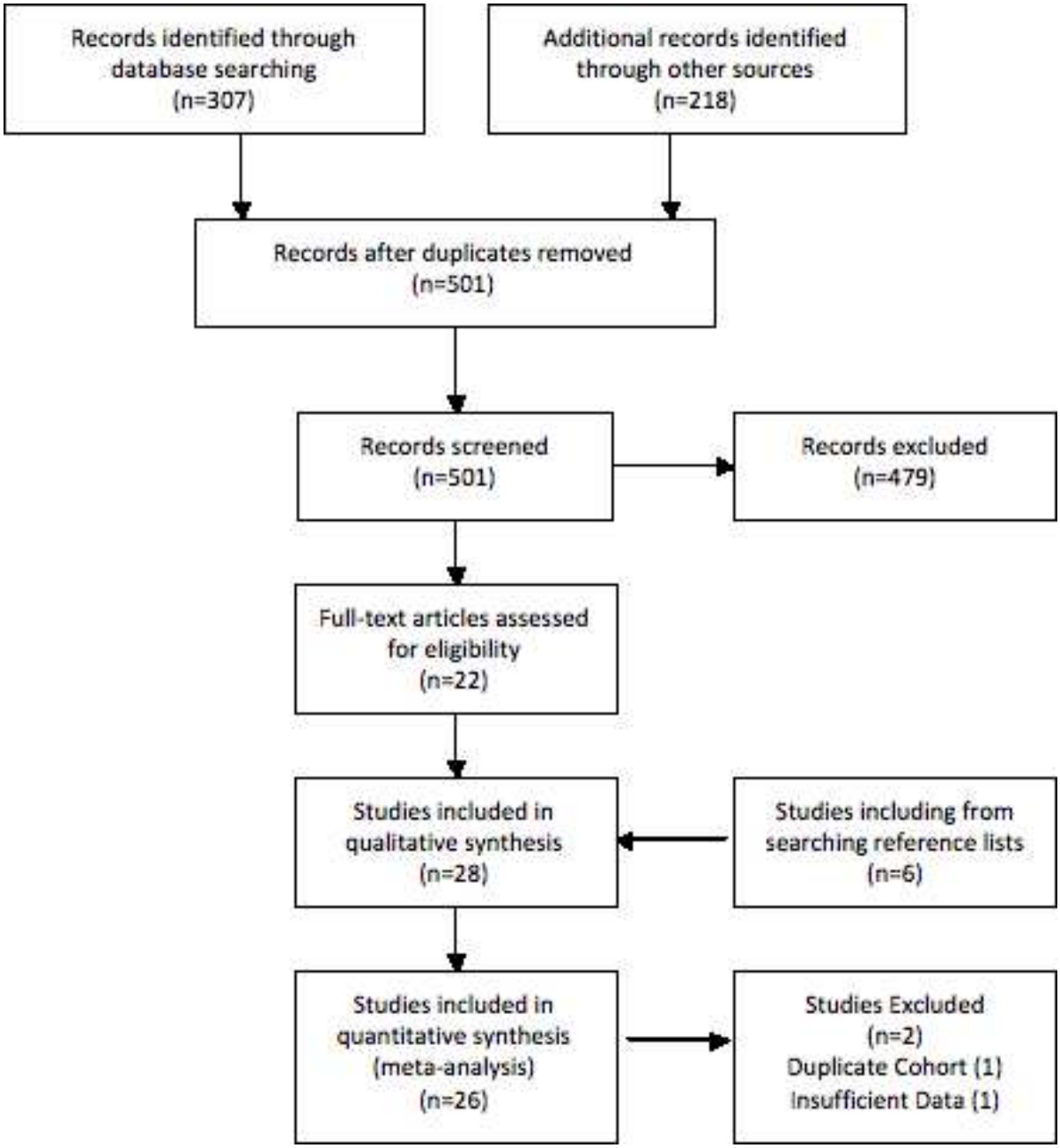


Figure 2-6. Funnel Plot of All Included Observational Studies

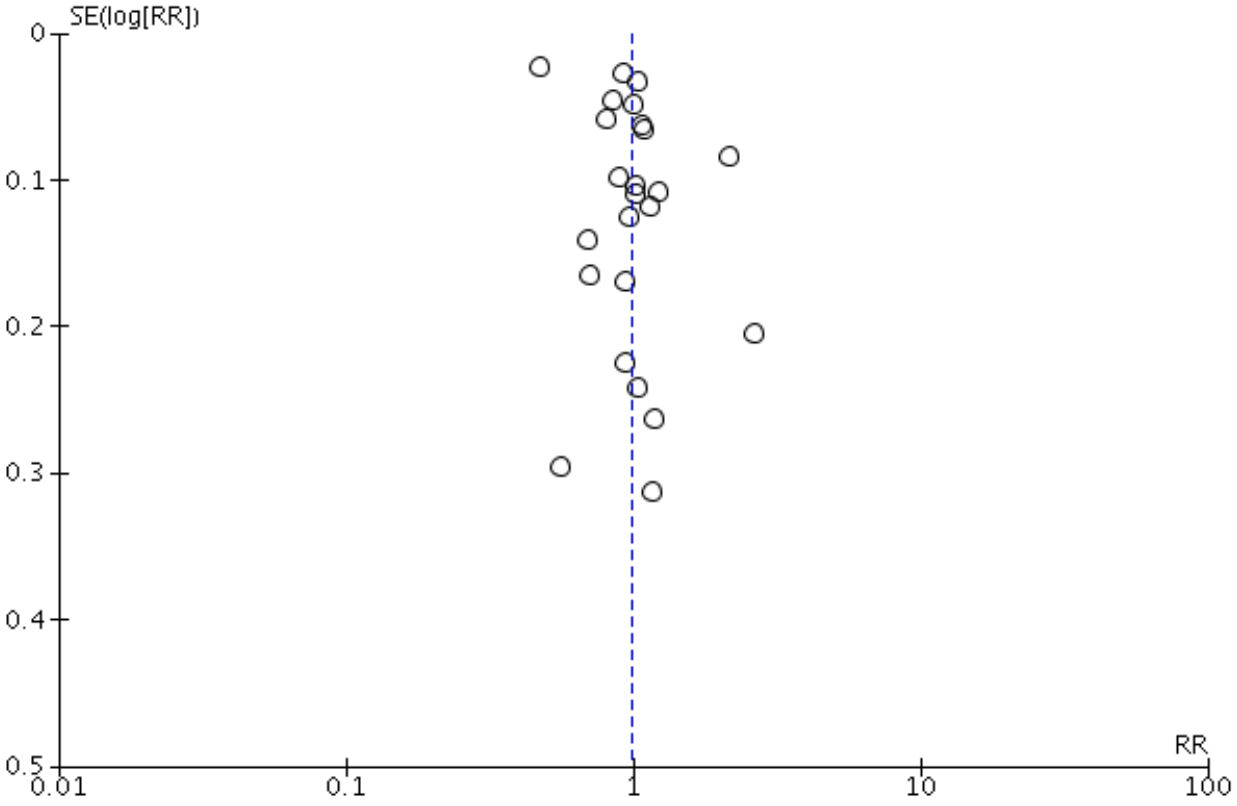


Figure 2-7. Current Metformin Use Vs. No Current Metformin Use in Western- and Asian-Based Cohort Studies

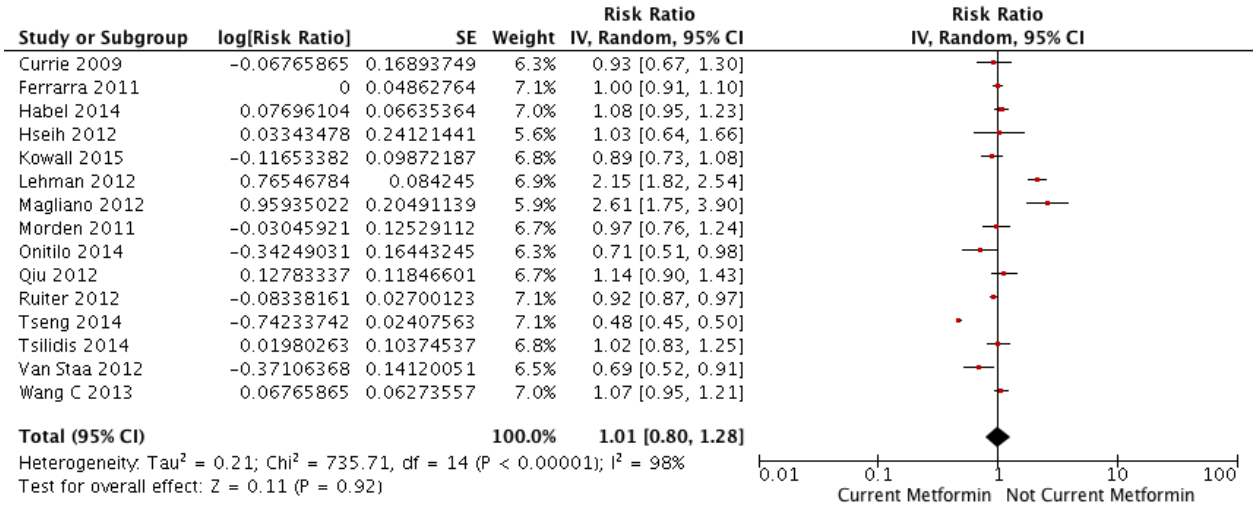


Figure 2-8. Current Metformin Use Vs. No Current Metformin Use in Western-Based Cohort Studies

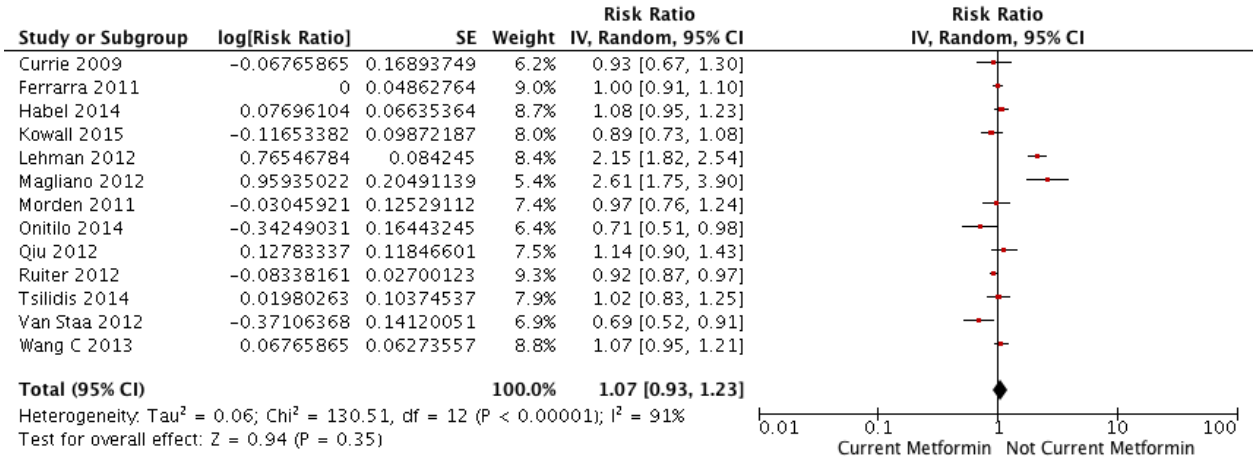


Figure 2-9. Current Metformin Use Vs. No Current Metformin Use in Asian-Based Cohort Studies

