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Understanding the Relationship Between Type 2 Diabetes and Bladder Cancer

by

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Dedicated to my greatest teachers: Mom and Dad.

Abstract

Individuals with type 2 diabetes (T2DM) have an increased risk of bladder cancer, relative to non-diabetic individuals. We aimed to investigate factors that may influence this association.

Some reports suggest an association between the glucose-lowering drug pioglitazone and bladder cancer. Our first objective was to quantify the potential risk of bladder cancer with pioglitazone use, using meta-analytic techniques. Other studies observed a time-varying risk of cancer in T2DM. Our second objective was to assess temporal trends in the risk of bladder cancer in newly diagnosed T2DM vs. non-diabetic individuals.

In our systematic review, we saw that pioglitazone use was associated with an increased risk of bladder cancer, but this was not seen with other drugs in the same class. In our administrative cohort study, bladder cancer risk was significantly elevated only in the first year following T2DM diagnosis, and only in the lowest category of physician visits before T2DM diagnosis.

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List of Abbreviations

ACE	Angiotensin Converting Enzyme
ADOPT	A Diabetes Outcome Progression Trial
aHR	Adjusted Hazard Ratio
BC	British Columbia
BCLHD	British Columbia Linked Health Databases
COPD	Chronic Obstructive Pulmonary Disease
CI	Confidence Interval
DMSC	Drug Safety Monitoring Committee
DNA	Deoxyribonucleic Acid
DPP4	Dipeptidyl Peptidase-4
EMA	European Medicines Agency
FDA	Food And Drug Administration
GLP1	Glucagon-Like Peptide-1
HbA1c	Glycated Haemaglobin
HR	Hazard Ratio
ICD-9/10	International Classification of Disease and Health Related Problems, $9^{th}/10^{th}$ revision
IGF1R	Insulin-Like Growth Factor-1 Receptor
IQR	Inter-Quartile Range
IR	Insulin Receptor or Incidence Rate
LKB1	Liver Kinase B1 (or Serine/threonine kinase 11 (STK11))
LTFU	Loss To Follow-Up

MET	Metformin
mg	Milligram
mTOR	Mammalian Target of Rapamycin
n/a	Not Applicable
n/r	Not Reported
OR	Odds Ratio
PPARγ	Peroxisome Proliferator Activated Receptor Gamma
PROactive	The Prospective Pioglitazone Clinical Trial In Macrovascular Events
PUNLMP	Papillary Urothelial Neoplasm Of Low Malignant Potential
PY	Person-Years
RCT	Randomized Control Trial (or Clinical Trial)
RECORD	Rosiglitazone Evaluated For Cardiovascular Outcomes In Oral Agent Combination Therapy For Type 2 Diabetes
RR	Relative Risk or Risk Ratio
SD	Standard Deviation
SES	Socioeconomic Status
SU	Sulfonylurea
T2DM	Type 2 Diabetes Mellitus
TNM	Tumor, Node, Metastasis
TURBT	Transurethral Resection of the Bladder Tumor
TZD	Thiazolidinedione (or Glitazone)
UK	United Kingdom

US(A)	United States (of America)

CHAPTER 1. INTRODUCTION

1.1 Background

1.1.1 Type 2 Diabetes

Two million Canadians suffer from diabetes today. This number is expected to nearly double by 2020, when 9.9% (or 3.7 million) of Canadians are expected to be living with diabetes.(1,2) The current economic burden of diabetes has a staggering annual cost of $12.2 billion and accounts for 3.5% of Canadian public healthcare spending.(3) With the rising prevalence of diabetes in Canada, the economic and human costs will continue to balloon.

Over 90% of diabetes is type 2 diabetes, sometimes referred to as adult-onset diabetes because it is most commonly diagnosed after the age of 30. Type 2 diabetes is a chronic disease characterized by ineffective insulin signaling, due to insulin resistance and/or insufficient insulin production. Insulin, a hormone produced by the pancreas, maintains glucose homeostasis by stimulating blood glucose absorption at the peripheral tissues, notably muscle and fat. Individuals with type 2 diabetes develop resistance to insulin more than a decade before diabetes is diagnosed.(4) As insulin resistance worsens, circulating insulin levels rise to maintain blood glucose homeostasis, creating a state of hyperinsulinemia. Eventually, hyperglycemia develops when the pancreas can no longer produce sufficient amounts of insulin to adequately regulate rising blood glucose

levels.(4,5) The current criteria for a diagnosis of diabetes is a fasting blood glucose level above 7.0 mmol/L or glycated haemaglobin (HbA1c) over 6.5%.(6,7)

Multiple factors increase the risk of developing type 2 diabetes and they are commonly related to a sedentary lifestyle, poor diet, obesity and genetics. Type 2 diabetes is associated with high blood pressure, high cholesterol, cardiovascular disease, older age (>40 years) and overweight/obesity; certain genetic factors, including ethnic descent and family history, can also predispose an individual to developing type 2 diabetes.(5) Individuals with type 2 diabetes are also at an increased risk of developing long-term complications, notably kidney disease, cardiovascular disease and blindness.(6) While there is a strong epidemiologic relationship between HbA1c, a measure of long-term blood glucose levels, and cardiovascular disease for people with type 2 diabetes(8,9), there is substantial evidence that improving glycemic control does not reduce the risk of important macrovascular outcomes.(10-12) Improved glycemic control is, however, associated with a reduced risk of microvascular disease, in particular diabetic retinopathy.(10,13) As well, management of related conditions, such as hypertension and cholesterol levels, further reduces the risk of cardiovascular disease in patients with type 2 diabetes.(14)

1.1.1.1 Pharmacotherapies for Type 2 Diabetes

Type 2 diabetes is treated with a combination of lifestyle modification (i.e., diet, weight loss and exercise) and pharmacologic agents.(6) The type and number of glucose-lowering agents generally reflect the duration and severity of diabetes. In Canada, the 2008 treatment guidelines state the first line therapy for type 2 diabetes should be metformin, an insulin-sensitizing agent that lowers blood glucose by amplifying cellular responses to endogenous insulin and by suppressing glycogenolysis at the liver.(6) When metformin alone cannot control blood glucose, and as type 2 diabetes progresses, second- and/or third-line treatments are added to maintain glycemic control. Commonly used agents include sulfonylureas and non-sulfonylurea secretagogues, which act on pancreatic islet cells to increase insulin secretion, and exogenous insulin injections.(15) Novel – and therefore less extensively-studied – agents have been added to glycemic control options over the past decade: dipeptidyl peptidase-4 (DPP4) inhibitors, glucagon-like peptide-1 (GLP1) analogues and thiazolidinediones (TZDs). DPP4 inhibitors and GLP1 analogues are non-sulfonylurea secretagogues that increase insulin secretion, whereas TZDs are insulin-sensitizing agents that stimulate peroxisome proliferator activated receptor gamma (PPARγ) to amplify cellular responses to endogenous insulin signals.(15)

1.1.2 Cancer

Five hundred Canadians are diagnosed with cancer each day.(16) More than 70% of cancers occur after the age of 60 and over a lifetime, 45% of men and 40% of women will develop cancer.(16,17) The most common (non-melanoma) cancers

among males are at the prostate, lung, colon/rectum and bladder and the most common cancers among females are at the breast, lung, colon/rectum and uterus.(16) With the aging baby-boomer population, the absolute number of new cases is expected to continue to grow.(16)

Cancer represents a class of serious diseases characterized by uncontrolled growth of abnormal cells. Cells become malignant due to mutations in the DNA sequence. Damage to DNA can cause protein abnormalities that lead to malignant transformations: alterations in the normal cell cycle (growth, proliferation and apoptosis), development of self-sustained and limitless growth, invasion of surrounding tissues and metastasis.(18) Although certain cancers are hereditary, most cancers are due to environmental factors that cause DNA damage (such as exposure to carcinogens, radiation, diet, alcohol and/or tobacco use).

There are over 100 different cancer types and even more cancer subtypes.(18) The cancer type, tumor stage and the patient's overall health determine the type of treatment (typically involve chemotherapy, radiation therapy and/or surgery) and influence the patient's prognosis.(19) The cost of treatment, management and care related to cancer are a substantial burden to the Canadian health care system, with estimated direct and indirect costs of over $14.2 billion annually.(20)

1.1.2.1 Bladder Cancer

In 2012, 7,800 new cases of bladder cancer were diagnosed in Canada, with an incidence rate of 27 per 100,000 in males and 8 per 100,000 in females.(16) Bladder cancer is the fourth most common cancer in men and the 10th most common cancer in women.(16)

Bladder cancer is a heterogeneous disease described by a tumor grading system and a TNM (tumor, node, metastasis) staging system.(21) Grading describes tissue pathology from lowest highest degree of tissue differentiation: papilloma, papillary urothelial neoplasm of low malignant potential (PUNLMP), low grade and high grade. Higher grades correlate with more aggressive tumors and a worse prognosis.(21,22) Staging describes primary tumors as: non-invasive (i.e., non-invasive papillary carcinoma (Ta) and carcinoma in situ (Tis)); invading the sub-epithelium (T1); invading the muscle (T2); invading perivesical tissue (T3); and invading the surrounding tissues (T4). Based on the primary tumor ("T") as well as the presence and number of regional lymph node ("N") and distant ("M") metastases, a tumor is classified into TNM stage groupings (0a, 0is, I, II, III, IV).(23) Over three-quarters of bladder cancers are staged as non-muscle invasive (stage groupings 0a, 0is, and I) and most commonly occur in the inner epithelium of the bladder wall.(22) The recurrence of non-muscle invasive bladder cancer is high, affecting 60% to 70% of patients. T1 tumors are often high grade and commonly progress and metastasize.(22)

Treatment options for patients with bladder cancer depend on tumor stage and grade. Gold standard treatment for non-muscle invasive tumors is transurethral resection of the bladder tumor (TURBT), and for higher grade tumors, immunotherapy (such as Bacillus Calmette–Guérin therapy) is added.(22,23) Muscle invasive tumors are treated with surgery and possible neoadjuvent chemotherapy.(23) Overall treatment success for bladder cancer, measured in 5-year survival of patients, ranges from 97% (stage I), to 65% and 56% (stages II and III, respectively) to 22% (stage IV), and males have a better all-stage survival (84%) than females (75%).(24) Muscle-invasive cancers are significantly more costly to treat than non-muscle invasive cancers.(25) Due to the high frequency of bladder cancer recurrence, the intensive and expensive life-long surveillance for recurrence, cytoscopic/surgical procedures and associated complications, the total direct and indirect costs for bladder cancer treatment are among the highest of all cancers.(25)

Detection and Diagnosis

Studies estimate the time for bladder cancer to develop ranges from less than 10 years to over 30 years, although the true latency period of bladder cancer is unknown.(21,26) Bladder cancer commonly presents with micro- or macroscopic hematuria (the former requiring laboratory investigation, the latter visible to patients) or non-specific symptoms such as fatigue, dysuria, or flank pain.(23) Guidelines recommend investigation of any hematuria.(23) Bladder cancer is found in 13% to 28% of cases of hematuria.(21) However, due to low bladder

cancer prevalence and poor positive predictive value of diagnostic tests, routine population screening for bladder cancer is not recommended.(27,28)

Risk Factors

Several well-documented factors are known to increase the risk of bladder tumor development and progression. Age and sex are key non-modifiable bladder cancer risk factors. More than 85% of individuals are over the age of 60 at the time of bladder cancer diagnosis, with a two to three fold increased risk in individuals over the age of 70, relative to individuals aged 55-69.(16,29,30) Sex contributes to a substantial difference in bladder cancer risk, with men being at three to four times the risk of women.(16)

Cigarette smoking is the primary modifiable risk factor for bladder cancer and accounts for up to half of cases.(31) Cigarette smokers have two to four times the risk of bladder cancer as that of non-smokers, and risk increases with the duration and amount of smoking.(32)

Chronic inflammation of the bladder is a reported bladder cancer risk factor. 20% to 30% of bladder cancer cases are attributed to *Schistosoma haematobium* infection in areas where this parasite is highly prevalent, notably Egypt.(33) Recurrent urinary tract infections, persistent bladder stones, and kidney infection are reported to increase bladder risk cancer.(21,23,34,35) An increased risk of bladder cancer has also been linked with pelvic irradiation.(36)

A well-documented association exists between bladder cancer and occupational exposure to dyes or other chemicals containing aromatic amines, which may account for 5% to 25% of all cases.(37) Notably, exposure to benzidine and beta-napthylamine is reported to increase the odds of bladder cancer by 83 and 150 times, respectively.(38) Other compounds linked to bladder cancer include phenacetin-containing analgesics, chlornaphazine cyclophosphamide, arsenic (in drinking water) and hair dyes.(35) Men more commonly work in jobs where exposure to these bladder carcinogens is possible and this may account for a portion of the risk difference between men and women. (34)

Other potential bladder cancer risk factors, particularly occupational exposures, have been noted in the literature; however evidence is unclear or conflicting. Comprehensive reviews of risk factors are summarized elsewhere (such as Matanoski and Elliott, 1981 and more recently Murta-Nascimento *et al*., 2007).(34,35)

1.1.3 Association Between Type 2 Diabetes and Cancer

Epidemiologic evidence indicates individuals with type 2 diabetes are at an increased risk of developing and dying from various types of cancer.(39-41) Relative to individuals without diabetes, individuals with type 2 diabetes are more likely to be diagnosed with liver cancer(42), pancreatic cancer(43), colorectal cancer(44), breast cancer(45), endometrial cancer(46), non-Hodgkin's

lymphoma(47), kidney cancer(48) and bladder cancer(49); the strength of association varies by cancer site, ranging from a relative risk of 1.20 for breast cancer to a relative risk of 2.50 for liver cancer. Men with type 2 diabetes are, however, less likely to be diagnosed with prostate cancer than non-diabetic males (50). Given the unique association between type 2 diabetes and each site-specific cancer, it has been suggested that research should focus on distinct cancer sites and not cancer globally.(40,41)

Biological mechanisms

The biological relationship between type 2 diabetes and cancer is complex and multi-factorial.(40) One leading hypothesis involves insulin and its receptors. Insulin activates the insulin receptor (IR) and homologous insulin-like growth factor-1 receptor (IGF1R).(49,50) Both IR and IGF1R are involved in cellular metabolism, differentiation and proliferation, and have anti-apoptotic effects.(51) Various tumor types, including breast, prostate, colon/rectum, bladder and others, express IR and/or IGF1R at higher levels than the undifferentiated tissues form which they arose.(51,52) Expression of IR, and especially IGF1R, on cancer cells plays a well-documented role in malignant transformation and growth.(51,53) Thus, the hyperinsulinemia known to occur in type 2 diabetes is hypothesized to be a key biological link between type 2 diabetes and cancer.(39,54) Other factors, including hyperglycemia and/or inflammatory processes, might also play a role in this complex relationship.(39)

Common risk factors

Type 2 diabetes and cancer share common risk factors. Notable non-modifiable risk factors for diabetes and various types of cancer are age, sex and race/ethnicity. Almost 90% of cancers and the majority of diabetes cases are diagnosed after the age of 50, and the risk of diagnosis of either disease increases with age.(16,55) Males have a higher age-adjusted incidence of diabetes than females, and a similar trend is observed for many cancers.(16,55) The risk of diabetes and of several cancer types is higher among certain ethnic groups, including African-Americans and First Nations, although socioeconomic differences and other biologic/genetic factors may influence this association.(2,6)

Type 2 diabetes and cancer also share several modifiable risk factors that increase the chance of developing either disease, notably: smoking, sedentary lifestyle, alcohol consumption and overweight/obesity.(39,40) The role of specific risk factors in the association between bladder cancer and tumor stage/severity in the type 2 diabetes population remains largely unexplored in epidemiologic studies.