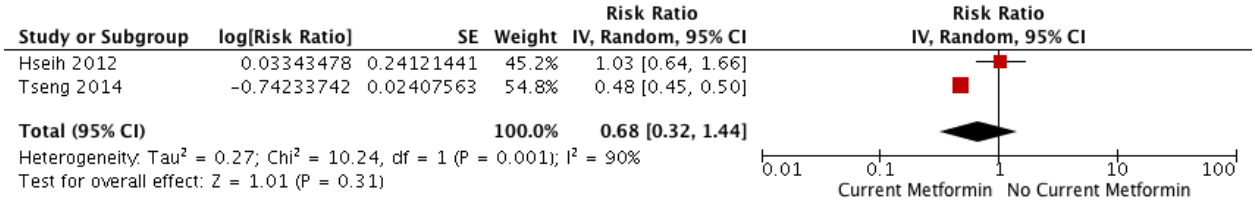


Figure 2-10. Current Metformin Use Vs. No Current Metformin Use in Western- and Asian-Based Case-Control Studies

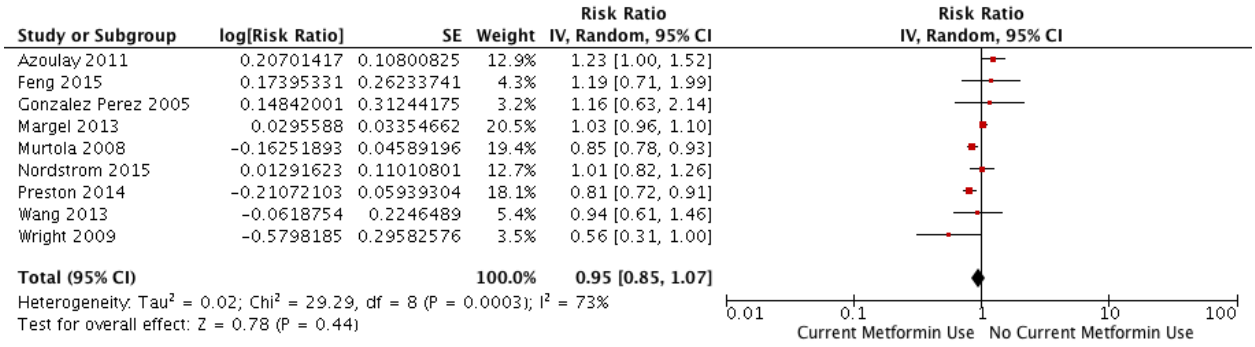


Figure 2-11. Current Metformin Use Vs. No Current Metformin Use in Western-Based Case-Control Studies

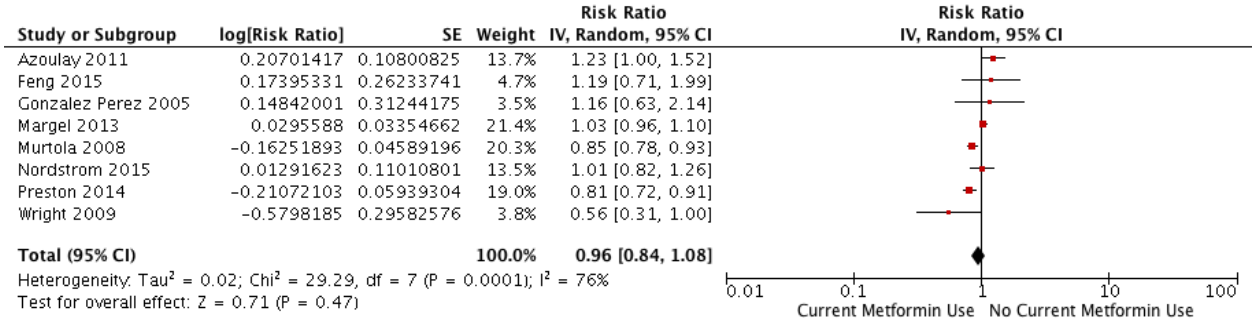


Figure 2-12. Current Metformin Use Vs. No Current Metformin Use in Asian-Based Case-Control Studies

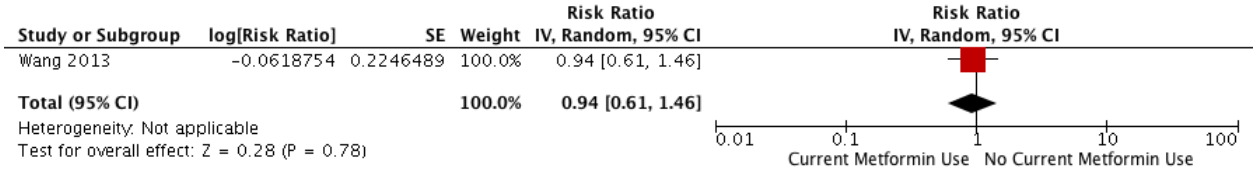


Figure 2-13. Risk of Bias ≤6; Current Metformin Use Vs. No Current Metformin Use in Western- and Asian-Based Cohorts

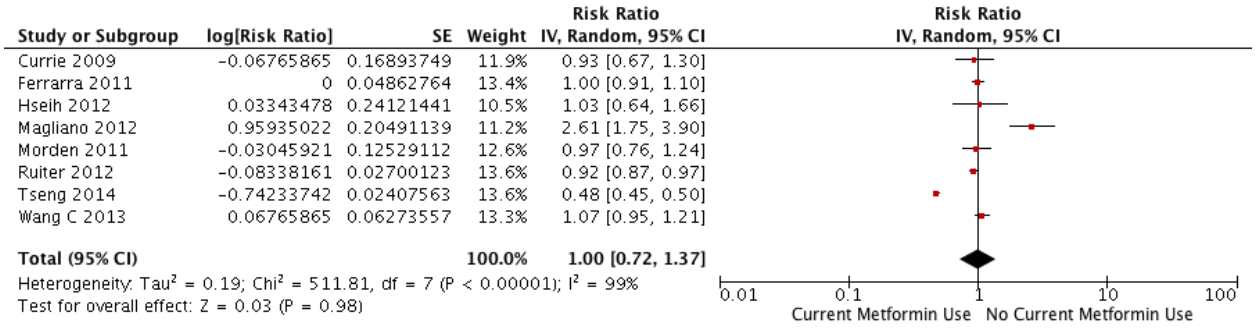


Figure 2-14. Risk of Bias ≤6; Current Metformin Use Vs. No Current Metformin Use in Western-Based Cohort Studies

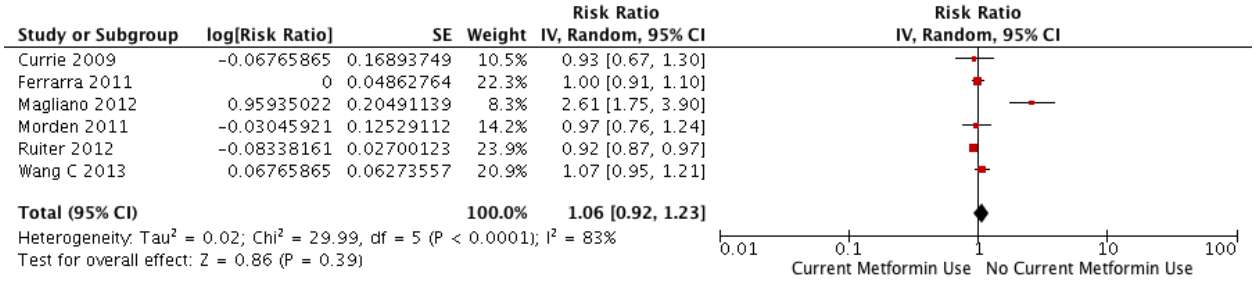


Figure 2-15. Risk of Bias ≤6; Current Metformin Use Vs. No Current Metformin Use in Asian-Based Cohort Studies

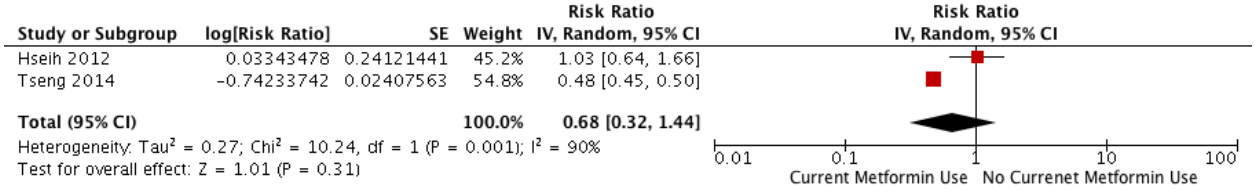


Figure 2-16. Risk of Bias ≤6; Current Metformin Use Vs. No Current Metformin Use in Western- and Asian-Based Case-Control Studies

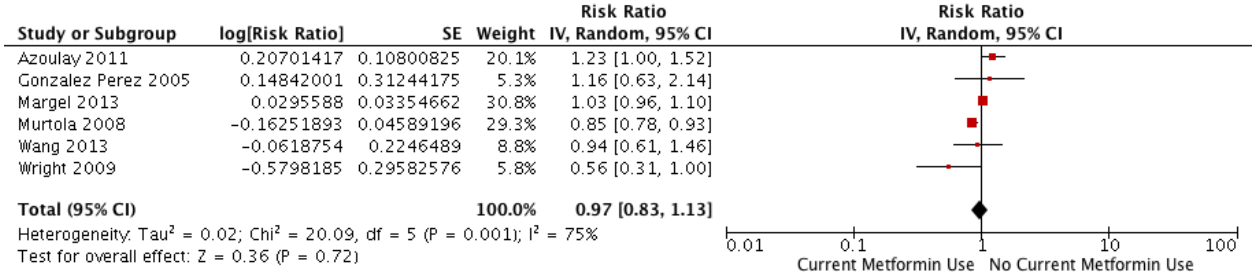


Figure 2-17 Risk of Bias ≤6; Current Metformin Use Vs. No Current Metformin Use in Western-Based Case-Controls

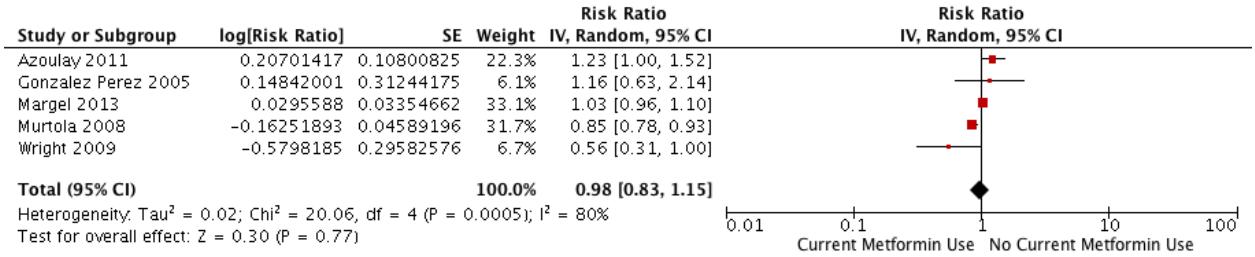


Figure 2-18. Risk of Bias ≤6; Current Metformin Use Vs. No Current Metformin Use in Asian Based Case-Controls

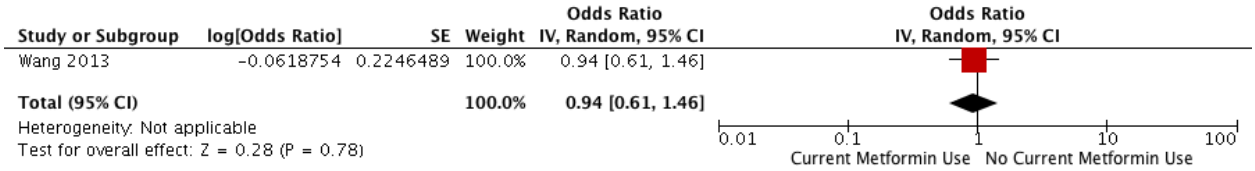


Figure 2-19. Risk of Bias >6; Current Metformin Use Vs. No Current Metformin Use in Western-Based Cohorts

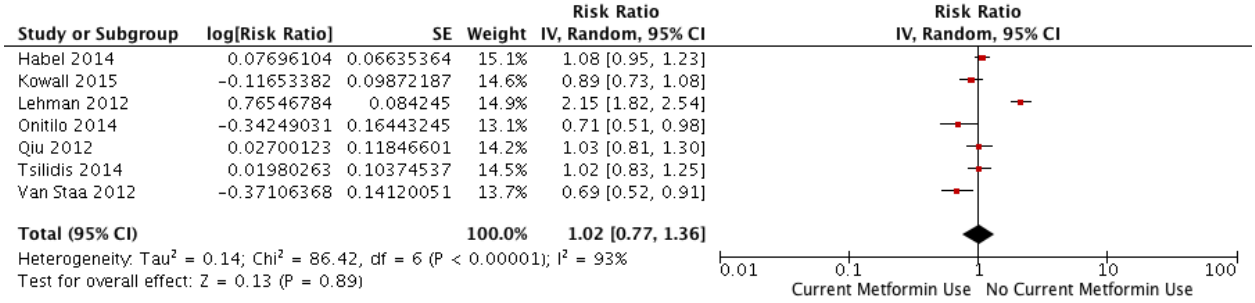


Figure 2-20. Risk of Bias >6; Current Metformin Use Vs. No Current Metformin Use in Western Based Case Controls

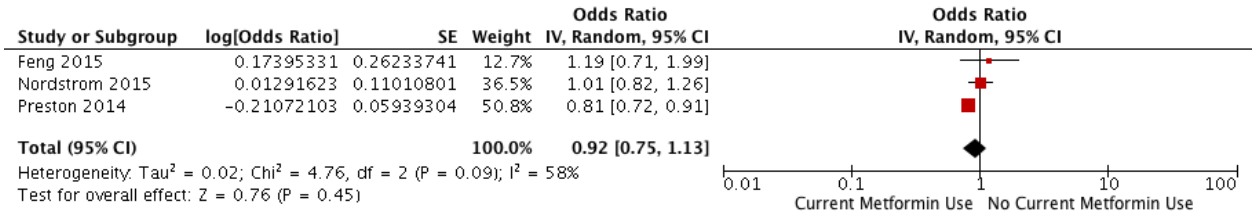
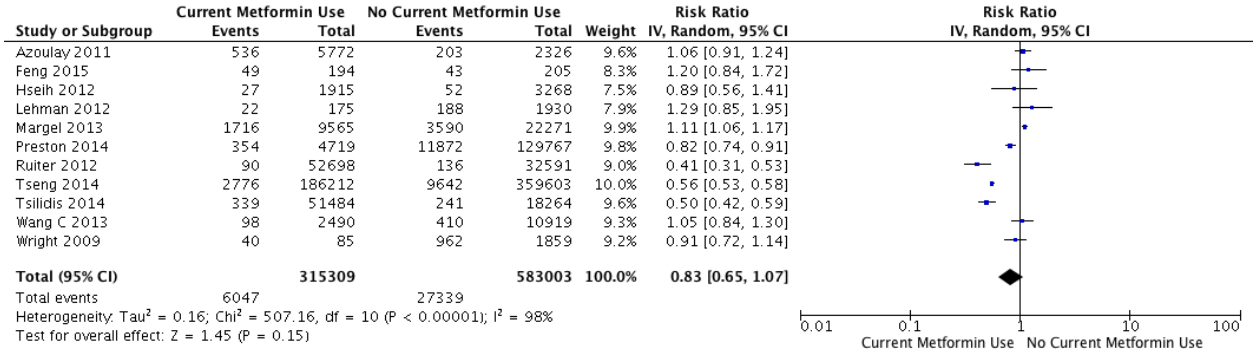


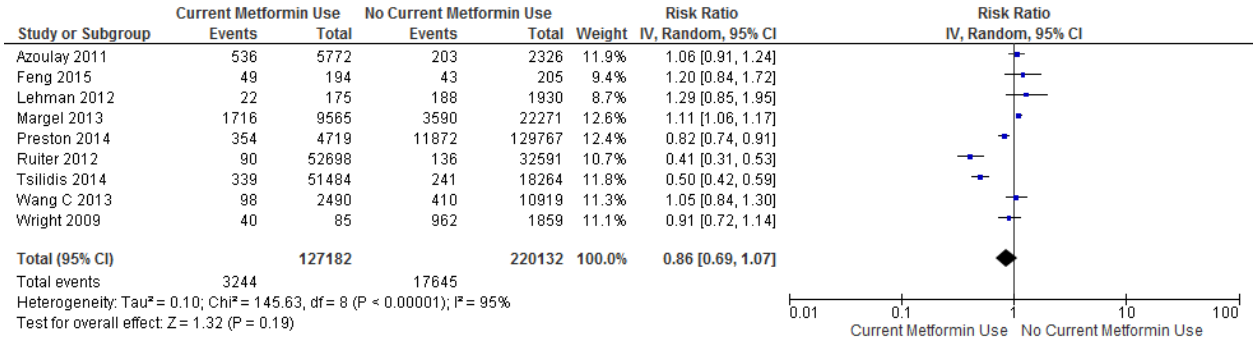
Figure 2-21. Current Metformin Use Vs. No Current Metformin Use in Western- and Asian-Based Observational Studies (Crude Risk Estimates)



Study or Subgroup	Current Metformin Use Events	Total	No Current Metformin Use Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Azoulay 2011	536	5772	203	2326	9.6%	1.06 [0.91, 1.24]
Feng 2015	49	194	43	205	8.3%	1.20 [0.84, 1.72]
Hseih 2012	27	1915	52	3268	7.5%	0.89 [0.56, 1.41]
Lehman 2012	22	175	188	1930	7.9%	1.29 [0.85, 1.95]
Margel 2013	1716	9565	3590	22271	9.9%	1.11 [1.06, 1.17]
Preston 2014	354	4719	11872	129767	9.8%	0.82 [0.74, 0.91]
Ruiter 2012	90	52698	136	32591	9.0%	0.41 [0.31, 0.53]
Tseng 2014	2776	186212	9642	359603	10.0%	0.56 [0.53, 0.58]
Tsilidis 2014	339	51484	241	18264	9.6%	0.50 [0.42, 0.59]
Wang C 2013	98	2490	410	10919	9.3%	1.05 [0.84, 1.30]
Wright 2009	40	85	962	1859	9.2%	0.91 [0.72, 1.14]
Total (95% CI)		**315309**		**583003**	**100.0%**	**0.83 [0.65, 1.07]**
Total events	6047		27339			

Heterogeneity: Tau² = 0.16; Chi² = 507.16, df = 10 (P < 0.00001); I² = 98%
Test for overall effect: Z = 1.45 (P = 0.15)

Figure 2-22. Current Metformin Use Vs. No Current Metformin Use in Western-Based Observational Studies (Crude Risk Estimates)



Study or Subgroup	Current Metformin Use Events	Total	No Current Metformin Use Events	Total	Weight	Risk Ratio IV, Random, 95% CI
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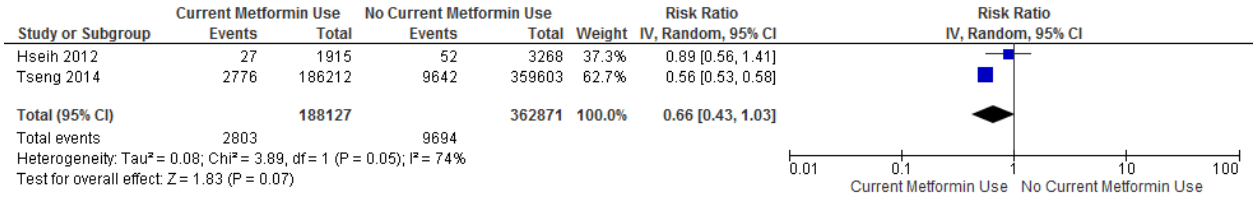
Wang C 2013	98	2490	410	10919	11.3%	1.05 [0.84, 1.30]
Wright 2009	40	85	962	1859	11.1%	0.91 [0.72, 1.14]
Total (95% CI)		**127182**		**220132**	**100.0%**	**0.86 [0.69, 1.07]**
Total events	3244		17645			

Heterogeneity: Tau² = 0.10; Chi² = 145.63, df = 8 (P < 0.00001); I² = 95%
Test for overall effect: Z = 1.32 (P = 0.19)

Figure 2-23. Current Metformin Use Vs. No Current Metformin Use in Asian-Based Observational Studies (Crude Risk Estimates)



Study or Subgroup	Current Metformin Use Events	Total	No Current Metformin Use Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Hseih 2012	27	1915	52	3268	37.3%	0.89 [0.56, 1.41]
Tseng 2014	2776	186212	9642	359603	62.7%	0.56 [0.53, 0.58]
Total (95% CI)		**188127**		**362871**	**100.0%**	**0.66 [0.43, 1.03]**
Total events	2803		9694			

Heterogeneity: Tau² = 0.08; Chi² = 3.89, df = 1 (P = 0.05); I² = 74%
Test for overall effect: Z = 1.83 (P = 0.07)

Table 2-1. Risk of bias assessment of randomized controlled trials

Study	Allocation sequence adequately generated?	Allocation adequately concealed?	Allocation adequately blinded?	Incomplete data adequately addressed?	Free of selective outcome reporting?	Free of other problems?	Overall risk of bias
Home 2009	Unclear	Yes	No	Unclear	Yes	No (Problematic lost to follow up)	High
Kahn 2006	Unclear	Yes	Yes	Unclear	Yes	No (differential withdrawal)	High

Table 2-2. Risk of bias analysis for cohort studies*

Study	Representative exposed cohort	Selection of unexposed cohort	Ascertainment of Exposure	Outcome not present at beginning	Comparability of cohorts	Assessment of outcome	Long follow up?	Adequate follow up?	Risk of bias
Currie 2009	Truly representative	Same community	Secure record	No	Adjusts for many factors including age and BMI but not PSA	Record linkage	No indication	NR	5
Ferrara 2011	Somewhat representative	Same community	Secure record	Yes	Adjusts for many factors including age but not BMI or PSA	Record linkage	No	NR	6
Geraldine 2012	Somewhat representative	Same community	Secure record	Yes	Adjusts for age and weight but not PSA	Record linkage	Yes	NR	7
Habel 2014	Somewhat representative	Same community	Secure record	Yes	Adjusts for many factors including age, BMI and PSA	Record linkage	Yes	NR	8
Hsieh 2012	Truly representative	Same community	Secure record	Yes	Only adjusts for age	Record linkage	No	NR	6