1.1.3.1 Glucose-Lowering Therapies and Cancer

In 2010, a joint consensus report from the American Cancer Society and the American Diabetes Association reviewed evidence on the relationship between diabetes and cancer, and highlighted the potential modifying role of glucose-lowering therapies.(39) Consistent with the hyperinsulinemia hypothesis, glucose-lowering therapies that act by increasing circulating levels of insulin (e.g.,

sulfonylureas and exogenous insulins) are generally associated with an increased risk of cancer, whereas insulin sensitizing therapies (e.g., metformin) are generally associated with a decreased risk of cancer. (39-41) The magnitude and direction of association varies by pharmacologic agent and cancer site.

Over the past decade, thiazolidinediones (TZDs), namely pioglitazone and rosiglitazone, have been added as glycemic control options for type 2 diabetes. These insulin sensitizing agents are typically used as second- or third-line agents in the treatment of type 2 diabetes, as they are associated with a number of important adverse events, including weight gain and fractures.(56,57) Post-marketing studies found a strong association between rosiglitazone and increased risk of cardiovascular events and death; its use has since declined.(58,59) Pioglitazone, however, may be cardioprotective.(60)

Research suggests TZDs also have anti-cancer effects through their receptor, $PPAR_{\gamma}$, a known activator of potent tumor suppression pathways such as mTOR and LKB1.(61) TZDs also have $PPAR_{\gamma}$-independent effects on suppression of cancer cell growth and division.(62) Clinical trials are currently investigating pioglitazone and rosiglitazone as potential cancer treatment drugs.(63-65)

1.1.4 Bladder Cancer in Individuals with Type 2 Diabetes

Epidemiologic Evidence

A systematic review of observational studies suggests the risk of bladder cancer is higher among individuals with diabetes. In a meta-analysis, the pooled risk of bladder cancer reported by cohort studies was 43% (18%-74%) higher in individuals with type 2 diabetes, and pooled odds from case-control studies showed a 37% (4%-80%) increase, relative to non-diabetic individuals.(49) A subsequently published study suggests the increased bladder cancer risk associated with diabetes is found especially among men.(66) Research suggests type 2 diabetes is associated with a higher number of bladder tumors and a higher tumor grade.(67) Individuals with type 2 diabetes and bladder cancer also have significantly reduced survival compared to non-diabetic individuals.(68)

Biological Evidence

IGF1R and IR play an important role in tumor growth, differentiation, motility and protection from apoptosis.(53,69) IGF1R is also overexpressed in malignant bladder cells and is indirectly stimulated by insulin, as insulin increases circulating levels of the IGF1R ligand, IGF-1.(70,71) Hyperinsulinemia in individuals with type 2 diabetes may therefore more strongly promote bladder cancer than in non-diabetic individuals.(39,51,70)

1.1.4.1 Factors Influencing the Association Between Type 2 Diabetes and Bladder Cancer

Thiazolidinediones and Bladder Cancer

Despite the presumed anti-cancer actions of TZDs, emerging biologic and epidemiologic studies have reported an elevated risk of bladder cancer in individuals using the TZD agent pioglitazone (Actos®, Takeda Pharmaceuticals). In animal studies, male rats exposed to pioglitazone developed more bladder tumors than controls. No risk difference was found in female rats or in mice of either sex.(72) One large placebo-controlled clinical trial PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) published in 2005, aimed primarily at assessing the effects of pioglitazone on cardiovascular outcomes, found bladder cancer in 14 of 2605 [0.54%] participants in the pioglitazone arm vs. six of 2633 [0.23%] participants in the placebo arm over an average follow-up of 2.9 years.(60) Subsequent blinded review of the cases by the Drug Safety Monitoring Committee (DSMC) eliminated 11 cases that occurred during the first year, leaving 6 in the pioglitazone arm and 3 in the control arm. All individuals had a history of smoking and other bladder cancer risk factors; the DSMC concluded it was not likely pioglitazone increases the risk of bladder cancer.(73)

Following reports from two large administrative cohort studies conducted in the US and France, which both suggested an increased risk of bladder cancer with pioglitazone use in a dose- and duration-dependent manner(74,75), France and Germany suspended pioglitazone from their markets in June of 2011. International regulatory agencies, including the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and Health

Canada have since reviewed available evidence on this potential association and concluded a positive risk to benefit balance, but warned against use of pioglitazone in those at a higher risk of developing bladder cancer.(76)

The role of TZDs in the association between T2DM and bladder cancer incidence and mortality, however, remains unclear. So far, no study has reported on bladder cancer mortality in individuals with T2DM using TZDs and only two large, well-conducted cohort studies have been published on bladder cancer incidence with pioglitazone use.(74,77) Although a number of smaller studies have been conducted, they suffer from problems with design and/or analysis(78,79); few studies include a long enough follow-up period to thoroughly explore an association with TZDs and incident bladder cancer.

Bladder Cancer Detection and Diagnosis

Emerging epidemiologic evidence from British Columbia, Ontario and Denmark suggests the risk of cancer in individuals with type 2 diabetes changes over time.(66,80,81) In the months shortly after type 2 diabetes diagnosis, the risk of cancer diagnosis at various sites, including breast, colon/rectum, prostate, ovary and thyroid, is significantly higher than in the general non-diabetic population; however the risk of cancer diagnosis declines in later periods. (66,80)

Interestingly, the frequency with which individuals visit the doctor prior to a diagnosis of type 2 diabetes may modify the likelihood of being subsequently

diagnosed with cancer. Research suggests an inverse relationship between the number of physician visits in the two years before type 2 diabetes diagnosis and the subsequent short-term (3 months or less) risk of breast, lung, cervical and prostate cancer, relative to the non-diabetes population.(80)

There is some evidence of a short-term increased risk of bladder cancer in individuals with newly diagnosed diabetes. It is possible that at the time of diabetes diagnosis, the physician conducts a thorough inventory of health problems, including routine history and physical examination, screening, bloodwork and urinalysis. During this diagnostic work-up, clinically detectable but previously undiagnosed health problems, such as bladder cancer, may be diagnosed, particularly if screening for the disease is not routinely conducted in the general population (as in the case for bladder cancer).(28,40) However, the effect of frequency of physician visits prior to type 2 diabetes diagnosis on the relationship between type 2 diabetes and bladder cancer has not yet been investigated.

1.2 Objectives

The objective of this series of studies is to explore the relationship between diabetes and bladder cancer by assessing factors that may influence the risk of bladder cancer among individuals with type 2 diabetes. The studies involve different sources of data and distinct methodologies. The first study systematically reviews all of the available literature on the use of TZDs, particularly pioglitazone, and bladder cancer risk. The second study focuses on the potential bias in detection of bladder cancer in individuals with newly diagnosed type 2 diabetes.

1.3 Summary of Research Projects

Project 1:

Pioglitazone and rosiglitazone use and risk of bladder cancer in type 2 diabetes: a systematic review and meta-analysis

Background: Individuals with type 2 diabetes have a 40% increased risk of bladder cancer. Thiazolidinediones, especially pioglitazone, may further increase the risk of bladder cancer. We systematically reviewed literature on bladder cancer risk in adults with type 2 diabetes using thiazolidinediones.

Methods: We searched 12 key biomedical databases (including MEDLINE, Embase and Scopus) and seven sources of grey literature for published and unpublished studies without language restrictions, up to March 2012, yielding 1787 studies. Inclusion criteria specified randomized trials, cohort and case-control studies reporting incident bladder cancer in individuals with type 2 diabetes ever vs. never exposed to pioglitazone (main outcome), rosiglitazone or any thiazolidinedione.

Results: We included 4 randomized trials, 5 cohort studies, and 1 case-control study, contributing 2,657,365 patients, 3,643 new cases of bladders cancer and an overall incidence rate of 53.1 per 100,000 person-years. One randomized trial reported pioglitazone use, which was non-significantly associated with bladder cancer (RR: 2.36, 95%CI 0.91-6.13). Cohort studies of thiazolidinediones (n=6,

pooled RR: 1.15, 95%CI 1.04-1.26, I^2=0%, p=0.005), and pioglitazone specifically (n=3, pooled RR: 1.22, 95%CI 1.07-1.39, I^2=0%, p=0.003), showed significant associations with bladder cancer. A significant association with bladder cancer was not observed among randomized trials of rosiglitazone (n=2, pooled RR: 0.87, 95%CI 0.34-2.23, I^2=0%, p=0.8).

Interpretation: The limited evidence available supports the hypothesis that treatment with thiazolidinediones, particularly pioglitazone, is associated with an increased risk of bladder cancer among adults with type 2 diabetes.

Project 2:

Detection bias and overestimation of bladder cancer risk in type 2 diabetes: a matched cohort study

Background: There is a 43% increased risk of bladder cancer in individuals with type 2 diabetes. We conducted a matched cohort study using linked administrative health databases to investigate if there is an increased risk of bladder cancer in individuals with newly diagnosed type 2 diabetes and if the risk is influenced by the frequency of physician visits prior to diabetes diagnosis, as a measure of detection bias.

Methods: We established a cohort of 185,100 adults from British Columbia, Canada with incident type 2 diabetes and 185,100 non-diabetic controls matched

1:1 on age, sex and index date (diabetes diagnosis date or matched control date), from 1996 to 2006. Individuals were free of diabetes and of bladder cancer in the two years before index and frequency of physician visits was used to examine detection bias. Unadjusted incidence rates and adjusted hazard ratios (aHR) for bladder cancer were calculated during different time windows following index date (<1.0, 1.0 to 2.0, 2.0 to 3.0 and 3.0 to 10.0 years). The analyses were stratified by the number of physician visits (≤12, 13 to 24 and ≥25 visits) in the two years prior to diabetes diagnosis and adjusted for age, sex, year of cohort entry and socioeconomic status.

Results: The study population was 54% men, average age was 60.7 (±13.5) years, and a total of 1171 new bladder cancers were diagnosed over a median of 4-years follow-up. In the first year following new diagnosis of type 2 diabetes, the incidence of bladder cancer in those with diabetes was 85.3 (95% confidence interval (CI): 72.0-100.4) per 100,000 person-years and in controls was 66.1 (95% CI: 54.5-79.4) (aHR 1.30 [95% CI: 1.02 to 1.67], *p*=0.03). This first-year increase in bladder cancer risk was seen only among those with the fewest physician visits in the 2 years before index (≤12 visits; aHR: 2.14 (95% CI: 1.29-3.55), *p*=0.003). Overall, after the first-year post-diagnosis, type 2 diabetes was not otherwise significantly associated with bladder cancer (aHR 1.08, 95% CI 0.95 to 1.23, *p*=0.24), however when considering the full follow-up period, the aHR was significantly increased: 1.13 (95% CI: 1.01 to 1.26; p=0.04).

Interpretation: Our results suggest that early detection bias may account for an overestimation in previously reported increased risks of bladder cancer associated with type 2 diabetes.

1.4. References

1. Public Health Association of Canada. Diabetes in Canada: report from the National Diabetes Surveillance System. Ottawa, ON; 2009 [cited 2012 Aug 17]. Available: http://www.phac-aspc.gc.ca/publicat/2009/ndssdic-snsddac-09/index-eng.php

2. Canadian Diabetes Association. At the tipping point: diabetes in British Columbia. Toronto, ON; 2011 [cited 2012 Aug 17]. Available: http://www.diabetes.ca/documents/get-involved/17620_Diabetes_Prog_Report_BC_2.pdf

3. Canadian Diabetes Association. An economic tsunami: the cost of diabetes in Canada. Toronto, ON; 2009 [cited 2012 Aug 17]. Available: http://scholar.google.com/scholar?q=related:cpaXKDZWR78J:scholar.google.com/&hl=en&num=30&as_sdt=0,5

4. Tabák AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimäki M, Witte DR. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. Lancet. 2009;373(9682):2215–21.

5. Inzucchi SE, Sherwin RS. The prevention of type 2 diabetes mellitus. Endocrinol Metab Clin N Am. 2005;34(1):199–219.

6. Canadian Diabetes Association. Clinical practice guidelines for the prevention and management of diabetes in Canada. Clinical Practice Guidelines Expert Committee. Can J Diabetes. 2008;32(suppl 1):S1-S201.

7. Goldenberg RM, Cheng AYY, Punthakee Z, Clement M. Canadian Diabetes Association position statement: use of glycated hemoglobin (A1C) in the diagnosis of diabetes mellitus. Can J Diabetes. 2011;35(3):247-249.

8. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. Br Med J. 2000;321(7258):405–412.

9. Held C, Gerstein HC, Yusuf S, et al. Glucose levels predict hospitalization for congestive heart failure in patients at high cardiovascular risk. Circulation. 2007;115(11):1371–1375.

10. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837–853.

11. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545–2559.

12. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360(2):129–139.

13. ACCORD Eye Study Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med. 2010;363(3):233–244.

14. Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med. 2011;364(9):829–841.

15. Krentz AJ. Comparative safety of newer oral antidiabetic drugs. Expert Opin Drug Saf. 2006;5(6):827–834.

16. Canadian Cancer Society's Steering Committee on Cancer Statistics. Canadian Cancer Statistics 2012. Toronto, ON: Canadian Cancer Society; 2012.

17. Canadian Cancer Society's Steering Committee on Cancer Statistics. Canadian Cancer Statistics 2011. Toronto, ON: Canadian Cancer Society; 2011.

18. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100(1):57–70.

19. American Society of Clinical Oncology. All About Cancer. Alexandria, VA; 2012 [cited 2012 Aug 17]. Available: http://www.cancer.net/patient/All+About+Cancer

20. Health Canada. The economic burden of illness in Canada, 1998. Health Canada, Ottawa, ON: Government of Canada; 2002.

21. Kirkali Z, Chan T, Manoharan M, et al. Bladder cancer: epidemiology, staging and grading, and diagnosis. Urol. 2005;66(6 Suppl 1):4–34.

22. Kassouf W, Kamat AM, Zlotta A. Canadian guidelines for treatment of non-muscle invasive bladder cancer: a focus on intravesical therapy. Can Urol Assoc J. 2010;4(3):168–173.

23. Sharma S, Ksheersagar P, Sharma P. Diagnosis and treatment of bladder cancer. Am Fam Physician. 2009;80(7):717–723.

24. Ries LAG, Reichman ME, Lewis DR, Hankey BF, Edwards BK. Cancer survival and incidence from the Surveillance, Epidemiology, and End Results (SEER) program. Oncologist. 2003;8(6):541–552.

25. Avritscher E, Cooksley C, Grossman H. Clinical model of lifetime cost of treating bladder cancer and associated complications. Urology. 2006; 68:549-553.

26. Friedman GD, Carroll PR, Cattolica EV, Hiatt RA. Can hematuria be a predictor as well as a symptom or sign of bladder cancer? Cancer Epidemiol Biomarkers Prev. 1996;5(12):993–996.

27. Logsetty S. Screening for Bladder Cancer. Public Health Association of Canada; 1993 [cited 2012 Aug 17]. Available: http://www.phac-aspc.gc.ca/publicat/clinic-clinique/pdf/s10c68e.pdf

28. Chou R, Dana T. Screening adults for bladder cancer: a review of the evidence for the U.S. preventive services task force. Ann Int Med. 2010;153(7):461–468.

29. British Columbia Cancer Agency. Cancer Statistics. Provincial Health Services Authority. Vancouver, BC; 2009 [cited 2012 Jun. 4]. Available: http://www.bccancer.bc.ca/ABCCA/NewsCentre/stats.htm

30. Miller, B.A., Kolonel, L.N., Bernstein, L., Young, Jr., J.L, Swanson, G.M., West, D., (Eds.). (1996). Racial/ethnic patterns of cancer in the United States, 1988-1992 (NIH Publication No. 96-4104). Bethesda, MD: National Cancer Institute.