Lehman 2012	Somewhat representative	Same community	Secure record	Yes	Adjusts for many variables like age but not BMI or PSA	Record linkage	Yes	NR	7
Kowall 2015	Truly representative	Same community	Secure Record	Yes	Adjusts for many variables like age and obesity but not PSA	Record Linkage	Yes	NR	7
Magliano 2012	Truly representative	Same community	No description	No	Only matched on age, sex and residence	Record linkage	Yes	No	4
Morden 2011	Select group of patients	Same community	Secure record	Yes	Adjusts for age but not BMI or PSA	Record linkage	No	NR	5
Onitilo 2014	Somewhat representative	Same community	Secure record	Yes	Adjusts for many factors like BMI and age but not PSA	Record linkage	Yes	NR	7
Qiu 2013	Truly representative	Same community	Secure record	Yes	Adjusts for age, BMI and PSA amongst other variables	Record linkage	No	NR	7
Ruiter 2012	Somewhat representative	Same community	Secure record	No	Adjusts for age but not BMI or PSA	Record linkage	No	NR	5
Tseng 2011	Truly representative	Same community	Secure record	Yes	Adjusts for some variables but not age, BMI or PSA	Record linkage	No	NR	6
Tseng 2014	Truly representative	Same community	Secure record	Yes	Adjusts for age, PSA and other factors	Record linkage	No	NR	6
Tsilidis 2014	Truly representative	Same community	Secure record	Yes	Adjusts for several factors like age and PSA but not	Record linkage	Yes	NR	7

					BMI				
van Staa 2012	Truly representative	Same community	Secure record	Yes	Adjusts for several factors like age and BMI but not PSA	Record linkage	Yes	NR	7
Wang C 2013	Somewhat representative	Same community	Secure record	Yes	None	Record linkage	Yes	NR	6

*BMI: Body mass index, PSA: Prostate specific antigen testing, NR: Not reported.

Table 2-3. Risk of bias analysis for case-control studies*

Study	Case Definition Adequate?	Representative Cases?	Selection of Controls	Definition of Controls	Comparability of Cases and Controls	Ascertainment of Exposure	Same Method Exposure Ascertainment for Cases and Controls	Non-response Rate	Risk of bias
Azoulay 2011	Yes with validation	Yes	Community controls	NR	Adjusts for many covariates including BMI and matches on age but not PSA	Secure record	Yes	NR	6
Feng 2015	Yes with validation	Yes	Community Controls	NR	Adjusts for many covariates including age, PSA and BMI	Interview	Yes	NR	7
Gonzalez-Perez 2005	Yes with validation	Yes	NR	NR	Adjusts for age, BMI among others but not PSA	Secure record	Yes	NR	5
Margel 2013	Yes with linkage	Yes	NR	No history of cancer	Adjusts for some covariates but not age, BMI or PSA	Secure record	Yes	NR	5
Murtola 2008	Yes with validation	Yes	Community controls	NR	Adjusts for age and other factors but not BMI or PSA	Secure record	Yes	NR	6
Nordstrom 2015	Yes, from a cancer registry	Yes, registry has 93% coverage	Community controls	No history of cancer	Adjusts for age, PSA and other but not BMI	Secure record	Yes	NR	7

Preston 2014	Yes with validation	Yes	Community controls	No history of cancer	Adjusts for many factors including age but not BMI or PSA	Secure record	Yes	NR	7
Wang 2013	Yes with validation	Yes	NR	NR	NR	Secure record	Yes	NR	4
Wright 2009	Yes with validation	No	Community controls	No history of cancer	Adjusts for age, BMI and PSA among many other covariates	Unblinded interview	Yes	Rates different and no designation	6

*NR: Not reported, BMI: Body mass index, PSA: Prostate specific antigen test.

Table 2-4. Characteristics of Included Studies*

Study	Data Source (Country)	Exposed and Comparison Groups	Study Period	Follow up Duration	Number of Exposed Patients	Number of Non Exposed Patients	Covariates in the model
Randomized Controlled Trials							
Home 2009, RECORD Study	Australasia, Europe	Current metformin Vs no current metformin use	2001-2008	5.5 years	3344	1103	N/A
Kahn 2006, ADOPT Study	Canada, Europe,	Metformin Vs. rosiglitazone	2000-2006	4 years	1454	2897	N/A

	USA	or glibenclamide use					
Cohorts							
Currie 2009	United KIngdom	Metformin Vs SU use	2000-N/A	N/A	31421	7439	Age, sex, smoking and prior cancer
Ferrara 2011	USA	Metformin ever Vs never use	1997-2005	2.5 years	N/A	N/A	Age, hypoglycemics, year of cohort entry, sex, race/ethnicity, A1C, diabetes duration, CHF, income, smoking, creatinine and new diabetes diagnosis
Geraldine 2012	Belgium	Metformin use Vs diet	1994-2008	4.1 years	2173	1068	Age, sex, weight and A1C
Habel 2014	USA	Metformin ever Vs never use	1997-2009	8.2 years	N/A	N/A	Ethnicity, birth year, income, education, BMI, alcohol use, smoking, diabetes duration, A1C, creatinine, PSA
Hsieh 2012	Taiwan	Metformin Vs SU use	2000-2008	N/A	1915	3268	Age
Kowall 2015	UK and Germany	Metformin Vs Sulfonylurea Use	Jan. 1995-Dec. 2013	5 years	N/A	N/A	age at first diabetes medication, sex, country, time between first diagnosis of diabetes and prescription of first diabetes drug, obesity, hypertension, hyperlipidemia, prevalence of microcomplications (retinopathy, neuropathy, or nephropathy), Charlson index, use of antihypertensives, agents, aspirin, statins, nonsteroidal anti-inflammatory drugs, and contraceptives
Lehman 2012	USA	Metformin Vs SU use	1999-2006	5.2 years	175	1930	Age, race/ethnicity, duration of diabetes, charlson comorbidity score, smoking status, LDL and A1C
Magliano 2012[#]	Australia	Metformin Vs	1993-	11 years	N/A	N/A	Age, sex and residence

		no metformin use	2010				
Morden 2011	USA	Metformin Vs no metformin use	2006-2008	1.9 years	N/A	N/A	Age, ethnicity, diabetes complications, obesity diagnosis, oral estrogen use, part D low income subsidy, Charlson comorbidity score, and tobacco exposure diagnosis
Onitilo 2014	USA	Metformin ever Vs never use	1995-2011	7.1 years	N/A	N/A	Myocardial infarction, CHF, peripheral vascular disease, rheumatic heart disease, renal insufficiency, charlson score. BMI, age, date of diagnosis, insurance, smoking and residence
Qiu 2013	United Kingdom	Metformin Vs SU use	1995-2008	2.9 years	22253	9993	Age, gender, baseline A1C, BMI, smoking, chronic disease score, oral hypoglycemic index date, number of oral hypoglycemics prescriptions prior to index date, hospitalization, use of cancer screening tests and duration of diabetes prior to index date
Ruiter 2012	Netherlands	Metformin Vs SU use	1998-2008	2.8 years	52698	32591	Age, sex, number of other medications in the year before start of hypoglycemic, number of hospitalizations before start of hypoglycemic and year
Tseng 2011	Taiwan	Metformin ever Vs never use	2003-2005	2 years	N/A	N/A	Age, diabetes duration, comorbidities, medications, residence and occupation
Tseng 2014	Taiwan	Metformin ever Vs never use	1996-2009	N/A	186212	359603	Age, nephropathy, hypertension, chronic obstructive pulmonary disease, stroke, ischemic heart disease, peripheral artery disease, eye disease, obesity, dyslipidemia, urinary tract infection, benign prostate hyperplasia, other cancers and use of statins, fibrates, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, Aspirin, ticlopidine, clopidogrel, dipyridamole and non-steroidal anti-inflammatory agents
Tsilidis 2014	United Kingdom	Metformin Vs SU use	1987-2010	5.1 years	51484	18264	Smoking status, BMI, alcohol use, use of Aspirin, non-steroidal anti-inflammatory drugs and statins, diabetes duration and year of first hypoglycemic prescription

van Staa 2012	United Kingdom	>60 months of metformin exposure Vs <6 months of exposure	1997-2006	4 years	N/A	N/A	Age, sex, year, socioeconomic status, smoking status, alcohol consumption, BMI, coronary heart disease, coronary revascularization hyperlipidemia, hypertension, peripheral vascular disease, renal impairment, stable angina and use of angiotensin receptor blockers, antiplatelets, beta blockers, calcium channel blockers, diuretics, non-steroidal anti-inflammatory drugs, Aspirin, statins, nitrates and other hypoglycemics
Wang C 2013	USA	Metformin ever Vs never use	2002-2012	6.2 years	2490	10919	N/A
Case Controls							
Azoulay 2011	United Kingdom	Metformin ever Vs never use	1988-2009	4.7 years	5772	2326	Patients were matched on age and date of cohort entry. Covariates were: A1C, alcohol use, BMI, smoking status, lower urinary tract symptoms, previous cancer and use of non-steroidal anti-inflammatory drugs, anti-hypertensives, statins and other hypoglycemic agents
Feng 2015	USA	Metformin Use Vs no diabetic medications	N/A	4 years	194	205	Adjusted for age, race/ethnicity, geographic region, prostate specific antigen levels, digital rectal examination findings, body mass index, prostate volume, family history of prostate cancer, coronary artery disease, smoking status, NSAIDs, statins, aspirin, and treatment group
Gonzalez-Perez 2005	United Kingdom	Metformin ever Vs never use	1995-2001	N/A	N/A	N/A	Age, year, use of non-steroidal anti-inflammatory drugs, BMI, history of prostatism and health service utilization
Margel 2013	Canada	Metformin ever Vs never use	1994-2008	2.9 years	9565	22271	Matched on age, year of cohort entry and duration of diabetes. Adjusted for use of other antidiabetic drugs, COX-2 inhibitors, statins and 5-alpha reductase inhibitors, weighted adjusted clinical groups comorbidity index, socioeconomic status and residence

Murtola 2008	Finland	Metformin ever Vs never use	1995-2002	N/A	N/A	N/A	Age, residence and use of Aspirin, cholesterol lowering drugs and antihypertensives
Nordstrom 2015	Sweden	Metformin Use Vs. No Use	2007-2012	N/A	N/A	N/A	Age, PSA, Charlson Index, educational level and use of aspirin, statin and antidiabetic medications
Preston 2014	Denmark	Metformin Vs SU use	1989-2011	N/A	4719	129767	Comorbidities, diabetic complications, marital status and use of statins, proton pump inhibitors and 5-alpha reductase inhibitors. Matched on age, sex and occupation
Wang 2013	Taiwan	Metformin use Vs no use	1998-2010	N/A	N/A	N/A	Matched on age, sex and occupation
Wright 2009	USA	Metformin use Vs no use	2002-2005	85	1859	N/A	Matched on Age. Covariates adjusted for include: Age, other hypoglycemics, prostate specific antigen screening history, family history of prostate cancer, BMI and use of statins, Aspirin and other hypoglycemics

*USA: United States of America, SU: Sulfonylurea, A1C: hemoglobin A1C, CHF: congestive heart failure, LDL: low density lipoprotein, BMI: body mass index, PSA: prostate specific antigen test.

#Used a competing risk model in their analysis

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Chapter 3: Metformin and the Risk of Prostate Cancer Across Racial/Ethnic Groups: A Population-Based Cohort Study

3.1 Introduction

Patients with diabetes are generally at an increased risk of several cancers, but are at a decreased risk of prostate cancer[1,2]. The lower risk of prostate cancer may be a consequence of lower testosterone levels attributed to the hyperinsulinemic state associated with diabetes[3]. Metformin, considered the first line therapy in type 2 diabetes, may influence the risk of prostate cancer through direct and indirect mechanisms. Metformin directly activates AMPK, consequently inhibiting mTOR, leading to decreased cellular proliferation, and limiting tumour growth[4]. Metformin's ability to reduce hyperinsulinemia may also reduce prostate cancer risk indirectly[5].

While previous systematic reviews have concluded there is no association between metformin exposure and prostate cancer risk, there was substantial heterogeneity due to differences in populations, statistical analysis and definitions of metformin exposure[7,8]. Further complicating the issue is potential effect modification by race/ethnicity. Although non-Asian individuals with diabetes have a lower risk of prostate cancer, Asian patients appear to have an increased risk[6,7]. However, Asian men in general may have a decreased risk of prostate cancer relative to the general Western population[8]. Furthermore, in older meta-analyses of metformin on prostate cancer risk, the effect of race/ethnicity was not considered.[9,10] We recently conducted a meta-analysis of all studies evaluating

the risk of prostate cancer among users and non-users of metformin, stratified by race/ethnicity. We did not find an association in Western or Asian men; however the designation of Western and Asian were determined by geography and our results were highly heterogenous[11].

Thus, we aimed to investigate the impact of metformin exposure on prostate cancer risk in Asian and non-Asian men within the same population. We hypothesized that metformin exposure would be associated with a reduction in the risk of prostate cancer, and that if present that this association would be greatest in magnitude among those of Chinese race/ethnicity.

3.2 Methods

3.2.1 Study Population

The study population for this analysis has been previously described[9]. Briefly, we used the linked databases from British Columbia, Canada's Population Data BC which includes demographics, administrative healthcare and prescription drug claims and data from the British Columbia Cancer Agency (BCCA), from April 1, 1994 to December 31, 2012[12–16]. Ethics approval was obtained by the University of Alberta Health Research Ethics Board (Pro00003385_AME5).

3.2.2 Diabetes Definition

Identification of incident cases of diabetes was based on a case definition adapted from the Canadian National Diabetes Surveillance System[17]. Individuals with diabetes and their index date of diagnosis were defined based on the earliest of: 1) a hospital admission for diabetes (ICD-9 code 250 or ICD-10 code E10-E14); 2) the second of two medical fee-for-service claims (ICD-9 code 250)

within a 2 year period; or 3) a dispensation of an oral hypoglycemic agent. To restrict the cohort to incident cases of diabetes, individuals with a hospital admission (ICD-9 code 250 or ICD-10 code E10-E14) or medical fee-for-service claim (ICD-9 code 250) for diabetes between April 1, 1994 and March 31, 1996 were excluded from analysis. Individuals less than 30 years of age at their index date were excluded, and the cohort was restricted to men.

3.2.3 Outcomes - Prostate Cancer

We excluded individuals with a diagnosis of prostate cancer or a censoring event within the first 6 months of follow-up to mitigate any potential detection or survival bias **(Figure 1)**[12]. After eliminating cases of cancer within the two years prior to the index date, cases of prostate cancer were identified (ICD-O-3 code C61) from the BCCA; this coding have been previously validated and is associated with a sensitivity of 69%, specificity of 100%, and a positive predictive value of 99%[18].

3.2.4 Exposures - Metformin

To account for potential changes in metformin therapy over time, we allowed metformin exposure to vary over time by segmenting follow-up into 6-month intervals. We first identified all prescription claims for metformin during follow-up and for each subsequent 6-month interval following diabetes diagnosis, we used a binary definition of metformin exposure (any or no use of metformin). We also calculated the total cumulative exposure to metformin in milligrams per day for each interval and stratified all patients who ever used metformin into time-varying tertiles of cumulative exposure. Men with diabetes, but without metformin exposure, were identified as our reference group for all analyses.

3.2.5 Exposures - Race/ethnicity

To assess the potential effects of race/ethnicity, we classified all individuals as Chinese, Indian or Other based on two previously validated surname algorithms. The first identifies Chinese individuals with a positive predictive value of 81%,[11] and the second identifies individuals of Indian descent with a positive predictive value of 77%.[12] The 2011 census for British Columbia indicates that 77.3% of our "Other" population should be of European origin while 0.55% are Carribean, 1.5% Latin, Central or South American, 1.3% African, 11.9% Other Asian, 1.0% Oceanic, 7.7% First Nations and 24.3% Canadian; however, this methodology allows individuals to identify as multiple ethnicities [19].

3.2.6 Statistical Analysis

We used Cox proportional hazards models to estimate the risk of prostate cancer between metformin exposure and our reference group, and for Chinese and Indian men compared to non-Chinese/non-Indians (hereafter, referred to as "Others"). We also tested interaction terms between race/ethnicity and metformin exposure, using a p-value of 0.1 as a criterion for significance. Individuals were followed from time of diabetes diagnosis until diagnosis of prostate cancer or censoring. Individuals were censored at the earliest of the end of the study period (December 31, 2012), departure from the database, death or diagnosis of a non-prostate cancer.

In addition to our metformin exposure variables and race/ethnicity, our regression models were hierarchically adjusted for age, socioeconomic class (SES) based on neighbourhood income quintiles derived from Canadian census data, number

of physician visits (updated within each 6-month interval), and use of other diabetes medications (sulfonylureas, acarbose, meglitinides, dipeptidyl peptidase IV inhibitors, glucagon-like peptide 1 receptor agonists, thiazolidinediones and insulin) using a similar time-varying cumulative exposure definition (updated within each 6-month interval).

We tested the proportional hazards assumption by analyzing Schoenfeld residuals and plotting them against time. No variables except age violated the proportional hazards assumption, thus all final adjusted models were also stratified by age. Missing SES data was handled using the missing indicator approach. All analyses were conducted using Stata 14 (College Station, Texas)

3.3 Results

3.3.1 Cohort Description

We identified 106 287 men with diabetes, of whom 40 050 were not exposed to metformin **(Figure 3-1)**. The metformin-exposed group was younger, had slightly more Indian men, but otherwise had a similar SES distribution and number of physician visits **(Table 3-1)**. The crude incidence of prostate cancer among those exposed vs not exposed to metformin was 105.4 vs 195.1 cases per 1,000 person-years, respectively **(**p=0.062) **(Table 3-1)**.

3.3.2 Metformin Exposure (Binary), Race/ethnicity and Prostate Cancer Risk

In the first stage of analysis, the hierarchical regression indicated age as the most important covariate and potential confounding variable (**Table 3-2**). There was a significant interaction (p=0.05) between Chinese race/ethnicity and

metformin exposure, thus we stratified the final regression model by Chinese race/ethnicity (**Table 3-3**). In this analysis, Chinese metformin users (adjusted hazard ratio (aHR): 1.42, 95% confidence interval:1.06-1.90) had an increased risk of prostate cancer while non-Chinese (aHR:1.05,0.97-1.12) men did not **(Table 3-3)**. However, these adjusted models (**Table 3-2 & 3-3**) resulted in a violation of the proportional hazards (PH) assumption, which was due to age as a covariate; we therefore stratified the analyses by age categories.

Among all ethnicities, users of metformin aged 40-49 (aHR:1.14, 0.79-1.63), 60-64 (aHR:0.96,0.82-1.12) and ≥65 (aHR:1.09, 0.98-1.21) years of age had similar risk of prostate cancer while users of metformin aged 50-59 had a decreased risk (aHR:0.86, 0.74-1.00) **(Table 3-4)**. Chinese men aged 40-49 (aHR:0.27,0.08-0.86), 50-59 (aHR:0.44,0.29-0.68), 60-64 (aHR:0.52,0.34-0.80) and ≥65 (aHR:0.60, 0.47-0.76) years old were at a decreased risk of prostate cancer, but there was no association between Indian men and prostate cancer **(Table 3-4)**. In this analysis, there was an interaction between Chinese race/ethnicity and metformin exposure in each age strata, thus we also stratified by Chinese status. Among Chinese men, 50-59 (aHR:1.09, 0.56-2.17) and 60-64 (aHR:1.19,0.61-2.31) year old users of metformin had similar risks of prostate cancer as non-users while users ≥65 (aHR:1.52, 1.05-2.20) had an increased risk **(Table 3-4)**. This increased risk among Chinese men overall **(Table 3-3)** is essentially driven by Chinese men ≥65 years old **(Table 3-4).** Non-Chinese users and non-users of metformin had similar risks of prostate cancer as those in the full cohort **(Table 3-4)**.

In Chinese and non-Chinese men, increasing age was associated with higher

prostate cancer risk while and in non-Chinese men, there was no association between Indian race/ethnicity and prostate cancer risk **(Table 3-3).** Higher SES results in an increased prostate cancer risk among non-Chinese but not Chinese men. More physician visits were also associated with less prostate cancer risk among non-Chinese men but not Chinese men **(Table 3-2)**.

3.3.3 Metformin Cumulative Dose, Race/ethnicity and Prostate Cancer Risk

In this analysis, we first conducted a hierarchical regression, which again indicated that age was most important covariate **(Table 3-5)**. There was no interaction between tertiles of metformin exposure and race/ethnicity; however because there was an interaction in the previous model, we stratified this model by Chinese race/ethnicity for exploratory purposes **(Table 3-6)**. In Chinese and non-Chinese individuals, no tertile of metformin exposure was associated with prostate cancer risk **(Table 3-6)**. The PH assumption was also violated in this model so we also stratified these results by age.

Among all ethnicities, 40-49 year olds in the 1st (aHR:0.66,0.39-1.11), 2nd (aHR:0.73,0.44-1.20) and 3rd (aHR:1.04,0.65-1.67) tertile of metformin exposure had similar risks of prostate cancer as non-users **(Table 3-7)**. Similar results are seen among men 60-64 and ≥65 year olds **(Table 3-7)**. However, men 50-59 in any tertile of metformin exposure and 60-64 year old men in the first tertile had a decreased risk of prostate cancer **(Table 3-7)**. Chinese men had a decreased risk of prostate cancer across all age strata (aHR range from 0.31-0.62) while Indian men did not **(Table 3-7)**. There was no interaction between any race/ethnicity or tertile of metformin exposure in any age strata but we stratified

our results for exploratory purposes. Chinese men in any age strata or metformin tertile were not associated with prostate cancer while non-Chinese men had similar risks seen in the full cohort.

Among Chinese men, higher SES and number of physician visits was not associated with prostate cancer risk **(Table 3-8).** Among non-Chinese men, higher SES increased prostate cancer risk and more physician visits decreased prostate cancer risk while Indian men had a similar risk of prostate cancer relative to Others **(Table 3-8)**.