31. Strope SA, Montie JE. The causal role of cigarette smoking in bladder cancer initiation and progression, and the role of urologists in smoking cessation. J Urol. 2008;180(1):31–37.

32. Zeegers MP, Tan FE, Dorant E, van Den Brandt PA. The impact of characteristics of cigarette smoking on urinary tract cancer risk: a meta-analysis of epidemiologic studies. Cancer. 2000;89(3):630–639.

33. Mostafa MH, Sheweita SA, O'Connor PJ. Relationship between schistosomiasis and bladder cancer. Clin Microbiol Rev. 1999;12(1):97–111.

34. Matanoski GM, Elliott EA. Bladder cancer epidemiology. Epidemiol Rev. 1981;3:203–229.

35. Murta-Nascimento C, Schmitz-Dräger BJ, Zeegers MP, Steineck G, Kogevinas M, Real FX, et al. Epidemiology of urinary bladder cancer: from tumor development to patient's death. World J Urol. 2007;25(3):285–95.

36. Quilty PM, Kerr GR. Bladder cancer following low or high dose pelvic irradiation. Clinic Radiol. 1987;38(6):583–5.

37. Olfert SM, Felknor SA, Delclos GL. An updated review of the literature: risk factors for bladder cancer with focus on occupational exposures. South Med J. 2006;99(11):1256–1263.

38. Rubino GF, Scansetti G, Piolatto G, Pira E. The carcinogenic effect of aromatic amines: an epidemiological study on the role of o-toluidine and 4,4'-methylene bis (2-methylaniline) in inducing bladder cancer in man. Environ Res. 1982;27(2):241–254.

39. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. Diabetes Care. 2010;33(7):1674–1785.

40. Johnson JA, Carstensen B, Witte D, et al. Diabetes and cancer (1): evaluating the temporal relationship between type 2 diabetes and cancer incidence. Diabetologia. 2012;55(6):1607–1618.

41. Renehan AG, Yeh H-C, Johnson JA, Wild SH, Gale EAM, Møller H, et al. Diabetes and cancer (2): evaluating the impact of diabetes on mortality in patients with cancer. Diabetologia. 2012;55(6):1619-1632.

42. El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. Clin Gastroenterol Hepatol. 2006;4(3):369–380.

43. Huxley R, Ansary-Moghaddam A, Berrington de González A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer. 2005;92(11):2076–2083.

44. Larsson SC, Giovannucci E, Wolk A. Diabetes and colorectal cancer incidence in the cohort of Swedish men. Diabetes Care. 2005;28(7):1805–1807.

45. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer. 2007;121(4):856–862.

46. Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia. 2007;50(7):1365–1374.

47. Mitri J, Castillo J, Pittas AG. Diabetes and risk of Non-Hodgkin's lymphoma: a meta-analysis of observational studies. Diabetes Care. 2008;31(12):2391–2397.

48. Larsson SC, Wolk A. Diabetes mellitus and incidence of kidney cancer: a meta-analysis of cohort studies. Diabetologia. 2011;54(5):1013–1018.

49. Larsson SC, Orsini N, Brismar K, Wolk A. Diabetes mellitus and risk of bladder cancer: a meta-analysis. Diabetologia. 2006;49(12):2819–2823.

50. Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev. 2006;15(11):2056–2062.

51. Fürstenberger G, Senn H-J. Insulin-like growth factors and cancer. Lancet Oncol. 2002;3(5):298–302.

52. Metalli D, Lovat F, Tripodi F, et al. The insulin-like growth factor receptor I promotes motility and invasion of bladder cancer cells through Akt- and mitogen-activated protein kinase-dependent activation of paxillin. Am J Pathol. 2010;176(6):2997–3006.

53. Belfiore A, Malaguarnera R. Insulin receptor and cancer. Endocr Relat Cancer. 2011;18(4):R125–147.

54. Johnson JA, Bowker SL. Intensive glycaemic control and cancer risk in type 2 diabetes: a meta-analysis of major trials. Diabetologia. 2011;54(1):25–31.

55. Johnson JA, Balko SU. Alberta Diabetes Surveillance System: Atlas 2011. Edmonton, AB: Alberta Diabetes Surveillance System. Edmonton, AB; 2011 [cited 2012 Aug 17]. Available: http://www.albertadiabetes.com/pubs.php

56. Nesto RW, Bell D, Bonow RO, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. Diabetes Care. 2004;27(1):256–263.

57. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. Can Med Assn J. 2009;180(1):32–39.

58. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007;356(24):2457–2471.

59. Morrow RL, Carney G, Wright JM, Bassett K, Sutherland J, Dormuth CR. Impact of rosiglitazone meta-analysis on use of glucose-lowering medications. Open Med. 2010;4(1):e50–59.

60. Dormandy JA, Charbonnel B, Eckland DJA, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005;366(9493):1279–1289.

61. Belfiore A, Genua M, Malaguarnera R. PPAR-gamma agonists and their effects on IGF-I receptor signaling: implications for cancer. PPAR Res.

2009;2009:1–18.

62. Wei S, Yang J, Lee S-L, Kulp SK, Chen C-S. PPARgamma-independent antitumor effects of thiazolidinediones. Cancer Lett. 2009;276(2):119–124.

63. Pioglitazone hydrochloride in treating patients with stage I, stage II, or stage III non-small cell lung cancer In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2012 Jun. 4]. Available from: http://clinicaltrials.gov/ct2/show/NCT01342770

64. Pioglitzaone for lung cancer chemoprevention. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2012 Aug 17] Available: http://clinicaltrials.gov/ct2/show/NCT00780234

65. Rosiglitazone (Avandia) vs. Placebo for Androgen Dependent Prostate Cancer. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2012 Aug 17] Available: http://clinicaltrials.gov/ct2/show/NCT00182052

66. Carstensen B, Witte DR, Friis S. Cancer occurrence in Danish diabetic patients: duration and insulin effects. Diabetologia. 2011;55(4):948-958.

67. Hwang EC, Kim YJ, Hwang IS, et al. Impact of diabetes mellitus on recurrence and progression in patients with non-muscle invasive bladder carcinoma: a retrospective cohort study. Int J Urol. 2011;18(11):769–776.

68. Currie CJ, Poole CD, Jenkins-Jones S, Gale EAM, Johnson JA, Morgan CL. Mortality after incident cancer in people with and without type 2 diabetes: impact of metformin on survival. Diabetes Care. 2012;35(2):299–304.

69. Papa V, Pezzino V, Costantino A, et al. Elevated insulin receptor content in human breast cancer. J Clin Invest. 1990;86(5):1503–1510.

70. Rochester MA, Patel N, Turney BW, et al. The type 1 insulin-like growth factor receptor is over-expressed in bladder cancer. Br J Urol Int. 2007;100(6):1396–1401.

71. Frystyk J, Vestbo E, Skjaerbaek C, Mogensen CE, Orskov H. Free insulin-like growth factors in human obesity. Metab Clin Exp. 1995;44(10 Suppl 4):37–44.

72. Actos: Scientific Discussion. European Public Assessment Report. European Medicines Agency. 2006 [cited 2012 Aug 17]. Available: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000285/WC500021381.pdf

73. Dormandy J, Bhattacharya M, van Troostenburg de Bruyn A-R. Safety and

tolerability of pioglitazone in high-risk patients with type 2 diabetes. Drug Saf. 2009;32(3):187–202.

74. Lewis JD, Ferrara A, Peng T, et al. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. Diabetes Care. 2011;34(4):916–922.

75. Caisse National d'Assurance Maladie. Risque de cancer de la vessie chez les personnes diabétiques traitées par pioglitazone en France : une étude de cohorte sur les données du SNIIRAM et du PMSI. Saint Denis, France; 2011 [cited 2012 Aug 17]. Available: http://www.afssaps.fr/var/afssaps_site/storage/original/application/b42a6bf9a1b63c3dbec7388d3914687b.pdf

76. Update on ongoing review of pioglitazone-containing medicines. European Medicines Agency; 2011 [cited 2012 Aug 17]. Available: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/06/news_detail_001275.jsp&mid=WC0b01ac058004d5c1&murl=menus/news_and_events/news_and_events.jsp&jsenabled=true

77. Neumann A, Weill A, Ricordeau P, Fagot JP, Alla F, Allemand H. Pioglitazone and risk of bladder cancer among diabetic patients in France: a population-based cohort study. Diabetologia. 2012;55(7):1953-1962.

78. Ramos-Nino ME, MacLean CD, Littenberg B. Association between cancer prevalence and use of thiazolidinediones: results from the Vermont Diabetes Information System. BMC Med. 2007;5(17):1-7.

79. Piccinni C, Motola D, Marchesini G, Poluzzi E. Assessing the association of pioglitazone use and bladder cancer through drug adverse event reporting. Diabetes Care. 2011;34(6):1369–1371.

80. Johnson JA, Bowker SL, Richardson K, Marra CA. Time-varying incidence of cancer after the onset of type 2 diabetes: evidence of potential detection bias. Diabetologia. 2011;54(9):2263-2271.

81. Lipscombe LL, Goodwin PJ, Zinman B, McLaughlin JR, Hux JE. Increased prevalence of prior breast cancer in women with newly diagnosed diabetes. Breast Cancer Res Treat. 2006;98(3):303–309.

CHAPTER 2. PIOGLITAZONE AND ROSIGLITAZONE USE AND RISK OF BLADDER CANCER IN TYPE 2 DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS

2.1 Introduction

Type 2 diabetes is associated with an increased risk of several types of cancer, including a 40% increased risk of bladder cancer, compared to those without diabetes.(1,2) The strong association with bladder cancer is hypothesized to be a result of hyperinsulinemia, whereby elevated insulin levels in type 2 diabetes stimulate insulin receptors on neoplastic cells, promoting cancer growth and division.(1,3-5) Additional risk factors for bladder cancer include older age, male sex, smoking, occupational and environmental exposures, and urinary tract disease.(6) Exogenous insulin and other glucose-lowering therapies such as the sulfonylureas, metformin, and the thiazolidinediones may further modify the risk of bladder cancer.(1)

Data from the placebo-controlled PROactive trial of pioglitazone suggested a higher incidence of bladder cancer among pioglitazone users compared with controls.(7) Subsequent data from other randomized trials and observational studies have reported conflicting results for pioglitazone, with various studies reporting a significant increase (8,9), a non-significant increase (10), and even a decreased risk (11) of bladder cancer.

To test the hypothesis that pioglitazone use is associated with an increased risk of bladder cancer, we conducted a systematic review and meta-analysis of randomized trials and observational studies in individuals with type 2 diabetes reporting bladder cancer with pioglitazone use. To clarify the possibility of a thiazolidinedione class effect, we also examined data for all thiazolidinediones and for rosiglitazone alone.

2.2 Methods

The protocol for this study was developed *a priori* to outline our search strategy, criteria for study selection, identify procedures for data abstraction and assessment of bias, and establish methods of data analysis.

Search strategy and selection criteria

We conducted a comprehensive search of the following key electronic biomedical databases from inception through March 2012: MEDLINE, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment, Cochrane Central Register of Controlled Trials, Science Citation Index Expanded, Conference Proceedings Citation Index - Science, Cochrane Library, Pubmed (cancer subset, limited to adults), Toxnet and Scopus. No study design filters or language restrictions were applied. The search strategy was broad, so to capture all potentially suitable studies and was created with the assistance of a librarian experienced in systematic reviews. A sample search is provided in Appendix A.

We also searched seven sources of grey-literature: conference proceedings from five international conferences of major diabetes and diabetes-related organizations from 2008 onward (International Society of Pharmacoepidemiology, American Diabetes Association, Canadian Diabetes Association, European Association for the Study of Diabetes and Canadian Association of Population Therapeutics); Google Scholar; clinical trials registries (clinicaltrials.gov and International Clinical Trials Registry Platform); databases of international drug safety surveillance agencies (Food and Drug Administration, Health Canada, and European Medicines Agency); hand searching from reference lists of relevant studies; consultation with experts in the field; and contacting authors of studies for additional information.

A checklist was used to assess whether studies met our inclusion criteria for population (individuals with type 2 diabetes), exposure (ever-use of any thiazolidinedione therapy), comparison group (no use of any thiazolidinedione therapy), outcome (any report of incident cancer, even if it was not a main outcome), and study design (randomized trials, cohort, and case-control studies, including case/non-case studies). We then restricted remaining studies to those reporting incident bladder cancer. Other exclusion criteria included duplicate reports from the same study, studies on individuals with type 1 diabetes exclusively, and descriptive observational studies.

Data collection

Two trained reviewers independently conducted study selection, data abstraction, and assessed risk of bias. Any discrepancies between reviewers were resolved through discussion and consensus or by JAJ. Risk of bias was evaluated using the Cochrane Risk of Bias Tool (14) for randomized trials and using a modified version of the Newcastle-Ottawa Scale (15) for cohort and case-control studies, with five of eight points or less indicating a high risk of bias.

Synthesis of data

We tabulated pertinent descriptive data from included studies. In a random effects model, we meta-analyzed adjusted risk estimates using inverse variance calculations for observational studies and used Mantel-Haenszel calculations to estimate unadjusted risk for randomized trials.(16) As a criterion for meta-analytic pooling, we considered a maximum heterogeneity (I^2) of no more than 75%. Heterogeneity was assessed as low (≤25%), moderate (>25-50%), and high (>50-75%), and we explored possible sources of heterogeneity if I^2 was larger than 25%.

In our primary analysis, we examined pioglitazone (Actos, Takeda Pharmaceuticals, Osaka, Japan) exposure and stratified our results by study design (randomized trial, cohort, and case-control studies). In secondary analyses, we considered rosiglitazone (Avandia, GlaxoSmithKline, London, UK) exposure and any thiazolidinedione exposure. Ascertainment of all thiazolidinedione exposures

was independent of other existing therapies or exposures. We planned subgroup analyses among monotherapy users for pioglitazone or rosiglitazone, but had insufficient reports to conduct such analyses. We were unable to assess publication bias through construction of funnel plots due to a limited number of reports.(17) All analyses were conducted using RevMan version 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark).

2.3 Results

Study selection

Our search of 12 key biomedical databases and seven different sources of grey literature returned 1787 results once duplicates were removed. After screening all titles and abstracts, 63 full text studies (62 in English, 1 in French) were pulled for further evaluation. A list of excluded studies is available in the supplementary on-line material. Studies were excluded only for the following reasons: no report of incident bladder cancer (*n*=39); no thiazolidinedione exposure reported (*n*=5); duplicate reports of the same study (*n*=4); no appropriate comparison group (*n*=3); and ineligible study design (n=2) (Figure 2.1).

Study characteristics

Nine full text publications (7,9-11,18-22) and one unpublished study (23) reporting incident bladder cancer were included in our review (Table 2.1). One observational study used a case/non-case design (9) and we included this study among case-control studies. No other case-control studies met our inclusion

criteria. One publication (24) reported unpublished cancer outcomes from two randomized trials that we included in this review (i.e., ADOPT (19) and RECORD (18)), was used to supplement cancer data for these trials. One included cohort study (21) was previously published as a government report (8), which was used to supplement data not found in the published study. Two studies (11,22) were conducted in the same population (Taiwan), but during different time intervals (2003-2005 (11) and 2006-2009 (22)) and with different drug exposure definitions (thiazolidinedione ever/never (11) and pioglitazone ever/never (22)); we included both studies. Overall, we analyzed ten different studies with a total of 3,542,664 participants and 3643 incident cases of bladder cancer.