3.4 Discussion

Using two definitions of metformin exposure and stratifying by age, there was no clear association between prostate cancer risk, metformin exposure and race/ethnicity. Using a binary definition of metformin exposure, non-Chinese users generally had similar risks of prostate cancer as non-users. However, non-Chinese 50-59 year old users had a decreased risk and Chinese users ≥65 years old may have an increased risk. When investigating a dose-response relationship between prostate cancer risk and metformin exposure, Chinese and non-Chinese men in any tertile of metformin risk had similar risks as those non-exposed. Though similar to the observation seen using the binary metformin definition, 50-59 year old non-Chinese users in any tertile had a decreased risk of prostate cancer but in both analyses, this decrease seems anomalous. There was also a decreased risk of prostate cancer among 60-64 year old non-Chinese men in the first tertile of metformin exposure, which may be another anomaly. Thus, taken together, our analyses suggest that there is no association between prostate

cancer risk and metformin exposure and that this does not vary between ethnic groups. However, there is some uncertainty regarding the risk of prostate cancer and metformin among Chinese men ≥65 years old, especially those in the 3rd tertile of metformin exposure, which would require a study with more power for further investigation.

There is little previous literature investigating the association between prostate cancer risk and metformin exposure in Indian populations, however previous systematic reviews conducted in Western countries did not find a relationship between prostate cancer and metformin exposure[10,20]. In Asian populations, two studies did not find a relationship between metformin exposure and prostate cancer risk[21,22]. However, using administrative data from Taiwan, Tseng et al. found that metformin users were substantially less likely to be diagnosed with prostate cancer[23].

We recently conducted a systematic review investigating this issue in the existing literature[11]. Among Non-Asian men, the risk of prostate cancer was similar between users and non-users of metformin (HR:1.03, 0.94-1.13, I^2=88%) and adding our findings to this analysis supports that conclusion and decreases heterogeneity (HR:1.03, 0.94-1.12, I^2=87%)[11]. Among Asian men, metformin users had a decreased, though statistically insignificant, risk of prostate cancer (HR:0.75, 0.42-1.34, I^2=90%) and our findings now further move this estimate to the null and reduce heterogeneity (HR:0.83, 0.48-1.43, I^2= 89%)[25]. Of note, this final estimate is based on 506 951 patients and is highly influenced by a single study (N=395 481); removing this one study clearly demonstrates that there is no association between metformin use and prostate cancer in Asian men (HR:1.02,

0.77-1.37, I^2=0). In sum (1) there is no association between metformin and prostate cancer and (2) this lack of association holds true across all ethnicities.

Our current results also indicate that Chinese men have a lower risk of prostate cancer. In either definition of metformin exposure, there is a consistent decreased risk of prostate cancer among Chinese men, but not Indian men. While the risk varies across age strata, pooling all age categories gives a similar estimate **(Appendix 3)**. This is in keeping with previous literature reporting that Asian men generally have a lower risk of prostate cancer than Western men, which may be due to genetics, lifestyle factors or screening policies[8]. However, incidence rates of prostate cancer in Asian countries are rising, potentially because of improved detection or adoption of Western lifestyles[8]. Thus immigration of Asian men to Western countries may affect their risk of prostate cancer. Asian men living in the United States have a higher risk than those living in Asia but it does not exceed the risk of non-Hispanic white men thus other factors are reducing the risk of prostate cancer in Asian men[8,24]. Moreover, the risk profile at the time of diagnosis is worse for Asian men, relative to non-Hispanic white men and this may differ by nativity[25]. Unfortunately, we were not able to account for immigration status in our study.

Our results indicated that prostate cancer risk may increase with SES **(Table 3-2 & 3-5).** This association could be secondary to higher health seeking behaviour among men in higher SES classes and thus increased detection. Previous studies using these databases have also suggested that detection bias may influence the relationship between diabetes and cancer[26–28]. Hence we considered whether there might be differences in access to health care, and a

potential for detection bias, by adjusting for the number of physician visits. Relative to Indian and Other ethnicities, Chinese men did have fewer physician visits (**Appendix 5**) and hence may have fewer opportunities to be screened for or diagnosed with prostate cancer. Furthermore, evidence suggests that ethnic minorities, including Chinese- and Indian-Canadians are less likely to receive a prostate specific antigen (PSA) test, see a specialist physician or be admitted to the hospital, further implicating detection bias as a limitation of our study[29]. Thus, while Chinese men may be expected to have lower risk of prostate cancer, the magnitude of observed risk reduction may be confounded to some degree by detection bias. Moreover, while Chinese-Canadians are less likely than other Canadians to see a general practitioner, Indian-Canadians are more likely to see their general physician,[14] offering a possible explanation for the similar frequency of physician visits between our Indian and Other groups and the statistically insignificant association between Indian descent and prostate cancer in our second analysis.

This work has several important limitations. First and foremost, the potential misclassification of Chinese, Indian and Other groups using the surname algorithms, as well as using an Other group which would be quite racially and ethnically diverse, consisting of individuals of European, South American, African, Middle Eastern and non-Chinese/Indian Asian descent. While the two surname algorithms we applied have been previously validated,[11,12] there may be some decay in their validity over time. One of the recognized limitations of the surname algorithms is the misclassification of individuals who have changed names, as is common with married women. Because our study included only

men, we anticipate that the positive predictive values for the surname algorithms may be even higher in our application.

Second, we were unable to stratify prostate cancer by severity. It has been reported, for example, that metformin use may be positively associated with high-grade prostate cancer, but negatively associated with low-grade prostate cancer[30]. Similarly, individuals with diabetes may be at a decreased risk of low but not high stage prostate cancer, while their risk of low and high-grade prostate cancer are similar[31,32]. Furthermore, Chinese individuals may have be more likely to be diagnosed with severe prostate cancer but have better survival than non-Hispanic white men. Third, the risk of low or high grade and localized or advanced prostate cancer may be modified by body mass index, which was not available in our data and we were unable to consider in our analysis[33,34]. Fourth, we were not able to assess PSA testing or digital rectal exams. However, adjusting by number of physician visits may act as a proxy for prostate cancer screening, either by PSA or digital rectal exam, because they are most likely to be completed during appointments with a general practitioner. We also did not have access to clinical information such as weight or body mass index, smoking status, family history. Finally, due to prostate cancer's long latency period, we may not have had sufficient follow-up to observe all cases.

3.4 Conclusion

Our results suggest that exposure to metformin is not associated with prostate cancer risk, nor is it associated with a differential effect on Chinese, Indian and Other racial/ethnic groups. Chinese men have a lower risk of prostate cancer, but

Indian men did not. Thus, the totality of evidence including our study strongly suggests that there is no clinically important association between the use of metformin and prostate cancer in men of any race/ethnicity with diabetes.

Table 3-1. Baseline Characteristics of 106 287 Men With Diabetes, Stratified According to Metformin Exposure

	No Metformin	Metformin Exposed
Number of Subjects (%)	40050 (37.7)	66237 (62.3)
Person-years at Risk	3661947	6060879
Number of Events (%)		
All Ages	1956 (1.8)	1749 (1.6)
30-39	1 (0)	0 (0)
40-49	56 (0.1)	91 (0.1)
50-59	404 (1.0)	469 (0.7)
60-64	392 (1.0)	376 (0.6)
≥65	1103 (2.8)	813 (1.2)
Incidence Rate (1000 person-years)		
All Ages	195.1 (186.6,203.9)	105.4 (100.6,110.5)
30-39	1.53 (0.22,10.9)	0
40-49	43.3 (33.3,56.3)	26.6 (21.6,32.6)
50-59	179.1 (162.5,197.5)	91.5 (83.6,100.2)
60-64	294.9 (267.1,325.6)	165.2 (149.4,182.8)
≥65	245.4 (231.3,260.3)	178.1 (166.2,190.7)
Median Follow Up (Years)	8.2	10.8
Race/ethnicity (%)		
Other	34703 (86.7)	56823 (85.8)
Chinese	3873 (9.7)	5899 (8.9)
Indian	1474 (3.7)	3515 (5.3)
Mean Age (SD)	62.2 (13.4)	58.6 (12.4)
30-39	4 084 (7.2)	3 310 (6.7)
40-49	8 661 (15.2)	10 231 (20.7)
50-59	13 503 (23.7)	15 901 (32.2)

60-64	7 405 (13.0)	6 898 (14.0)
≥65	23 264 (40.9)	13 030 (26.4)
SES Quintile 1	7627 (19.0)	12400 (18.7)
SES Quintile 2	7415 (18.5)	12069 (18.2)
SES Quintile 3	6935 (17.3)	11273 (17.0)
SES Quintile 4	6839 (17.1)	10680 (16.1)
SES Quintile 5	6532 (16.3)	9541 (14.4)
SES Missing	4702 (11.7)	10274 (15.5)
Number of Physician Visits		
<2	19289 (48.1)	31398 (47.4)
≥2	20761(51.8)	34839 (52.6)

Table 3-2. Association between prostate cancer and any exposure to metformin adjusted for race/ethnicity alone, race/ethnicity and age; race/ethnicity, age and socioeconomic class (SES); race/ethnicity, age, SES and time-varying number of physician visits; and race/ethnicity, age, SES, time-varying number of physician visits and other diabetes medications (acarbose, meglitinides, incretin-mimetics, thiazolidinediones, sulfonylureas and insulin)

	Hazard Ratio (95% Confidence Interval)				
Covariate	Race/ethnicity Adjusted	Race/ethnicity and Age Adjusted	Race/ethnicity, Age and SES Adjusted	Race/ethnicity, Age, SES, Time-Varying Physician Visits Adjusted	Race/ethnicity, Age, SES, Time-Varying Physician Visits and Other Diabetes Medications Adjusted
No Metformin	Ref	Ref	Ref	Ref	Ref
Metformin	0.91 (0.85,0.98)	1.03 (0.96,1.11)	1.04 (0.97,1.12)	1.05 (0.97,1.12)	1.05 (0.98,1.13)
Race/ethnicity					
Other	Ref	Ref	Ref	Ref	Ref
Chinese	0.47 (0.39,0.57)	0.52 (0.43,0.62)	0.53 (0.44,0.64)	0.53 (0.44,0.63)	0.52 (0.44,0.63)
Indian	0.56 (0.44,0.71)	0.72 (0.57,0.93)	0.75 (0.59,0.96)	0.75 (0.59,0.96)	0.75 (0.58,0.95)
Age		1.06 (1.06,1.06)	1.06 (1.06,1.06)	1.06 (1.06,1.06)	1.06 (1.06,1.06)
SES					
SES Quintile 1			Ref	Ref	Ref
SES Quintile 2			1.02 (0.92,1.14)	1.02 (0.92, 0.92,1.14)	1.02 (0.92,1.14)
SES Quintile 3			1.02 (0.92,1.14)	1.02 (0.92,1.14)	1.02 (0.92,1.14)
SES Quintile 4			1.11 (0.99, 1.23)	1.10 (0.99,1.23)	1.10 (0.99,1.23)
SES Quintile 5			1.18 (0.77,1.00)	1.18 (1.06, 1.31)	1.18 (1.06,1.31)
SES			0.88	0.87 (0.77,	0.88 (0.77, 1.01)