We assigned a high risk of bias to two randomized trials due to important differential losses to follow-up (18,19); to one unpublished randomized trial with insufficient reporting of methods and early termination (23); and to one observational study with inadequately defined cases and unrepresentative controls.(9) No cohort study was at a high risk of bias (Table 2.2).

Systematic review of bladder cancer incidence

Randomized trials

All four randomized trials included individuals with type 2 diabetes randomly assigned to thiazolidinedione therapy and assessed the following non-cancer outcomes: cardiovascular outcomes (18), HbA1c levels (19,23), and macrovascular morbidity and mortality.(7) Two trials were open-label (18,23) and

one study (23) was unpublished. All randomized trials presented data on bladder cancer as crude numbers, lacking further demographic information. We combined participants from three randomized trials (the fourth study (23) lacked information on follow-up time) to estimate the incidence rate (per 100,000 person-years) of bladder cancer: 101.0 among those who used thiazolidinediones and 65.5 among those who did not use thiazolidinediones. In the PROactive study (7), the incidence rate (per 100,000 person-years) was 186.9 among pioglitazone users and 79.3 among controls. Comparatively, in the ADOPT (19) and RECORD (18) trials, incidence rates (per 100,000 person-years) for rosiglitazone users were 102.4 and 48.6, respectively; and for comparators were 87.4 and 40.7, respectively.

Observational studies

Observational studies reported results according to demographic or clinical features. Three studies reported a higher risk of bladder cancer in males exposed to thiazolidinediones compared with females (8,10,11), and one study reported history of bladder disease to predict bladder cancer independent of thiazolidinedione exposure.(11)

Neumann *et al* (2012) reported incidence rates for bladder cancer, standardized to the world population, as 14.6 for males and 2.0 for females, per 100,000 person-years.(8)

Lewis *et al.* (2011) (10), Tseng (2012) (22) and Neumann *et al* (2012) (21) reported bladder cancer incidence rates among pioglitazone users as 81.5, 104.5 and 49.4 per 100,000 person-years, respectively; the same studies reported bladder cancer incidence rates among pioglitazone non-users as 68.8, 78.9 and 42.8 per 100,000 person-years, respectively. Thiazolidinedione use, reported by Oliveria *et al* (2008) (20) and by Tseng (2011) (11), was associated with a bladder cancer incidence rate of 53.4 and 32.44 per 100,000 person years, respectively; bladder cancer incidence rates among thiazolidinedione never-users reported by these studies were 50.9 and 65.6 per 100,000 person-years, respectively.

Systematic review and meta-analysis of pioglitazone use and bladder cancer

All studies of all designs assessing pioglitazone exposure reported ever-use to be associated with an elevated (7,10,22) or significantly increased (8,9) risk of bladder cancer, compared with never-use (Table 2.3). Three studies assessed cumulative pioglitazone exposure (10,21,22). One study observed a significant association with bladder cancer after >12 months exposure (8) and both studies that assessed exposure >24 months (10,21) found a significant association with bladder cancer. Three studies explored a dose-response relationship; two reported a cumulative pioglitazone dose of more than 28,000 mg to be significantly (8) and non-significantly (10) associated with elevated risks of bladder cancer, ranging from 40% to 75%.

Five studies were available for meta-analysis: one randomized trial, three cohort studies, and one case-control (case/non-case) study.(7,9,10,21,22) The randomized trial observed 14 bladder cancers among 2605 pioglitazone participants and six cases of bladder cancer among 2633 controls, giving a relative risk of 2.36 (95% CI 0.91 to 6.13) (Table 2.3). We observed a significantly increased risk of bladder cancer associated with pioglitazone use among cohort studies, representing 1,739,087 individuals (pooled RR: 1.22, 95% CI 1.07 to 1.39, n=3, I^2=0%, p=0.003) (Figure 2.2).

Systematic review and meta-analysis of rosiglitazone use and bladder cancer

Two randomized trials (n=8798) and one cohort study reported bladder cancer among rosiglitazone users (Table 2.3).(18,19,21) The cohort study was designed to assess pioglitazone exposure and bladder cancer incidence and included rosiglitazone ever-use as a subgroup.(8) Both randomized trials compared rosiglitazone to other glucose lowering therapies and only one (18) was blinded. We observed no association between bladder cancer and rosiglitazone use from the randomized trials (pooled RR: 0.87, 95% CI 0.34 to 2.23, n=2 I^2=0%, p=0.8) (Figure 2.3) or the cohort study (HR: 1.08, 95% CI 0.92 to 1.26).

Systematic review and meta-analysis of any thiazolidinedione exposure and bladder cancer

The pooled unadjusted risk ratio from four randomized trials reporting any thiazolidinedione exposure, representing 14,422 individuals, was 1.45 (95% CI

0.75 to 2.83, n=4, I^2=2%, p=0.3) (Figure 2.4a).(7,18,19,23) There was also an increased risk of bladder cancer associated with any thiazolidinedione exposure among five cohort studies reporting six estimates, representing 2,043,858 individuals (pooled adjusted RR: 1.15, 95% CI 1.04 to 1.26, n=6, I^2=0%, p=0.005) (Figure 2.4b).(10,11,20-22)

2.4 Interpretation

Main Findings

In this rigorous systematic review and meta-analysis of randomized and non-randomized studies, we observed an increased risk of bladder cancer associated with use of thiazolidinediones. In particular, use of pioglitazone was associated with an increased risk of bladder cancer based on over 1.7 million individuals pooled in estimates from cohort studies (pooled RR: 1.22; 95% CI 1.07 to 1.39), which was consistent with estimates from the randomized trials and the case/non-case study. We observed no association between rosiglitazone use and bladder cancer.

Comparison with other studies

Thiazolidinediones are insulin receptor sensitizers and exert their effects through activation of the peroxisome proliferator-activated receptor (PPARγ).(25) Although studies suggest PPARγ is involved in known tumor suppression pathways, such as mTOR and LKB-1 (25,26), mechanisms linking thiazolidinediones with the development or progression of bladder neoplasms

have not been fully elucidated. Pre-clinical research using female rats exposed to rosiglitazone found more bladder tumors among rats treated with rosiglitazone than controls (27); another study found significantly more bladder tumors in male rats treated with pioglitazone than in controls.(28) The latter study reported no difference in the occurrence of other cancers.

Concerns of a potential association between pioglitazone use and bladder cancer in humans emerged after publication of the PROactive study, which reported a non-significant increased risk of bladder cancer among participants exposed to pioglitazone compared to controls (14 of 2605 [0.54%] vs. six of 2633 [0.23%], respectively).(7) Subsequent review of these cases suggests the true incidence rates were actually lower in both groups.(29) Three subsequent observational studies supported the initial findings of the PROactive study and further suggested dose and duration relationships.(8-10) In response these findings, the France and Germany suspended pioglitazone from their markets; the European Medicines Agency called for close selection and monitoring of patients (13), and the US Food and Drug Administration issued warnings against using pioglitazone in patients with active or previous bladder cancer.(12)

Limitations

There are some limitations to this research, mostly predicated on the lack of primary studies available for synthesis and the differences among study designs. We did not have individual patient data and were therefore unable to exclude the

small number of individuals with type 1 diabetes, examine other known risk factors for bladder cancer (especially smoking and occupational exposure), or control for duration of exposure. Our definition of ever or never exposure to agents captured real-world prescription patterns of glucose-lowering agents (i.e., combination therapy), but may have led to conflicting associations between other agents (e.g., insulin, sulfonylureas, metformin) and bladder cancer (1); this may have biased our estimate in a non-differential manner. The high risk of bias among randomized trials is a limitation but does not meaningfully change our interpretation of estimates for rare and unexpected events such as bladder cancer. Further, randomized trial results parallel results from observational studies, which were at low risk of bias. In observational studies, bladder cancer was captured through usual care, where more severe and symptomatic (and thus most easily recognized) cases are more likely to be captured. Consequently, we may have underestimated the true number of cancer cases, although this is unlikely to affect the relative risk estimate.

Conclusions

Our results suggest an association between pioglitazone use and bladder cancer in adults with type 2 diabetes. Given the limited evidence among rosiglitazone users, it remains unclear if the association with bladder cancer is a class effect of all thiazolidinediones. Evidence surrounding the association between pioglitazone and bladder cancer requires cautious interpretation, as our evidence is based on only three, albeit large and well-conducted observational studies.(8,10,10,21,22)

Future research is required to improve our understanding and should include large population-based cohort studies involving individuals with type 2 diabetes; include a reference group of individuals without diabetes; have a minimum dose and duration of exposure; and account for important bladder cancer risk factors (such as smoking status and history of bladder disease).(30)

Although the absolute risk of bladder cancer is small, other evidence-based treatments for type 2 diabetes may be equally effective and do not carry a risk of cancer. This study quantifies the association between pioglitazone use and bladder cancer and may help inform decisions around safer use of pioglitazone in individuals with type 2 diabetes.

Figure 2.1: Flow chart of study selection process

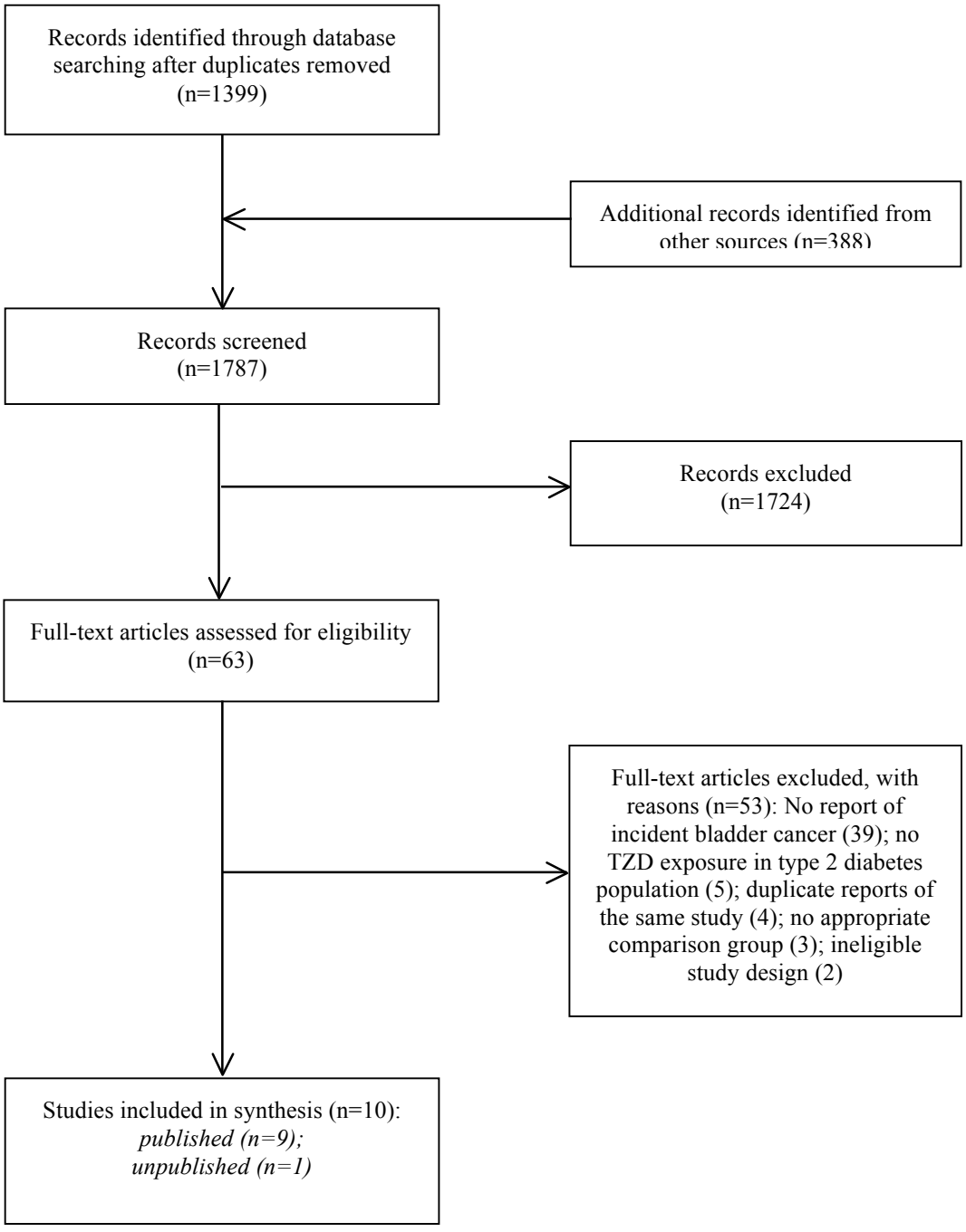


Table 2.1: Characteristics of included studies

RANDOMIZED TRIALS								
Source (Country)	**Study period**	**Mean follow-up time (years)**	**Study sample size**	**Overall Risk of Bias**	**Events in exposed group (N)**	**Exposed group (N)**	**Events in comparison group (N)**	**Comparison group (N)**
Dormandy 2005 (PROactive Study, Multicentre)	2001-2004	2.9	5,238	Unclear	14	2,605	6	2,633
Home 2010 (ADOPT, Multi-Centre)	2000-2006	3.4	4,351	High	2	1,456	8	2,895
Home 2010 (RECORD, Multi-Centre)	2001-2008	5.5	4,447	High	6	2,220	5	2,227
Sanofi-Aventis 2009 (Multi-centre, USA)	2006-2008	n/r (12-week trial,10% LTFU)	386	High	2	256	0	130
COHORT STUDIES								
Source (Country)	**Study period**	**Mean follow-up time (years)**	**Study Sample size**	**Overall Risk of Bias (/8)***	**Events in exposed group (N)**	**Exposed group (N)**	**Events in comparison group (N)**	**Comparison group (N)**
Neumann 2012 (National Health Insurance, France)	2006-2009	2.4 (exposed group)	1,491,060	7	175	155,535	1,841	1,335,525
Lewis 2011 (Kaiser Permanente, Northern California, USA)	1997-2008	3.3 (cases) 6.2 (controls)	193,099	7	90	30,173	791	162,926
Oliveria 2008 (Source not reported, USA)	2000-2004	3.9	191,223	6	n/r	n/r	n/r	n/r
Tseng 2011 (National Health Insurance, Taiwan)	2003-2005	3.0	998,847	6	1	1028	221	112,520
Tseng 2012 (National Health Insurance, Taiwan)	2006-2009	n/r	54,928	6	10	2,545	155	52,383
CASE-CONTROL STUDIES								
Source (Country)	**Study period**	**Mean follow-up time (years)**	**Study sample size**	**Overall Risk of Bias (/8)***	**Events in exposed group (N)**	**Exposed group (N)**	**Events in comparison group (N)**	**Comparison group (N)**
Piccinni 2011 (FDA Adverse Event Reporting System, USA)**	2004-2009	n/a	599,085	4	31	37,841	107	561,244
TABLE FOOTNOTE:	* higher score corresponds to lower risk of bias; ≤5 indicates high risk of bias ** case/non-case study design Abbreviations: n/r, not reported; n/a, not applicable; LTFU, Lost to follow-up							

Table 2.2: Risk of bias assessment

RANDOMIZED CONTROL TRIALS									
Study Name	**Cochrane Risk of Bias Scale**	**Sequence generation**	**Allocation Concealment**	**Blinding of participants, personnel, outcome assessors**	**Incomplete health data**	**Selective outcome reporting**	**Other sources of bias (ex. involvement of industry)**	**Overall Risk of Bias**	
Dormandy 2005	RCT (PROactive)	Unclear	Yes	Yes	Yes	Unclear	Unclear (Industry sponsored)	Unclear	
Kahn 2006	RCT (ADOPT)	Unclear	Yes	Unclear	No	Yes	No (very high attrition rate; Industry sponsored)	High	
Home 2009	RCT (RECORD)	Yes	Yes	Unclear	Yes	Yes	No (differential withdrawls; Industry sponsored)	High	
Sanofi-Aventis 2008 NCT00283049	RCT	Unclear	Unclear	No	Yes	Yes	Unclear (Industry sponsored)	High	
COHORT STUDIES									
Study Name	**Newcastle-Ottawa Scale: Cohort Studies**	**1. Representativeness of exposed cohort**	**2. Representativeness of unexposed cohort**	**3. Ascertainment of exposure**	**4. Demonstrate outcome was not present at study start**	**5. Comparability of cohorts on basis of design and analysis**	**6. Assessment of outcome**	**7. Was follow-up long enough for outcome to occur**	**8. Adequacy of follow-up of cohorts**	**Overall Risk of Bias (/8)**
Neumann 2011	Retrospective Cohort	* (a) truly representative	* (a) same community	* (a) secure record	* (a) yes	* controls for: age, sex, smoking, other glucose-lowering drugs	* (b) record linkage	* (a) Yes (>1 year)	(d) not stated	7
Lewis 2011	Retrospective Cohort	* (a) truly representative	* (a) same community	* (a) secure record	* (a) yes	* controls for: age, sex, smoking (proxy), use of other glucose-lowering drugs	* (b) record linkage	* (a) Yes (>1 year)	(d) not stated	7
Oliveria 2008	Cohort Study	* (a) truly representative	* (a) same community	* (a) secure record	* (a) yes	Controls for: age, sex but not smoking or use of other glucose-lowering drugs	* (a,b) independent assessment and record linkage	* (a) Yes (>1 year)	(d) not stated	6
Tseng 2011	Cohort Study	* (a) truly representative	* (a) same community	* (a) secure record	* (a) yes	Controls for: age, sex, use of other glucose-lowering drugs but not smoking	* (b) record linkage	* (a) Yes (>1 year)	(d) not stated	6
Tseng 2012	Cohort Study	* (a) truly representative	* (a) same community	* (a) secure record	* (a) yes	Controls for: age, sex, use of other glucose-lowering drugs but not smoking	* (b) record linkage	* (a) Yes (>1 year)	(d) not stated	6
CASE-CONTROL STUDIES										
Study Name	**Newcastle-Ottawa Scale: Case-Control**	**1. Adequate case definition**	**2. Representativeness of the cases**	**3. Selection of Controls**	**4. Definition of Controls**	**5. Comparability of cases & controls on basis of design or analysis**	**6. Ascertainment of exposure**	**7. Same method of ascertainment for cases and controls**	**8. Non-response rate**	**Overall Risk of Bias (/8)**
Piccinni 2011	Case/Non-case methodology	(b) record linkage	* (a) consecutive series	* (a) controls from same community	(b) not stated	No adjustment (stratification on sex)	(d) written report	* (a) yes	* (a) yes	4

NOTE: For Cochrane Risk of Bias Scale assessment key see http://hiv.cochrane.org/sites/hiv.cochrane.org/files/uploads/Ch08_Bias.pdf.
For Newcastle Ottawa Scale assessment key see http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp Higher score corresponds to lower risk of bias; ≤5 indicates high risk of bias.

Table 2.3: Reported estimates for exposure comparisons, by cancer site and study design

Study Design	Source (Country)	TZD exposure	Comparison	Risk Estimate	Covariates
Randomized Trial	ADOPT, Kahn 2006	Rosiglitazone (monotherapy)	No TZD use (Metformin or Glibenclamide monotherapy)	RR: 0.50 (0.11, 2.34)*	not applicable
	PROactive Study, Dormandy 2005	Pioglitazone	No TZD use	RR: 2.36 (0.91, 6.13)*	not applicable
	RECORD, Home 2009	Rosiglitazone (+ Sulfonylureas OR Metformin)	No TZD use (Sulfonylurea AND metformin)	RR: 1.20 (0.37, 3.94)*	not applicable
	Sanofi-Aventis 2009	TZD (unspecified) (+ insulin glargine and sulfonylurea or metformin)	No TZD use (Insulin glargine, Metformin and Sulfonylurea)	RR: 2.55 (0.12, 52.70)*	not applicable
Cohort	Neumann 2012	Pioglitazone	No Pioglitazone use	HR:1.22 (1.05-1.43)	Age, sex, use of other glucose-lowering agents
		Rosiglitazone	No Rosiglitazone use	HR:1.08 (0.92 1.26)	
	Lewis 2011	Pioglitazone	No Pioglitazone use	HR 1.2 (0.9, 1.5)	Age, sex, race/ethnicity, smoking status, use of other diabetes medications, newly diagnosed diabetes during followup, duration of diabetes, baseline HbA1C, Congestive heart failure, income, renal function, history of bladder conditions (urinary tract infections, urolithiasis, incontinence and 'other bladder or urethral conditions'), other cancer prior to baseline, time since starting and duration of pioglitazone use.
	Oliveria 2008	TZD (unspecified)	No TZD use	RR: 1.05 (0.71, 1.54)	Age, sex, and selected cancer risk factors: hepatitis virus -B and -C, cirrhosis, alcoholism, polyps, obesity, ulcerative colitis, Crohn's disease, cystic fibrosis, chronic pancreatitis, dermatomyositis, polymyositis, idiopathic deep vein thrombosis, partial gastrectomy, pelvic radiation and schistosomiasis

	Tseng 2011	Pioglitazone or Rosiglitazone	No TZD use	RR: 0.80 (0.34, 1.90)	Age, sex, presence of diabetes, nephropathy, urinary tract diseases, other oral hypoglycemic agents, insulin, hypertension, COPD, stroke, Ischaemic heart disease, peripheral arterial disease, eye disease, dyslipidemia, statin use, Fibrate use, ACE inhibitor/angiotensin receptor blocker, Calcium channel blocker, living region, occupation (surrogate for SES)
	Tseng 2012	Pioglitazone	No Pioglitazone use	HR: 1.305 (0.661-2.576)	Age, Sex, diabetes, nephropathy, urinary tract diseases, other OHA, insulin, hypertension, COPD, stroke, Ischaemic heart disease, peripheral arterial disease, eye disease, dyslipidemia, rosiglitazone, sulfonylurea, meglitinide, metformin, acarabose, insulin, statin fibrate ACE inhibitor/angiotensin receptor blocker, Calcium channel blocker, region of residence, occupation and other (non-bladder) cancer before baseline
Case-Control	Piccinni 2011**	Pioglitazone	No Pioglitazone use	OR: 4.30 (2.82, 6.52)	No adjustments or matching variables reported
TABLE FOOTNOTES:	*Risk estimate calculated from raw (unadjusted) values ** case/non-case study design Abbreviations: thiazolidinedione (TZD), chronic obstructive pulmonary disease (COPD), angiotensin-converting enzyme (ACE), socioeconomic status (SES)				

Figure 2.2: Meta-analysis of cohort studies reporting ever vs. never exposure to pioglitazone in individuals with type 2 diabetes

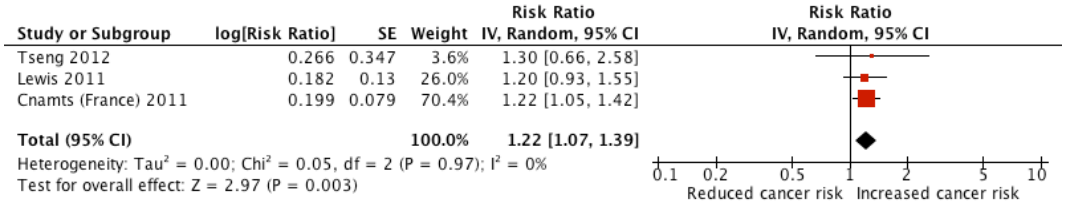


Figure 2.3: Meta-analysis of randomized trials reporting ever vs. never exposure to rosiglitazone in individuals with type 2 diabetes

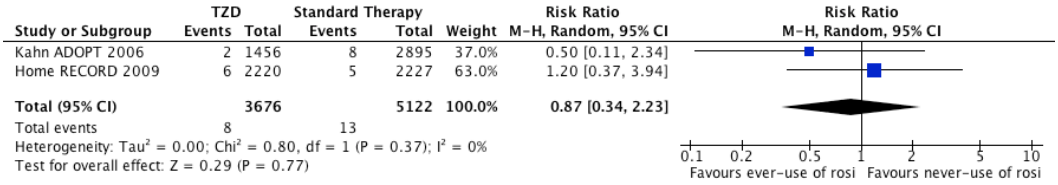
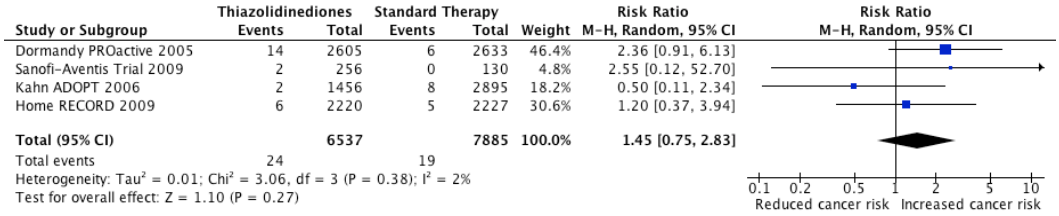
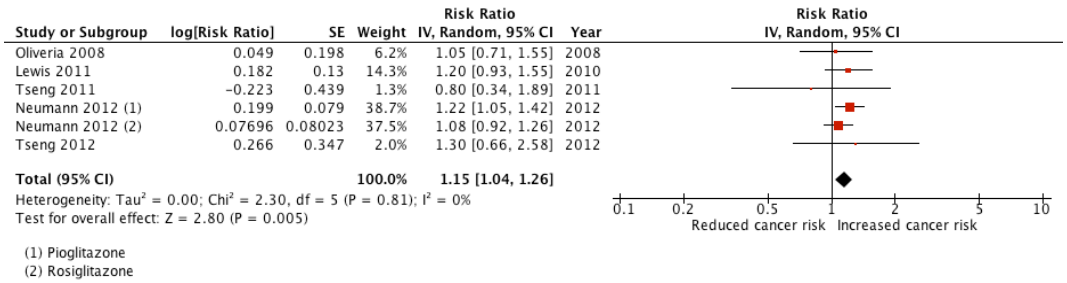


Figure 2.4: Meta-analyses of risk of bladder cancer **a.** randomized trials and **b.** cohort studies reporting ever vs. never exposure to any thiazolidinediones

a.



b.



2.5 References

1. Giovannucci E, Harlan DM, Archer MC et al. Diabetes and cancer: a consensus report. Diabetes Care. 2010;33(7):1674–1685.

2. Larsson SC, Orsini N, Brismar K et al. Diabetes mellitus and risk of bladder cancer: a meta-analysis. Diabetologia. 2006;49(12):2819–2823.

3. Yoshimura R, Matsuyama M, Segawa Y et al. Expression of peroxisome proliferator-activated receptors (PPARs) in human urinary bladder carcinoma and growth inhibition by its agonists. Int J Cancer. 2003;104(5):597–602.

4. Johnson JA, Bowker SL. Intensive glycaemic control and cancer risk in type 2 diabetes: a meta-analysis of major trials. Diabetologia. 2011;54(1):25–31.

5. Belfiore A, Malaguarnera R. Insulin receptor and cancer. Endocr Relat Cancer. 2011;18(4):R125–R147.

6. Kakehi Y, Hirao Y, Kim W-J et al. Bladder Cancer Working Group report. Jpn J Clin Oncol. 2010;40 Suppl 1:i57–64.

7. Dormandy JA, Charbonnel B, Eckland DJA et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005;366(9493):1279–1289.

8. Caisse National d'Assurance Maladie. Risque de cancer de la vessie chez les personnes diabétiques traitées par pioglitazone en France : une étude de cohorte sur les données du SNIIRAM et du PMSI. Saint Denis, France; 2011 [cited 2012 Aug 17]. Available: http://www.afssaps.fr/var/afssaps_site/storage/original/application/b42a6bf9a1b63c3dbec7388d3914687b.pdf

9. Piccinni C, Motola D, Marchesini G et al. Assessing the association of pioglitazone use and bladder cancer through drug adverse event reporting. Diabetes Care. 2011;34(6):1369–1371.

10. Lewis JD, Ferrara A, Peng T et al. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. Diabetes Care. 2011;34(4):916–922.

11. Tseng C-H. Diabetes and risk of bladder cancer: a study using the National Health Insurance database in Taiwan. Diabetologia. 2011;54(8):2009–2015.

12. FDA Drug Safety Communication: Updated drug labels for pioglitazone-

containing medicines. Food and Drug Administration. [cited 2012 Aug 17] Available: http://www.fda.gov/Drugs/DrugSafety/ucm266555.htm

13. European Medicines Agency clarifies opinion on pioglitazone and the risk of bladder cancer. European Medicines Agency. [cited 2012 Aug 17] Available: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/10/WC500116936.pdf

14. Higgins J, Altman D. Assessing Risk of Bias in Included Studies. In: Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews. Chichester UK: John Wiley & Sons, Ltd. 2008.

15. Wells G, Shea B, O'Connell D et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. [cited 2012 Aug 17] Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

16. Higgins J, Altman D. Including Non-Randomized Trials. In: Higgins J, Green S, editors. Cochrane Handbook of Systematic Reviews of Interventions. Chichester, UK: John Wiley & Sons, Ltd. 2008.

17. Higgins J, Altman D. Addressing Reporting Biases. In: Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Chichester, UK: John Wiley & Sons, Ltd. 2008.

18. Home PD, Pocock SJ, Beck-Nielsen H et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009;373(9681):2125–2135.

19. Kahn SE, Haffner SM, Heise MA et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. New Engl J Med. 2006;355(23):2427–2443.

20. Oliveria SA, Koro C, Ulcickas Yood M et al. Cancer incidence among patients treated with antidiabetic therapy. Diabetes & Metabolic Syndrome: Clinical Resarch & Reviews. 2008;2:45–57.

21. Neumann A, Weill A, Ricordeau P, Fagot JP, Alla F, Allemand H. Pioglitazone and risk of bladder cancer among diabetic patients in France: a population-based cohort study. Diabetologia. 2012;55(7):1953-1962.

22. Tseng C-H. Pioglitazone and Bladder Cancer. Diabetes Care. 2012;35(2):278–280.

23. Insulin glargine injection treatment in place of thiazolidinedione (TZD), sulfonylurea, or metformin in triple agent therapy for type 2 diabetes

mellitus (T2DM) subjects with unsatisfactory control. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2012 Aug 17]. Available: http://clinicaltrials.gov/ct2/show/NCT00283049

24. Home PD, Kahn SE, Jones NP et al. Experience of malignancies with oral glucose-lowering drugs in the randomised controlled ADOPT (A Diabetes Outcome Progression Trial) and RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) clinical trials. Diabetologia. 2010;53(9):1838–1845.

25. Giannini S, Serio M, Galli A. Pleiotropic effects of thiazolidinediones: taking a look beyond antidiabetic activity. J Endocrinol Invest. 2004;27(10):982–991.

26. Mansure JJ, Nassim R, Kassouf W. Peroxisome proliferator-activated receptor gamma in bladder cancer: a promising therapeutic target. Cancer Biol Ther. 2009;8(7):6–15.

27. Lubet RA, Fischer SM, Steele VE, Juliana MM, Desmond R, Grubbs CJ. Rosiglitazone, a PPAR gamma agonist: potent promoter of hydroxybutyl(butyl)nitrosamine-induced urinary bladder cancers. Int J Cancer. 2008;123(10):2254–2259.