Missing	[redacted]	(0.77,1.00)	1.00)	
Number of Physician Visits				
<2			Ref	Ref
≥2			0.93 (0.86,1.01)	0.94 (0.87, 1.01)

Table 3-3. Association between prostate cancer and metformin after adjusted for race/ethnicity, age, SES, time-varying physician visits and other diabetes medications (acarbose, meglitinides, incretin-mimetics, thiazolidinediones, sulfonylureas and insulin) and stratified by race/ethnicity

	Hazard Ratio (95% Confidence Interval)	
Covariate	Chinese Only	Non-Chinese
Diabetes, No Metformin	Ref	Ref
Any Metformin Exposure	1.42 (1.06,1.90)	1.05 (0.97,1.12)
Race/ethnicity		
Other		
Chinese		
Indian		0.74 (0.58,0.95)
Age	1.08 (1.06,1.09)	1.06 (1.06,1.06)
SES		
SES Quintile 1	Ref	Ref
SES Quintile 2	0.77 (0.52,1.15)	1.05 (0.94,1.17)
SES Quintile 3	0.74 (0.46,1.18)	1.04 (0.93,1.17)
SES Quintile 4	0.97 (0.61,1.51)	1.12 (1.00,1.25)
SES Quintile 5	1.17 (0.76,1.80)	1.18 (1.06,1.32)
SES Missing	0.68 (0.42,1.09)	0.91 (0.79,1.04)
Number of Physician Visits		
<2	Ref	Ref
≥2	1.29 (0.93,1.79)	0.92 (0.85,1.00)

Table 3-4. Association Between Prostate Cancer and Any Metformin Exposure, Stratified by Age, After Adjusting for SES, Time-varying Physician Visits and Other Diabetes Medications

All Ethnicities				
Age (years)	40-49	50-59	60-64	≥65
No Metformin	Ref	Ref	Ref	Ref
Any Metformin	1.14 (0.79,1.63)	**0.86 (0.74,1.00)**	0.96 (0.82,1.12)	1.09 (0.98,1.21)
Other	Ref	Ref	Ref	Ref
Chinese	**0.27 (0.08,0.86)**	**0.44 (0.29,0.68)**	**0.52 (0.34,0.80)**	**0.60 (0.47,0.76)**
Indian	1.08 (0.43,2.71)	0.60 (0.36,1.00)	0.60 (0.33,1.06)	0.89 (0.63,1.25)
Chinese				
No Metformin	Ref	Ref	Ref	Ref
Any Metformin		1.09 (0.56,2.17)	1.19, (0.61,2.31)	**1.52 (1.05,2.20)**
Non-Chinese				
No Metformin	Ref	Ref	Ref	Ref
Any Metformin	1.13 (0.79,1.63)	**0.86 (0.74,1.00)**	0.96 (0.82,1.12)	1.09 (0.99,1.21)
Other	Ref	Ref	Ref	Ref
Indian	0.31 (0.06,1.67)	1.34 (0.66,2.73)	1.11 (0.48,2.55)	0.96 (0.54,1.71)

*There were insufficient events among all 30-39 year old men and 40-49 year old Chinese men to give stable hazard ratios

Table 3-5. Association between prostate cancer and tertiles of metformin exposure adjusted for race/ethnicity alone, race/ethnicity and age; race/ethnicity, age and socioeconomic class (SES); race/ethnicity, age, SES and time-varying number of physician visits; and race/ethnicity, age, SES, time-varying number of physician visits and other diabetes medications (acarbose, meglitinides, incretin-mimetics, thiazolidinediones, sulfonylureas and insulin).

	Hazard Ratio (95% Confidence Interval)				
Covariate	Race/ethnicity Adjusted	Race/ethnicity and Age Adjusted	Race/ethnicity, Age and SES Adjusted	Race/ethnicity, Age, SES, Time-Varying Physician Visits Adjusted	Race/ethnicity, Age, SES, Time-Varying Physician Visits and Other Diabetes Medications Adjusted
No Metformin	Ref	Ref	Ref	Ref	Ref
Metformin Exposure Tertile 1	0.75 (0.67,0.83)	0.85 (0.77,0.94)	0.86 (0.77,0.95)	0.86 (0.77,0.95)	0.86 (0.77, 0.95)
Metformin Exposure Tertile 2	0.83 (0.75,0.91)	0.94 (0.86,1.04)	0.95 (0.86,1.05)	0.96 (0.87,1.05)	0.96 (0.87,1.06)
Metformin Exposure Tertile 3	0.79 (0.72,0.87)	0.96 (0.87,1.06)	0.97 (0.88, 1.08)	0.98 (0.89,1.08)	0.99 (0.89,1.10)
Race/ethnicity					
Other	Ref	Ref	Ref	Ref	Ref
Chinese	0.49 (0.41, 0.60)	0.55 (0.45,0.66)	0.56 (0.46, 0.68)	0.56 (0.46,0.68)	0.55 (0.46, 0.67)
Indian	0.59 (0.45,0.77)	0.79 (0.61,1.03)	0.82 (0.63,1.06)	0.82 (0.63, 1.06)	0.81 (0.62, 1.06)
Age		1.06 (1.06,1.06)	1.06 (1.06,1.06)	1.06 (1.06, 1.06)	1.06 (1.06,1.06)
SES					
SES Quintile 1			Ref	Ref	Ref
SES Quintile 2			1.02 (0.92, 1.14)	1.02 (0.92,1.14)	1.02 (0.92,1.14)
SES Quintile 3			1.02 (0.92, 1.14)	1.02 (0.92,1.14)	1.02 (0.91,1.14)
SES Quintile 4			1.10 (0.99, 1.23)	1.10 (0.99,1.23)	1.10 (0.99,1.23)

SES Quintile 5	[redacted]	1.18 (1.06, 1.31)	1.18 (1.06,1.31)	1.17 (1.05,1.30)
SES Missing		0.88 (0.78,1.01)	0.88 (0.77,1.01)	0.89 (0.78,1.02)
Number of Physician Visits				
<2			Ref	Ref
≥2			0.94 (0.87,1.02)	0.95 (0.88,1.02)

Table 3-6. Association between prostate cancer and tertiles of metformin exposure after adjusting for race/ethnicity, age, SES, time-varying number of physician visits and other diabetes medications (acarbose, meglitinides, incretin-mimetics, thiazolidinediones, sulfonylureas and insulin) in Chinese and non-Chinese Individuals

	Hazard Ratio (95% Confidence Interval)	
Covariate	Chinese Only	Non-Chinese
No Metformin	Ref	Ref
Metformin Tertile 1	1.02 (0.70,1.49)	0.86 (0.77,0.95)
Metformin Tertile 2	1.00 (0.67,1.49)	0.95 (0.86,1.05)
Metformin Tertile 3	1.48 (0.95,2.31)	0.98 (0.89,1.09)
Race/ethnicity		
Other	Ref	Ref
Chinese		
Indian		0.81 (0.62,1.05)
Age	1.07 (1.06,1.09)	1.06 (1.05,1.06)
SES		
SES Quintile 1	Ref	Ref
SES Quintile 2	0.77 (0.51,1.14)	1.04 (0.93,1.17)
SES Quintile 3	0.74 (0.46,1.19)	1.04 (0.93,1.16)
SES Quintile 4	0.97 (0.62,1.53)	1.12 (1.00,1.25)
SES Quintile 5	1.17 (0.76,1.79)	1.19 (1.05,1.32)
SES Missing	0.69 (0.43,1.10)	0.91 (0.80,1.05)
Number of Physician Visits		
<2	Ref	Ref
≥2	1.35 (0.98,1.87)	0.93 (0.86,1.00)

Table 3-7. Association Between Prostate Cancer and Tertiles of Metformin Exposure, Stratified by Age, After Adjusting for SES, Time-varying Physician Visits and Other Diabetes Medications

All Ethnicities				
Age (years)	40-49	50-59	60-64	≥65
No Metformin	Ref	Ref	Ref	Ref
Met Tertile 1	0.66 (0.39,1.11)	**0.68 (0.55,0.84)**	**0.71 (0.56,0.90)**	1.02 (0.89,1.18)
Met Tertile 2	0.73 (0.44,1.20)	**0.75 (0.61,0.92)**	0.87 (0.71,1.08)	1.08 (0.94,1.24)
Met Tertile 3	1.04 (0.65,1.67)	**0.79 (0.64,0.96)**	0.95 (0.77,1.18)	0.97 (0.83,1.14)
Other	Ref	Ref	Ref	Ref
Chinese	**0.31 (0.10,1.00)**	**0.51 (0.34,0.78)**	**0.52 (0.33,0.83)**	**0.62 (0.48,0.79)**
Indian	0.81 (0.25,2.59)	0.61 (0.34,1.08)	0.67 (0.37,1.22)	1.02 (0.71,1.46)
Chinese Only				
No Metformin	Ref	Ref	Ref	Ref
Met Tertile 1		1.21 (0.49,2.96)	0.42 (0.11,1.58)	0.91 (0.43,1.91)
Met Tertile 2		0.77 (0.26,2.33)	0.71 (0.23,2.25)	0.61 (0.23,1.61)
Met Tertile 3		1.00 (0.30,3.37)	0.64 (0.16,2.46)	1.24 (0.45,3.41)
Non-Chinese Only				
No Metformin	Ref	Ref	Ref	Ref
Met Tertile 1	0.66 (0.40,1.11)	**0.68 (0.55,0.84)**	**0.71 (0.56,0.90)**	1.03 (0.89,1.19)
Met Tertile 2	0.74 (0.45,1.21)	**0.75 (0.61,0.92)**	0.88 (0.71,1.09)	1.08 (0.94,1.25)
Met Tertile 3	1.04 (0.64,1.67)	**0.79 (0.64,0.96)**	0.95 (0.76,1.18)	0.98 (0.83,1.14)
Other	Ref	Ref	Ref	Ref
Indian	0.80 (0.25,2.59)	0.61 (0.34,1.08)	0.67 (0.46,1.21)	1.02 (0.71,1.46)

*There were insufficient events among all 30-39 and Chinese 40-49 year old men to give stable hazard ratios

Table 3-8. Number of Physician Visits by Ethnic Group During Follow-up Period

	Number of Physician Visits (%)	
Race/ethnicity	<2	≥2
Other	100 462 (52.1)	88 823 (46.9)
Chinese	11 056 (63.7)	6 313 (36.4)
Indian	3 420 (52.1)	3 144 (47.9)