28. Actos (pioglitazone hydrochloride): full prescribing information. Takeda Pharmaceuticals. [cited 2012 Aug 17]. Available: http://general.takedapharm.com/content/file/pi.pdf?applicationcode=8a9c4571-a123-4477-91de-b9cafe7d07e3&filetypecode=actospi

29. Hillaire-Buys D, Faillie J-L, Montastruc J-L. Pioglitazone and bladder cancer. Lancet. 2011. 29;378(9802):1543–1544.

30. Johnson J, Carstensen B, Witte D, Bowker S, Lipscombe L, Renehan A. Diabetes and Cancer (1): Evaluating the temporal relationship between type 2 diabetes and cancer incidence. Diabetologia. 2012;55(6):1607–1618.

CHAPTER 3. DETECTION BIAS AND OVERESTIMATION OF BLADDER CANCER RISK IN TYPE 2 DIABETES: A MATCHED COHORT STUDY

3.1 Introduction

Studies suggest people with type 2 diabetes are at an increased risk of several types of cancer, including breast, colorectal, pancreatic, endometrial and liver cancers.(1-5) Similarly, meta-analyses of observational studies suggests a statistically significant 37% to 43% increased risk of bladder cancer in those with diabetes.(6)

Epidemiologic evidence also suggests there is an initial period of elevated risk for most solid cancers (colorectal, endometrial, lung, breast, cervical, ovarian, prostate) in the months immediately following a diabetes diagnosis, which is followed by a decline and leveling off of risk after the first year.(7,8) This pattern suggests a potential detection bias surrounding the time of a new diabetes diagnosis, but the influence of time trends and detection bias on the seemingly increased risk of bladder cancer has not been assessed.(1-5) Conceptually, individuals with fewer physician visits may be hypothesized to have a lower likelihood of detection of a pre-symptomatic bladder cancer before diabetes diagnosis, while those with more visits may be more likely to have an incidental bladder cancer found, such as during routine urinalysis. Thus, the risk of bladder cancer diagnosis after diabetes diagnosis may be higher among those with fewer

physician visits (and lower among those with more frequent physician visits): if this is the case, the reported increase in bladder cancer risk may be attributable to detection bias.

With the recent attention to bladder cancer and diabetes, especially with reports of an increased risk associated with pioglitazone (9-12), we must understand temporal trends and the potential influence of detection bias on bladder cancer in individuals with diabetes.(7) Therefore, we examined the time-varying risk of bladder cancer in a large population-based cohort of individuals with a new diagnosis of type-2 diabetes relative to non-diabetic controls, to assess a potential detection bias.

3.2 Methods

Study design

Our study population for this analysis has been previously described.(7) Briefly, we used the British Columbia Linked Health Databases (BCLHD) from British Columbia, Canada, which includes administrative health claims, demographic data and information from the BC Cancer Agency, from April 1st 1996 through March 31st 2006 to identify a retrospective cohort of individuals over the age of 30 years with incident type 2 diabetes (N=185,100). The same number of controls was selected from individuals without diabetes on March 31st 2006, with 1:1 matching on birth year and sex. The date of type 2 diabetes diagnosis was

assigned as the index date for each matched pair. To protect patient confidentiality, our dataset was void of all traceable personal identifiers. Ethics approvals from the University of British Columbia Behavioral Research Ethics Board and the University of Alberta Health Research Ethics Board were obtained.

Type 2 diabetes was identified using the established definition given by the Canadian National Diabetes Surveillance System (13), and defined as the earlier of 1) a hospital admission for diabetes (ICD-9 code 250) or 2) the second of two medical fee-for-service claims coded with ICD-9 code 250 within a 2-year period. Individuals who met this definition before April 1st 1996, and women with gestational diabetes (ICD-9 code 648.8) were excluded.

After exclusion of individuals with any cancer diagnosis in the two years before the index date, we identified incident cases of bladder cancer (ICD-0-3 code C67.X) following the index date. Individuals were censored at the earlier of the end of study (March 31st 2006) or departure from BCLHD (i.e., British Columbia), and the follow-up was terminated at death.

Statistical analyses

We first calculated unadjusted bladder cancer incidence rates during the following time windows after the index date: <1.0, 1.0 to 2.0, 2.0 to 3.0, 3.0 to 10.0 years. We then estimated adjusted time-varying hazard ratios (HRs) for developing bladder cancer during the time windows, using Cox regression with time since the

index date as the time scale and the non-diabetes control cohort as the reference group. All models were adjusted for age, sex, index year and median household income quintiles as an indicator of socioeconomic status.

To explore potential detection bias, we hypothesized that the risk of bladder cancer would differ by the frequency of visits to physicians in the two years prior to the index date. Physician visits in the two years prior to the index date were categorized as: ≤12 visits (low), 13 to 24 visits (medium) and ≥25 visits (high). We tested an interaction term between diabetes status and number of physician visits; finding a statistically significant interaction, we then stratified our incidence rate calculations and regression models by the physician visit categories. To graphically display changes in bladder cancer risk over time, adjusted HRs were calculated and plotted at regular intervals throughout follow-up; we used a lowess curve to smooth the plotted representation of the time-varying bladder cancer risk in each category. Results with $p<0.05$ were interpreted as statistically significant. All analyses were conducted in Stata (version 11SE, StataCorp, College Station, Texas); graphs were created in R.(14)

3.3 Results

Our cohort was comprised of 185,100 individuals with incident type 2 diabetes and 775,398 person-years (PY) of follow-up; and 185,100 matched controls without diabetes and 795,167 PY of follow-up (Table 3.1). Fifty-four percent of

individuals were male and the mean (SD) age at the time of diabetes diagnosis (or index date for controls) was 60.7 (13.5) years. Individuals with incident type 2 diabetes were more likely to have a low socioeconomic status: 23% in the lowest socioeconomic quintile vs. 16 % in the highest quintile, compared with, respectively, 19% and 21% in the non-diabetes cohort. The incident type 2 diabetes and non-diabetes cohorts had an approximately equal median (IQR) duration of cancer free years in the databases before index (4.0 (1.8 to 6.7) vs. 4.1 (1.9 to 6.8), respectively). Follow-up length after index was similar in both cohorts: 3.8 (1.7 to 6.5) years in the diabetes cohort vs. 3.9 (1.8 to 6.6) years in the non-diabetes cohort (Table 3.1).

Incidence of Bladder Cancer

During the entire follow-up period, 603 (0.33%) individuals with incident type 2 diabetes and 568 (0.31%) non-diabetic controls were diagnosed with bladder cancer. Individuals who eventually developed bladder cancer were older at index date (mean (SD): 69.5 (10.0) vs. 60.7 (13.5) years), more often male (81% vs. 54%) and had more physician visits (median (IQR): 22 (12 to 39) vs. 19 (9 to 34)) in the 2 years prior to the index date than those who did not develop bladder cancer (Table 3.1). The overall incidence of bladder cancer over the duration of follow-up was 77.8 (95% CI 71.7 to 84.2) per 100,000 PY for those with diabetes vs. 71.4 (95% CI 65.7 to 77.6) per 100,000 PY for those without. In adjusted analyses, diabetes was significantly associated with an increased risk of bladder cancer: adjusted hazard ratio (HR) 1.13 (95% CI 1.01 to 1.26), p=0.04.

Time Varying Risks of Bladder Cancer

In the first year following index, the incidence rates of bladder cancer in the diabetes and non-diabetes cohorts were 85.3 (95% CI 72.0 to 100.4) and 66.1 (95% CI 54.5 to 79.4) per 100,000 person-years, respectively, giving an adjusted hazard ratio (HR) of 1.30 (95% CI 1.02 to 1.67, p=0.03). Diabetes was not associated with an increased risk of bladder cancer in any subsequent time window (Table 3.2), and the overall risk of bladder cancer, when excluding the first year of follow-up, was 1.08 (95% CI 0.95 to 1.23, p=0.24) (Table 3.2, Figure 3.1).

Potential Detection Bias Related to Medical Visits

The incident type 2 diabetes cohort had a greater number of physician visits in the two years before the index date (i.e., diabetes diagnosis) than the non-diabetes cohort (median (IQR): 23 (13 to 39) vs. 16 (7 to 30)). We observed a statistically significant interaction between diabetes status and the frequency of physician visits in the 2 years before the index date in the time windows of 0 to 1 year (p=0.017) and 1 to 2 years (p=0.012). Therefore, we stratified regression models according to the number of physician visits prior to index date (Table 3.2). In the first year of follow-up, the significantly elevated risk of bladder cancer was confined to those who had the fewest previous physician visits (adjusted HR for ≤12 visits: 2.14; 95% CI 1.29 to 3.55 vs. adjusted HR for 13 to 24 visits: 1.27; 95% CI 0.82 to 1.97 vs. adjusted HR for ≥25 visits: 0.99; 95% CI 0.68 to 1.43; p-

value for trend: 0.018) (Table 3.2). In subsequent time periods, estimates in all physician visit frequency categories approached the null and were not statistically significant (Table 3.2, Figure 3.1).

3.4 Interpretation

Major findings

Overall, we observed a statistically significant 13% relative increase in the risk of developing bladder cancer over a period of up to 10 years after the diagnosis of type 2 diabetes. However, our more detailed analyses suggest the increased risk of bladder cancer occurred in the first year after type 2 diabetes diagnosis, and predominantly among the individuals who previously accessed physician services the least. Indeed, we found no significant increased risk of bladder cancer among those with type 2 diabetes in time periods 2-years and beyond, regardless of controlling for detection bias (i.e., the frequency of previous physician visits).

Evidence for detection bias

There is a growing body of observational studies on the risk of various cancer in people with type 2 diabetes, including an estimated 43% increased risk of bladder cancer among individuals with diabetes of any duration.(6,7,15,16) Consistent with evidence from several other cancers in people with diabetes (7,8), our results show a significantly elevated overall risk of bladder cancer in individuals with type 2 diabetes, that, when split into time windows, shows a highly elevated risk

of bladder cancer in the months immediately following type 2 diabetes diagnosis which declines to approximately the level of the non-diabetes population over time.

Bladder cancer is not routinely screened for during a regular doctor's visit and is often discovered incidentally during routine urinalyses.(17) Approximately one in 10 cases of hematuria are due to an underlying bladder cancer.(18) Individuals who previously visited the doctor infrequently, and thus had less opportunity for investigation of potential symptoms, may be more likely to have an undiagnosed bladder cancer at the time of diabetes diagnosis than those who had more frequent physician contact; this suggests a mechanism for potential detection bias. Similarly, among those with fewer (≤12) physician visits in the two years before diabetes diagnosis, workup at the time of diabetes diagnosis may allow bladder cancer to be detected sooner: the below-the-null "rebound" of bladder cancer risk observed in this group during the second year after diabetes diagnosis (index) suggests cases that would have been detected in year 2 were shifted to the first year, thereby depleting these "susceptible" individuals from the subsequent time point. We observed no difference in bladder cancer risk between diabetes and non-diabetes individuals in the highest physician visit category. In this category, frequent physician visits may be driven by serious and/or multiple health problems; in this group, diabetes status may no longer differentially impact the likelihood of discovering bladder cancer, Alternatively, frequent physician visits may reflect "health-seeking" (i.e., regular exercise, eating a healthy diet and not

smoking); such behaviours may prevent the otherwise potentially elevated bladder cancer risk in the diabetes group.

Study limitations

Despite some strengths, this work has several important limitations. First, we lacked potentially important clinical information, such as smoking (a known risk factor for bladder cancer and thus a potential confounder) or frequency of urinalyses (to further explore our detection bias hypothesis). We did, however, adjust for socioeconomic status, which is correlated with smoking status. Confounding by smoking is unlikely to be time dependent and thus our time-specific findings may not be subject to this limitation. Second, our follow-up period of up to 10 years (median four years) may not have been long enough to capture latent bladder cancer risk, when the estimated latency period may extend up to 30 years.(19) Third, our diagnoses of diabetes were based entirely on claims data, and given the number of individuals with undiagnosed diabetes in the community it is almost certain that there were individuals with diabetes in the control group. Given that the diagnostic workup for a diagnosis of diabetes is associated with a (short term) increased risk of bladder cancer diagnosis, undiagnosed diabetes in the control group would not influence our findings in an important way, as they would not have received this workup. Fourth, we did not examine another "tracer" condition. If our hypotheses are correct, other new diagnoses such as hypothyroidism or chronic obstructive pulmonary disease

(COPD) could also lead to spuriously increased diagnoses of new cancers because of detection bias.

Conclusions and implications

We observed a significantly increased risk of bladder cancer in individuals with newly diagnosed type 2 diabetes, compared to individuals without diabetes; however this increased risk in the type 2 diabetes population was limited to the first year following diabetes diagnosis, and only among individuals with the least (≤12) physician visits in the two years before diabetes diagnosis. Subsequent to the first year following diabetes diagnosis, the risk of bladder cancer was equal to that of individuals without diabetes. This pattern suggests a potential detection bias of bladder cancer in individuals with type 2 diabetes. Studies that fail to account for time since diabetes diagnosis and frequency of physician visits may overestimate the long-term risk of bladder cancer in individuals with type 2 diabetes. Moreover, our findings suggest that associations between diabetes (and possibly other "newly diagnosed" conditions) and risk of other cancers might, at least in part, be a result of detection biases.