Figure 3-1. Flowchart of Cohort Selection

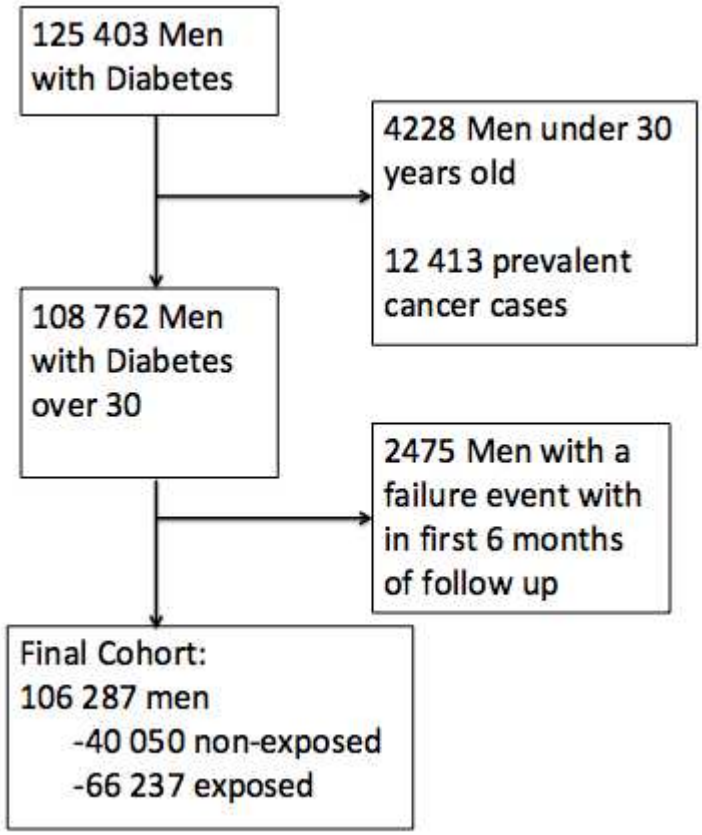
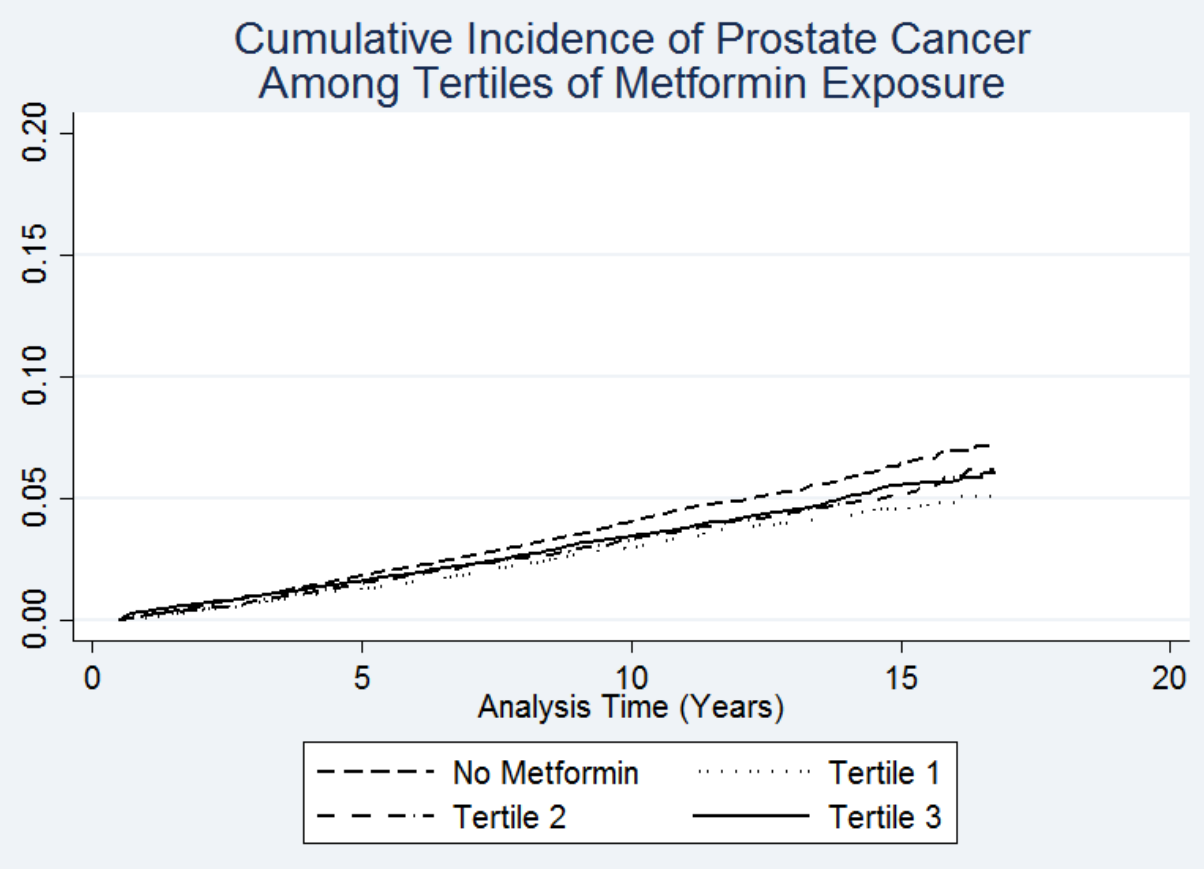


Figure 3-2. Cumulative Incidence Curve Comparing Prostate Cancer Incidence Over Time Between Each Metformin Exposure Group



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Chapter 4. Conclusion

4.1 Summary of Findings

Individuals with diabetes have an increased risk of many cancers but a decreased risk of prostate cancer[1,2]. Epidemiologic studies indicate that metformin may reduce the risk of many cancers but its effect on prostate cancer is less well understood. While *in vitro* studies indicate that metformin has anti-neoplastic potential, it may also increase testosterone levels, a risk factor for prostate cancer[3]. Hence, metformin use could increase or decrease prostate cancer risk. Moreover, the risk of prostate cancer is lower among Asian men without diabetes relative to Western men. However, in Asian men with diabetes, where the risk of prostate cancer is higher, metformin may have differential effects in Asian and Western men[4,5].

Using two different methodologic approaches in this thesis, we investigated the potential effects of metformin on prostate cancer risk in men with type 2 diabetes, and the potential mediating role of race/ethnicity. The first chapter, a systematic review and meta-analysis of the existing literature, did not associate metformin exposure with prostate cancer in Western-based studies. Asian-based studies indicated a reduced risk of prostate cancer, but after removing a single, highly influential, study, the association regressed to the null with no heterogeneity between studies. This interpretation remained despite stratification of our findings by study quality, study design and definition of metformin exposure. Thus, we did not find conclusive evidence that metformin exposure influences prostate cancer risk, a finding which is congruent with a previously conducted meta-analysis[1]. However, like the previous reports, our meta-analysis was plagued with

significant heterogeneity, even when pooling crude estimates, likely due to differences in methodology, health care utilization and clinical characteristics of the patients under study. The determination of race/ethnicity was also based on the geographic location of the study.

Hence, we conducted our own retrospective cohort study investigating this association, exploring the role of race/ethnicity within the same large Canadian population, using administrative databases from British Columbia. We used previously validated surname algorithms to identify men as Chinese or Indian within the population, and compared their risk of prostate cancer to men from the remainder of the population. Despite adjustment for health care utilization and other demographic variables, we did not identify a consistent association between metformin exposure and prostate cancer risk, using two different definitions of metformin exposure. There was an interaction between race/ethnicity and one definition metformin exposure (any or no use), but following stratification by race/ethnicity, there were no significant differences in the association between metformin exposure and prostate cancer in any race/ethnicity strata.

There was also no interaction between race/ethnicity and tertiles of metformin exposure, further suggesting there is no association between metformin, prostate cancer and race/ethnicity, nor is there a dose response relationship. And although we were not able to adjust for clinical factors such as body mass index, glycemic control or number of screening tests for prostate cancer, our study, in

conjunction with similar studies with similar results, indicated that there likely is not an association between prostate cancer and metformin exposure.

Interestingly, we did see a substantially lower risk of prostate cancer in men identified as Chinese, but not in Indian men. There was also an increased risk in individuals in higher socioeconomic classes. These patterns could be due to detection bias stemming from reduced healthcare utilization by Chinese populations and increased utilization among higher socioeconomic classes. However, the lower risk in Asian men has been reported in the literature, primarily among men still living in Asian countries but also among Asian men living in Western countries[4,6]. Thus the lower risk may be real, and due to genetic or lifestyle factors[4].

4.2 Strengths and Limitations

Our systematic review contains some limitations. The most prominent is the heterogeneity observed which could be due to differences in the clinical characteristics of the population, administration of prostate cancer screening programs in each country and use of these programs by patients or the methodology and statistical analysis used in each study. We were also relegated to defining race/ethnicity based on geography, based on the country where the studies were conducted, and given contemporary immigration pattern, there is likely misclassification of race/ethnicity, especially among Western countries. Finally, we did not have access to individual data and clinical parameters thus residual confounding could occur. However, our review explored several databases, included grey literature, utilized duplicate study selection and

extraction and assessed the impact of study quality and definition of metformin exposure on our results.

Our retrospective cohort study also possessed some limitations. For example, the database used was not clinically rich, and thus we did not know each individual's body mass index, glycemic control, history of prostate cancer screening or the stage and grade of prostate cancer. However, previous studies that were capable of adjusting for these factors achieved similar results[7–9]. Also, the surname algorithms we employed may degrade over time and validity could be influenced by name changes following marriage; however because this is less likely in males, the algorithm may perform better in our all male population. Furthermore, the algorithm was only capable of identifying those of Chinese and Indian descent. All other individuals were pooled into a third group, which could consist of individuals of European, South American, African, Middle Eastern and non-Chinese/Indian Asian descent. However, our cohort study also had several strengths. Using a time-varying cumulative exposure definition ensures an accurate representation of metformin use. We were also able to negate the effect of differential prostate cancer screening strategies by conducting our study in a large population served by a single payer healthcare system, over a long follow-up period. Finally, by using duration of diabetes as our underlying timescale, we are able to mitigate the effect of disease duration on our results.

4.3 Implications

Including our studies, there are now 27 studies and 8 systematic reviews investigating the association between metformin exposure and prostate cancer.

A majority of these studies have concluded that metformin exposure does not affect prostate cancer risk. No study has comprehensively studied the subject by adjusting for all major confounders such as body mass index, prostate cancer screening, glycemic control, duration of diabetes and age in an incident type 2 diabetes cohort followed over a long period. However, a series of studies have been conducted that each account for some of these factors at once. If taken as a whole, the current body of evidence indicates a null association between prostate cancer and metformin. While there are few established risk factors for prostate cancer, making residual confounding possible, based on the current evidence, there is a shrinking number of factors that could present an alternate interpretation, suggesting that any further resources intended to investigate methods of prostate cancer prevention should be directed elsewhere.

There are also 8 clinical trials registered at clinicaltrials.gov investigating the potential for metformin to improve survival in prostate cancer either alone or in combination with another anti-neoplastic medication[10]. However, because current observational studies do not indicate metformin can prevent prostate cancer and because the rationale driving these trials are likely also predicated on similar *in vitro* studies that we cite, it may also be unlikely that metformin could improve survival among prostate cancer patients. While metformin is currently not used in clinical practice to prevent prostate cancer, coupled with the existing literature, our study should temper any previous enthusiasm towards metformin's clinical benefit beyond its current use.

4.4 Conclusion

Men with diabetes appear to be at reduced risk of prostate cancer. This risk seems to be substantially lower in diabetic men of Chinese descent. Contrary to

in vitro and epidemiologic studies promoting the anti-neoplastic effects of metformin, our studies indicate that metformin exposure does not reduce the risk of prostate cancer among men with diabetes in Western or Asian populations. In conjunction with the existing body of evidence, there likely is no additional clinical role of metformin in disease states outside of its established use. Thus, until further compelling evidence suggests otherwise, additional studies investigating this association will be increasingly difficult to justify.

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