Table 3.1: Population characteristics at index

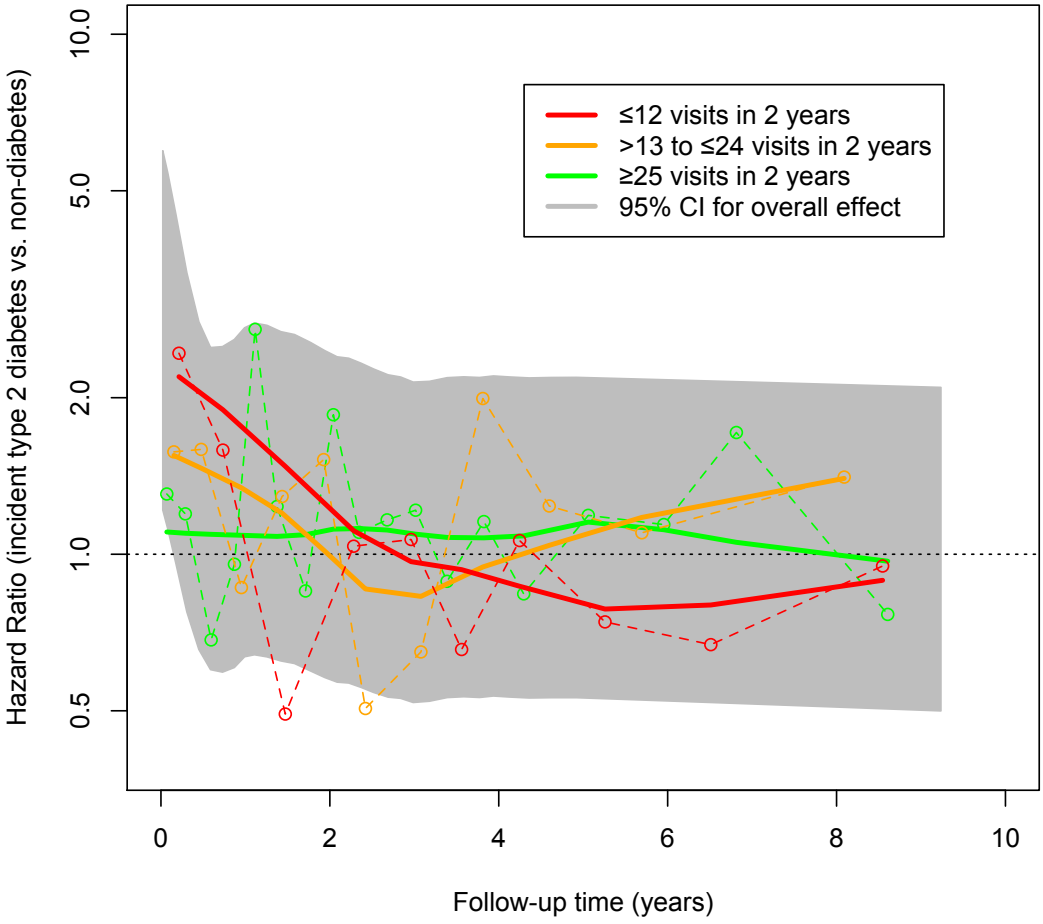
Bladder Cancer	No Diabetes (N=185,100)					Incident Type 2 Diabetes (N=185,100)				
	No (N=184,532)		Yes (N=568)		***Total***	No (N=184,497)		Yes (N=603)		***Total***
	N	% (No DM)	N	% (No DM)	***N (No DM)***	N	% (T2DM)	N	% (T2DM)	***N*** ***% (T2DM)***
Sex										
Women	84,391	46	115	0.06	***84,506 46***	84,401	46	105	0.06	***84,506 46***
Men	100,141	54	453	0.25	***100,594 54***	100,096	54	498	0.27	***100,594 54***
Age (years) at cohort entry										
30-39	12,309	7	2	0.001	***12,311 7***	12,262	7	-	-	***12,262 7***
40-49	30,340	16	17	0.01	***30,357 16***	30,383	16	27	0.02	***30,410 16***
50-59	47,411	26	70	0.04	***47,481 26***	47,469	26	70	0.04	***47,539 26***
60-69	45,258	25	186	0.10	***45,444 25***	45,111	24	214	0.12	***45,325 24***
70-79	34,052	18	207	0.11	***34,259 19***	34,156	18	216	0.12	***34,372 18***
80+	15,162	8	86	0.05	***15,248 8***	15,116	8	76	0.04	***15,192 8***
Mean±SD	60.7±13.5		69.9±10.2		***60.71±13.5***	60.71±13.5		69.1±9.7		***60.7±13.5***
Year (April 1 - March 31) of cohort entry										
Apr 1 1996	17,387	9	113	0.06	***17,500 9***	17,378	9	122	0.07	***17,500 9***
Apr 1 1997	17,304	9	95	0.05	***17,399 9***	17,300	9	99	0.05	***17,399 9***
Apr 1 1998	16,554	9	68	0.04	***16,622 9***	16,544	9	78	0.04	***16,622 9***
Apr 1 1999	17,494	10	73	0.04	***17,567 9***	17,483	9	84	0.05	***17,567 9***
Apr 1 2000	17,727	10	60	0.03	***17,787 10***	17,732	10	55	0.03	***17,787 10***
Apr 1 2001	18,380	10	55	0.03	***18,435 10***	18,387	10	48	0.03	***18,435 10***
Apr 1 2002	19,278	10	39	0.02	***19,317 10***	19,266	10	51	0.03	***19,317 10***
Apr 1 2003	19,516	11	28	0.02	***19,544 11***	19,515	11	29	0.02	***19,544 11***
Apr 1 2004	20,840	11	26	0.01	***20,866 11***	20,838	11	28	0.02	***20,866 11***
Apr 1 2005	20,052	11	11	0.01	***20,063 11***	20,054	11	9	0.01	***20,063 11***
Socio-Economic Status (SES) Quintile										
Q1 (low)	34,868	19	96	0.05	***34,964 19***	42,979	23	152	0.08	***43,131 23***
Q2	34,000	18	114	0.06	***34,114 18***	39,045	21	109	0.06	***39,154 21***
Q3	34,700	19	96	0.05	***34,796 19***	35,051	19	121	0.07	***35,172 19***
Q4	35,784	19	117	0.06	***35,901 19***	32,464	18	105	0.06	***32,569 18***
Q5 (high)	37,930	20	122	0.07	***38,052 21***	29,051	16	98	0.05	***29,149 16***
Missing	7,250	4	23	0.01	***7,273 4***	5,907	3	18	0.01	***5,925 3***
Number of physician visits in 2 years before index										
≤12	77,708	42	197	0.11	***77,905 42***	45,813	24.75	118	0.06	***45,931 25***
13 to 24	47,681	26	150	0.08	***47,831 26***	53,121	28.70	179	0.10	***53,300 29***
≥25	59,143	32	221	0.12	***59,364 32***	85,563	46.23	306	0.17	***85,869 46***
Follow-up years at risk of cancer										
Median	3.95		2.85		***3.95***	3.83		2.52		***3.84***
(IQR)	(1.82-6.59)		(1.36-4.69)		***(1.82-6.58)***	(1.71-6.46)		(1.03-4.45)		***(1.71-6.46)***
Cancer-free years in database before index										
Median	4.12		5.68		***4.13***	4.01		5.79		***4.01***
(IQR)	(1.94-6.77)		(3.68-8.08)		***(1.94-6.78)***	(1.83-6.64)		(3.46-7.92)		***(1.83-6.65)***

Table 3.2: Unadjusted bladder cancer incidence rates in newly diagnosed type 2 diabetes and non-diabetes cohorts and adjusted bladder cancer hazard ratios, by time since diabetes diagnosis and number of physician visits in the 2 years prior to cohort index (type 2 diabetes diagnosis)

	0-1 year since index date			1-2 years since index date			2-3 years since index date			3-10 years since index date		
	#	Crude IR /100,000 PY (95% CI)	Adjusted* HR (95% CI)	#	Crude IR /100,000 PY (95% CI)	Adjusted* HR (95% CI)	#	Crude IR /100,000 PY (95% CI)	Adjusted* HR (95% CI)	#	Crude IR /100,000 PY (95% CI)	Adjusted* HR (95% CI)
≤12 visits												
T2DM	34	80.1 (55.5-112.0)	**2.14 (1.29-3.55)**	7	19.4 (7.8-39.9)	0.44 (0.19-1.00)	20	66.0 (40.3-102.0)	1.04 (0.59-1.81)	57	64.4 (48.7-83.4)	0.84 (0.61-1.16)
Non-DM	27	37.2 (24.5-54.2)	Ref	27	44.1 (29.0-64.1)	Ref	32	62.7 (42.9-88.5)	Ref	111	75.8 (62.4-91.3)	Ref
13-24 visits												
T2DM	46	93.4 (68.4-124.6)	1.27 (0.82-1.97)	33	79.2 (54.5-111.2)	1.33 (0.79-2.26)	21	60.4 (37.4-92.3)	0.64 (0.37-1.11)	79	80.0 (63.4-99.7)	1.32 (0.94-1.85)
Non-DM	35	78.4 (54.6-109.0)	Ref	24	63.0 (40.4-93.7)	Ref	32	99.7 (68.2-140.7)	Ref	59	63.7 (48.5-82.2)	Ref
≥25 visits												
T2DM	65	83.0 (64.0-105.8)	0.99 (0.68-1.43)	63	95.2 (73.1-121.8)	1.46 (0.96-2.20)	55	98.9 (74.5-128.7)	1.25 (0.82-1.91)	123	80.2 (66.7-95.7)	1.07 (0.82-1.39)
Non-DM	52	94.0 (70.2-123.3)	Ref	35	74.1 (51.6-103.1)	Ref	36	89.8 (62.9-124.3)	Ref	98	86.1 (69.9-104.9)	Ref
Overall (categories combined)												
T2DM	145	85.3 (72.0-100.4)	**1.30 (1.02-1.67)**	103	71.5 (58.4-86.7)	1.27 (0.95-1.69)	96	79.5 (64.4-97.1)	1.01 (0.76-1.33)	259	76.0 (67.0-85.9)	1.05 (0.88-1.24)
Non-DM	114	66.1 (54.5-79.4)	Ref	86	58.7 (46.9-72.4)	Ref	100	81.1 (66.0-98.7)	Ref	268	76.0 (67.1-85.6)	Ref

Abbreviations: HR, hazard ratio; IR, incidence rate; PY, person-years; CI, confidence interval; Ref, reference category
Number of incident cases of bladder cancer
* Adjusted for: sex, year of birth, SES, year of cohort entry

Figure 3.1: Risk of bladder cancer by frequency of physician visits 2 years before index. Adjusted Hazard Ratios for each physician visit category (≤12 visits, red; 13 to 24 visits, orange; ≥25 visits, green) calculated at multiple points throughout follow-up, were plotted (hollow circles, connected by dotted line). The time-varying risk of bladder cancer is estimated with the solid trend lines. The 95% confidence interval for the overall (i.e., non-stratified) effect is shaded in grey (trend line for overall risk not shown).



3.5 References

1. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer. 2007;121(4):856–62.

2. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst. 2005;97(22):1679–87.

3. Huxley R, Ansary-Moghaddam A, Berrington de González A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer. 2005;92(11):2076–83.

4. Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia. 2007;50(7):1365–74.

5. Wang C, Wang X, Gong G, Ben Q, Qiu W, Chen Y, et al. Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: a systematic review and meta-analysis of cohort studies. Int J Cancer. 2012;130(7):1639–48.

6. Larsson SC, Orsini N, Brismar K, Wolk A. Diabetes mellitus and risk of bladder cancer: a meta-analysis. Diabetologia. 2006;49(12):2819–23.

7. Johnson JA, Bowker SL, Richardson K, Marra CA. Time-varying incidence of cancer after the onset of type 2 diabetes: evidence of potential detection bias. Diabetologia. 2011;54(9):2263–71.

8. Carstensen B, Witte DR, Friis S. Cancer occurrence in Danish diabetic patients: duration and insulin effects. Diabetologia. 2012;55(4):948–58.

9. Colmers IN, Bowker SL, Majumdar SR, Johnson JA. Pioglitazone and rosiglitazone use and risk of bladder cancer in type 2 diabetes: a systematic review and meta-analysis. Can Med Assoc J. July 03, 2012 [*E-pub ahead of print*]

10. Neumann A, Weill A, Ricordeau P, Fagot JP, Alla F, Allemand H. Pioglitazone and risk of bladder cancer among diabetic patients in France: a population-based cohort study. Diabetologia. 2012;55(7):1953-1962.

11. Lewis JD, Ferrara A, Peng T, Hedderson M, Bilker WB, Quesenberry CP, et al. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. Diabetes Care. 2011;34(4):916–22.

12. Azoulay L, Yin H, Filion KB, Assayag J, Majdan A, Pollak MN, et al. The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study. BMJ. 2012;344:e3645.

13. Responding to the challenge of diabetes in Canada: first report of the national diabetes surveillance system (NDSS). Public Health Association of Canada, Government of Canada. Ottawa, ON; 2003 [cited 2012 Aug 17]. Available: http://www.phac-aspc.gc.ca/ccdpc-cpcmc/ndss-snsd/english/pubs_reports/pdf/WEB_NDSS_English_Report-nocover.pdf

14. R Development Core Team (2008). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available: http://www.R-project.org

15. Renehan AG, Yeh H-C, Johnson JA, Wild SH, Gale EAM, Møller H, et al. Diabetes and cancer (2): evaluating the impact of diabetes on mortality in patients with cancer. Diabetologia. 2012;55(6):1619–32.

16. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. Diabetes Care. 2010;33(7):1674–1785.

17. Logsetty S. Screening for Bladder Cancer. Public Health Agency of Canada. Ottawa, ON; 1993 [cited 2012 Aug 14]. Available: http://www.phac-aspc.gc.ca/publicat/clinic-clinique/pdf/s10c68e.pdf

18. Khadra MH, Pickard RS, Charlton M, Powell PH, Neal DE. A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. J Urol. 2000;163(2):524–7.

19. Kirkali Z, Chan T, Manoharan M, Algaba F, Busch C, Cheng L, et al. Bladder cancer: epidemiology, staging and grading, and diagnosis. Urology. 2005;66(6 Suppl 1):4–34.

CHAPTER 4. GENERAL DISCUSSION AND CONCLUSIONS

4.1 Summary

For this thesis, we conducted two research studies exploring factors that may influence the observed increased risk of bladder cancer in individuals with type 2 diabetes. Given the recent international attention to this association, particularly among individuals using pioglitazone, our research objectives were relevant to this contemporary topic.

The first objective was to summarize and quantify evidence on the risk of bladder cancer in individuals with type 2 diabetes using thiazolidinediones, particularly pioglitazone, relative to diabetic individuals using other glucose-lowering drugs. We observed an increased risk of bladder cancer with use of any thiazolidinedione and an even higher risk among pioglitazone users, but did not observe an increased risk with rosiglitazone alone. Our observation that, at the epidemiologic level, the risk of bladder cancer is increased among pioglitazone users compared to non-users is corroborated by evidence from animal models and proposed cellular mechanisms.(1,2)

Our second objective was to explore potential bias in the detection of bladder cancer in individuals with newly diagnosed type 2 diabetes, relative to individuals without diabetes. Individuals had a significantly increased risk of bladder cancer

shortly following a diagnosis of type 2 diabetes, although we observed no elevated long-term risk of bladder cancer. Further, the risk of bladder cancer was highest among individuals with diabetes who had the fewest number of physician visits before diabetes diagnosis; in fact, the elevated risk of bladder cancer was statistically significant only in this group. Our findings are consistent with emerging studies that observed a highly elevated risks of cancer shortly after type 2 diabetes diagnosis, but a lesser or null risk over the long term.(3,4) As well, a recent study noted an inverse association between the number of physician visits and risk of various cancers.(3) These findings suggest that the elevated risk of bladder cancer from previous cohort studies may be largely attributed to a detection bias among individuals with type 2 diabetes.

4.2 Strengths and Limitations

Type 2 diabetes and bladder cancer are long-term illnesses and both are becoming increasingly prevalent.(5-8) Individuals with type 2 diabetes not only have a higher risk of developing bladder cancer than individuals without diabetes, but are also more likely to die from bladder cancer.(9-11) The public health burden of these diseases is substantial: bladder cancer is estimated to have one of the highest costs of treatment among all cancers, and type 2 diabetes is among the most costly chronic diseases in Canada.(12,13) Exploring factors that influence bladder cancer risk in people with type 2 diabetes can provide clues to effective prevention and management of these chronic diseases.

The first project has several notable strengths. We addressed the timely question of whether individuals with type 2 diabetes have an elevated risk of bladder cancer with pioglitazone use, which has recently been under scrutiny by international drug regulatory bodies.(14-16) We used meta-analytic techniques to summarize evidence from both clinical trials and observational studies. In summarizing data from both study designs in this way, we generated a more complete synthesis of the available evidence on the risk of bladder cancer among pioglitazone users than was previously available. Further, we sought to determine whether the signal for bladder cancer was a class effect of all thiazolidinediones. In addition to summarizing and quantifying estimates from available evidence, our review identified areas for additional research and highlighted key methodological improvements required for pharmacoepidemiologic studies to better assess the potential association between thiazolidinediones, particularly pioglitazone, and bladder cancer.(17)

A key strength of the second project was that we described a bias in bladder cancer detection that was previously unexplored among individuals with type 2 diabetes; specifically, we assessed two key variables: time since type 2 diabetes diagnosis, and frequency of prior physician visits. A major advantage of this study was our population-based administrative dataset from British Columbia, which we used to define a cohort of individuals with newly diagnosed type 2 diabetes and a cohort of individuals without diabetes that provided the baseline population risk of cancer. The benefits of defining our study population this way were recently

highlighted by the international Diabetes and Cancer Research Consortium.(18) Our minimum cancer-free period not only increased the chance that cancers captured during follow-up were truly incident, but also allowed us to capture the number of outpatient or inpatient physician visits before index for each individual. This latter variable allowed us to explore the association between the frequency of physician visits during this two-year period before index and the risk of short-term and long-term bladder cancer diagnosis.

Our studies were nonetheless limited by several factors. In spite of being the fourth most common cancer among men, bladder cancer is a rare outcome, with 7,800 new cases annually in a population of almost 35 million Canadians, and with an estimated latency period between 10 and 30 years(7,19,20) Epidemiologic studies with prospectively collected data, including clinical trials, must therefore use large populations with a long duration of follow-up to reliably capture and predict the risk of bladder cancer. For observational studies, such datasets are largely limited to administrative databases that can be linked to various sources of health information (such as hospital discharges, cancer registries and vital statistics); however administrative datasets are typically void of clinical variables that contain information on key bladder cancer risk factors, such as smoking status and occupational exposure to bladder carcinogens. Thus, both projects were limited by the rarity of bladder cancer, which contributed to reduced precision of the risk estimates. Both projects were limited by the inability (neither at the meta-analytic level nor in the BCLHD dataset) to adjust for important bladder cancer

risk factors (such as smoking status and occupational exposure to aromatic amines). We were also unable, due to absence of relevant information, to explore potential differences in bladder tumor type or severity in the diabetic population compared to the general non-diabetic population.

Our systematic review and meta-analysis was most notably limited by the paucity of evidence on our research question. We could therefore not determine whether the potentially elevated bladder cancer risk observed with pioglitazone use extends to the thiazolidinedione class, although the available evidence suggests it may not be the case. Thiazolidinediones are typically prescribed as second- or third-line treatment options, with thiazolidinedione use in Ontario averaging around 5% of all glucose-lowering drug prescriptions between 1999 and 2009 (21); British Columbia estimates only 3.5 thiazolidinedione users per 1000 individuals.(22)) The relative rarity of thiazolidinedione exposure, compounded with the rarity of bladder cancer, limited the precision of estimates for the risk of bladder cancer with pioglitazone or rosiglitazone use. Our cohort study also had several limitations. Evidence suggests some bladder cancers may require more than 30 years to develop (20), thus, we would not have captured any potentially increased risks occurring after our 10 year follow-up. A recent study from Denmark, where follow-up extended up to 15 years, found no long-term increase in the risk of bladder cancer in individuals with newly diagnosed diabetes, although the authors did observe similar trends in short-term bladder cancer risk.(4) Another important limitation with our dataset is that we were unable to

determine the frequency of physician visits throughout follow-up and could therefore not assess a potential surveillance bias (where more frequent physician visits over follow-up might be associated with an increased risk of bladder cancer diagnosis).

4.3 Implications

Research implications

The summary of evidence on the timely topic of bladder cancer among individuals with type 2 diabetes using pioglitazone has called attention to the need for additional evidence with stronger methodologies. Given the low prevalence of bladder cancer and of pioglitazone use, large studies with a long duration of follow-up will be required to address this research question with sufficient power. Pharmacoepidemiologic studies should ideally include variables on key bladder cancer risk factors (notably age, sex, occupational exposures and smoking status), and, in light of project 2, should use an incident type 2 diabetes cohort and account for health care utilization patterns so to address potential changes in risk over the course of diabetes. International collaboration on this topic are underway (through the international Diabetes and Cancer Research Consortium), where affiliates will contribute data to an international meta-analysis of pioglitazone use and risk of bladder cancer in individuals with type 2 diabetes.

The observed temporal pattern in project 2 suggests a bias in bladder cancer detection among individuals with newly diagnosed type 2 diabetes. Further, bias in the detection of bladder cancer (or symptoms thereof) in the short term might be particularly exaggerated among those with the least number of physician visits before a diagnosis of type 2 diabetes, but might be minimized among those with the most frequent physician visits. Future studies must therefore consider the impact of physician visits on the short-term risk of bladder cancer.

Several factors may further influence the long-term risk of bladder cancer diagnosis. First, the decline in bladder cancer risk may be due to "depletion of susceptibles" – that is, loss of "at-risk" individuals from the diabetes cohort because they had already been diagnosed at an earlier time. This is supported by the fact that bladder cancer risk in the incident diabetes group in the lowest physician visits category falls below the risk of the non-diabetes cohort over the long term; yet when the entire follow-up period is considered, the risk in the lowest physician visits category is equal in the diabetes and the non-diabetes groups. Emerging studies may wish to interpret their results in light of this phenomenon. Second, the frequency of physician visits before diabetes diagnosis may reflect the overall health of individuals, which may influence the risk of bladder cancer diagnosis. It is possible that those with the most physician visits are the sickest individuals and in this state, diabetes status may no longer differentially impact the risk of bladder cancer. In that case, the late rise in bladder cancer risk observed in the intermediate category may represent the true

long-term impact of the metabolic derangements that accompany diabetes on the risk of bladder cancer. Third, and alternatively, the observed bias might be exactly the opposite, where those individuals with the most frequent physician visits represent healthier individuals, who have regular check-ups with their physicians. These individuals may also be more likely to follow other healthy behaviours, such as engaging in regular physical activity, eating a healthy diet, and most importantly in the case of bladder cancer, not smoking. These healthy behaviours may minimize any potential association between type 2 diabetes and bladder cancer. Fourth, the long-term risk of bladder cancer may be influenced by the frequency of physician visits during follow-up, where closer surveillance of individuals with type 2 diabetes may increase the opportunity to detect bladder cancer (a so-called surveillance bias).

Our study on bladder cancer in individuals with type 2 diabetes highlights the importance for epidemiologic studies to consider temporal relationships between diabetes onset and cancer in addition to patterns in health care utilization prior to a diagnosis of diabetes. In continuing to explore the relationship between type 2 diabetes and bladder cancer, future studies should also consider overall health status and health care utilization patterns after diabetes onset.

Projects 1 and 2, although not directly related, may be unified through the idea of a detection bias for bladder cancer among pioglitazone users. Pioglitazone has been observed to reduce platelet aggregation(23-25), which may increase the risk

of hematuria, particularly microscopic hematuria. In turn, the incidental discovery of hematuria among pioglitazone users (but not among users of other glucose-lowering agents) may lead to further investigation, thereby increasing the chance of detecting undiagnosed bladder cancer. This potentially important confounding factor has not been addressed in the literature on pioglitazone use and bladder cancer. Future pharmacoepidemiologic studies should account for potential differences in work-up for bladder cancer between drug groups.

Clinical implications

The association between type 2 diabetes and bladder cancer has been recognized at the epidemiologic level for several years and is now gaining attention at the clinical level, particularly in light of the recent attention to pioglitazone and bladder cancer.(26-28) Some regulatory agencies acted quickly to remove pioglitazone from their markets, while other agencies, including the FDA, EMA and Health Canada, still recognize the benefit of this glucose-control option for many diabetic individuals, with warnings against the prescription of pioglitazone in populations at risk of bladder cancer.(16,27,28) Clinicians are therefore encouraged to carefully select and monitor individuals using pioglitazone; researchers must be aware of potential biases introduced with selective prescription of pioglitazone.

Through our work and the work of others, physicians may become more aware of the increased possibility of discovering undiagnosed cancers, including bladder

cancer, in patients with newly diagnosed type 2 diabetes. Given the worse prognosis for cancer among individuals with type 2 diabetes, our work highlights the importance of regular physician visits for patients with diabetes, to attain appropriate assessment and follow-up for all health concerns.

4.4 Conclusions

In this work, we identified a clear signal for an increased risk of bladder cancer among individuals with type 2 diabetes using pioglitazone and we described a potential bias in the detection of bladder cancer among individuals with newly diagnosed type 2 diabetes. This work contributes to our understanding of risk factors for bladder cancer among individuals with type 2 diabetes and thereby identifies areas for improvement of clinical practice as well research methods. With a better understanding of factors that influence the association between type 2 diabetes and bladder cancer, we can identify ways to prevent the human and public health burden of these two chronic and costly diseases.

4.5 References

1. Rochester MA, Patel N, Turney BW, et al. The type 1 insulin-like growth factor receptor is over-expressed in bladder cancer. Br J Urol Int. 2007;100(6):1396–1401.

2. Actos: Scientific Discussion. European Public Assessment Report. London, England: European Medicines Agency; 2006 [cited 2012 Aug 17]. Available: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000285/WC500021381.pdf

3. Johnson JA, Bowker SL, Richardson K, Marra CA. Time-varying incidence of cancer after the onset of type 2 diabetes: evidence of potential detection bias. Diabetologia. 2011;54(9):2263-2271.

4. Carstensen B, Witte DR, Friis S. Cancer occurrence in Danish diabetic patients: duration and insulin effects. Diabetologia. 2011;55(4):948-958.

5. An economic tsunami: the cost of diabetes in Canada. Toronto, ON: Canadian Diabetes Association; 2009 [cited 2012 Aug 17]. Available: http://scholar.google.com/scholar?q=related:cpaXKDZWR78J:scholar.google.com/&hl=en&num=30&as_sdt=0,5

6. Avritscher E, Cooksley C, Grossman H. Clinical model of lifetime cost of treating bladder cancer and associated complications. Urology. 2006; 68:549-553.

7. Canadian Cancer Society's Steering Committee on Cancer Statistics. Canadian Cancer Statistics 2012. Toronto, ON: Canadian Cancer Society; 2012.

8. Diabetes in Canada: report from the National Diabetes Surveillance System. Ottawa, ON: Public Health Association of Canada; 2009. [cited 2012 Aug 17]. Available: http://www.phac-aspc.gc.ca/publicat/2009/ndssdic-snsddac-09/index-eng.php

9. Tseng C-H, Chong C-K, Tseng C-P, Chan T-T. Age-related risk of mortality from bladder cancer in diabetic patients: a 12-year follow-up of a national cohort in Taiwan. Ann Med. 2009;41(5):371–379.

10. Verlato G, Zoppini G, Bonora E, Muggeo M. Mortality from site-specific malignancies in type 2 diabetic patients from Verona. Diabetes Care. 2003;26(4):1047–1051.

11. Currie CJ, Poole CD, Jenkins-Jones S, Gale EAM, Johnson JA, Morgan CL. Mortality After incident cancer in people with and without type 2

diabetes: impact of metformin on survival. Diabetes Care. 2012;35(2):299–304.

12. Logsetty S. Screening for Bladder Cancer. Public Health Association of Canada. Ottawa, ON; 1993 [cited 2012 Aug 17]. Available: http://www.phac-aspc.gc.ca/publicat/clinic-clinique/pdf/s10c68e.pdf

13. Patra J, Popova S, Rehm J, Bondy S, Giesbrecht RFN. Economic cost of chronic disease in Canada. Ontario Chronic Disease Prevention Alliance and the Ontario Public Health Association; 2007 [cited 2012 Aug 17]. Available: http://www.ocdpa.on.ca/OCDPA/docs/OCDPA_EconomicCosts.pdf

14. Drug safety communication: Ongoing safety review of Actos (pioglitazone) and potential increased risk of bladder cancer after two years exposure. United States Food and Drug Administration. Silver Spring, MD; 2010 [cited 2012 Aug 17]. Available: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm226257.htm

15. Update on ongoing review of pioglitazone-containing medicines. European Medicines Agency. London, England; 2011. [cited 2012 Aug 17]. Available: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/06/news_detail_001275.jsp&mid=WC0b01ac058004d5c1&murl=menus/news_and_events/news_and_events.jsp&jsenabled=true

16. Health Canada reviewing diabetes drug pioglitazone (Actos) and potential risk of bladder cancer. Health Canada, Government of Canada. Ottawa, ON; 2011 [cited 2012 Aug 17]. Available: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2011/2011_79-eng.php

17. Colmers IN, Bowker SL, Majumdar SR, Johnson JA. Pioglitazone and rosiglitazone use and risk of bladder cancer in type 2 diabetes: a systematic review and meta-analysis. Can Med Assn J. (*in press*)

18. J Johnson JA, Carstensen B, Witte D, et al. Diabetes and cancer (1): evaluating the temporal relationship between type 2 diabetes and cancer incidence. Diabetologia. 2012;55(6):1607–1618.

19. Friedman GD, Carroll PR, Cattolica EV, Hiatt RA. Can hematuria be a predictor as well as a symptom or sign of bladder cancer? Cancer Epidemiol Biomarkers Prev. 1996;5(12):993–996.

20. Kirkali Z, Chan T, Manoharan M, et al. Bladder cancer: epidemiology, staging and grading, and diagnosis. Urology. 2005;66(6 Suppl 1):4–34.

21. Current Utilization of Second- and Third-Line Therapies in Patients with

Type 2 Diabetes. Canadian Agency for Drugs and Technologies in Health (CADTH). [cited 2012 Aug 17]. 2010. Available from: http://cadth-acmts.ca/media/pdf/C1110_Current_Practice_Report_final.pdf

22. Morrow RL, Carney G, Wright JM, Bassett K, Sutherland J, Dormuth CR. Impact of rosiglitazone meta-analysis on use of glucose-lowering medications. Open Med. 2010;4(1):e50–59.

23. Li D, Chen K, Sinha N, et al. The effects of PPAR-gamma ligand pioglitazone on platelet aggregation and arterial thrombus formation. Cardiovasc Res. 2005;1;65(4):907–912.

24. Borchert M, Schöndorf T, Lübben G, Forst T, Pfützner A. Review of the pleiotropic effects of peroxisome proliferator-activated receptor gamma agonists on platelet function. Diabetes Technol Ther. 2007;9(5):410–420.

25. Mongan J, Mieszczanska HZ, Smith BH, Messing SP, Phipps RP, Francis CW. Pioglitazone inhibits platelet function and potentiates the effects of aspirin: a prospective observation study. Thromb Res. 2012;129(6):760–764.

26. Larsson SC, Orsini N, Brismar K, Wolk A. Diabetes mellitus and risk of bladder cancer: a meta-analysis. Diabetologia. 2006;49(12):2819–2823.

27. Updated drug labels for pioglitazone-containing medicines. United States Food and Drug Administration. Silver Spring, MD; 2011 [cited 2012 Aug 17]. Available: http://www.fda.gov/Drugs/DrugSafety/ucm266555.htm

28. European Medicines Agency clarifies opinion on pioglitazone and the risk of bladder cancer. European Medicines Agency. London, England; 2011 [cited 2012 Aug 17]. Available: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/10/WC500116936.pdf

APPENDIX A

Sample search strategy (MEDLINE)

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present

1. thiazoles/ or thiazolidinediones/
2. rosiglitazone.mp.
3. pioglitazone.mp.
4. troglitazone.mp.
5. (avandia or actos or rozulin).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
6. glitazone.mp.
7. or/1-6
8. diabetes mellitus/ or exp diabetes mellitus, type 2/ or donohue syndrome/
9. ((diabet* or DM) adj5 ("type 2" or "type ii" or matur* onset or late onset)).mp.
10. T2DM.ti,ab.
11. (gestation* or pregnan*).ti.
12. or/8-10
13. 12 not 11
14. exp Neoplasms/

15. (cancer* or malignan* or carcino* or neoplas* or tumor* or tumour* or metasta*).mp.

16. (melanoma* or sarcoma* or adenoma* or adenosarcoma* or adenocarcinoma* or carcinosarcoma* or chondrosarcoma* or fibrosarcoma* or dermatofibrosarcoma* or neurofibrosarcoma* or hemangiosarcoma* or leiomyosarcoma* or liposarcoma* or myosarcoma* or rhabdomyosarcoma* or myxosarcoma* or osteosarcoma* or lymphoma*).mp.

17. or/14-16

18. (necrosis or TNF).ti.

19. 17 not 18

20. 7 and 13 and 19

21. limit 20 to (comment or editorial or news or newspaper article or letter)

22. 20 not 21