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Antidiabetic Agents and Cancer Outcomes: Are There Differences Between Agents?

by

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Abstract

There is substantial evidence of the elevated risk of cancer among individuals with type 2 diabetes. Very little is known, however, about the role that antidiabetic therapies play in this relationship. The objective of this program of research was to examine whether there is a therapeutic risk associated with antidiabetic therapies that increase circulating insulin levels, such as sulfonylureas and exogenous insulin, or a therapeutic benefit associated with antidiabetic therapies that reduce insulin resistance, such as metformin and the glitazones. This objective was achieved through four related population-based cohort studies using the administrative databases from Saskatchewan Health. The first study looked at the effect of the older antidiabetic therapies metformin and sulfonylureas on cancer mortality. The focus of the second study was to explore more closely the effect of metformin and sulfonylurea by using a time-varying Cox regression to define drug exposures. The third study looked more closely at the effect of exogenous insulin therapy and cancer mortality, and the last study focused on the more recently available antidiabetic therapy the glitazones and cancer mortality.

We found that individuals with type 2 diabetes exposed to sulfonylurea monotherapy had a significantly increased risk of cancer-related mortality, compared to patients exposed to metformin. We also observed a dose-response gradient with exogenous insulin therapy and cancer mortality, whereby individuals exposed to higher levels of insulin had a higher risk of cancer mortality. In the last study, we found that the newer class of antidiabetic therapies, the glitazones, were associated with a decreased risk of cancer mortality.

These finding add further support that antidiabetic therapies may play a moderating role in the relationship between type 2 diabetes and cancer outcomes. However, it is unclear whether the increased risk of cancer mortality we observed was related to a toxic effect of sulfonylureas and exogenous insulin or a protective effect of metformin and glitazones, or due to some unmeasured effect related to both choice of drug therapy and cancer risk. Future research should incorporate a non-diabetes control cohort for comparison and examine the more proximal outcome measure cancer incidence.

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CHAPTER 1: INTRODUCTIOIN

1.1 Statement of the Problem

1.1.1 Type 2 Diabetes and Cancer

The public health burden of type 2 diabetes in Canada is substantial. Diabetes is a chronic disease that affects approximately 7.6% of Canadians aged 20 years and older (approximately 1.9 million people), with type 2 diabetes accounting for 90% to 95% of all diagnosed cases of diabetes.[1] However, the overall prevalence of diabetes may in fact be much higher than 7.6%, since it is estimated that approximately 33% of all cases of diabetes are undiagnosed in Canada.[2,3] By 2011, the number of Canadians with diagnosed diabetes is forecasted to be about 2.6 million; this represents an increase by about 33% since 2006.[4] The majority of the public health burden attributed to diabetes is a result of the morbidity and mortality related to microvascular (i.e. retinopathy, neuropathy, and nephropathy) and macrovascular (i.e. cardiovascular disease) complications in this patient population. In 2005-2006, among adults aged 20 years and older, overall death rates were twice as high in individuals with diabetes compared to individuals without diabetes.[4]

Similarly, cancer is also a chronic disease that places a considerable burden on the Canadian health care system. In 2005, the overall prevalence of cancer in the Canadian population was 2.2%.[5] The most prevalent cancer site among men is the prostate, followed by colorectal, bladder, and lung cancer.[5] Breast cancer is the most common site in women, which is also followed by colorectal, uterine, and lung cancer.[5] A recent increase in the number of incident cancer cases and deaths is a direct result of a growing and aging population in Canada.[5]

There is substantial evidence of an increased risk of cancer among individuals with type 2 diabetes. The association appears to be linked through the metabolic syndrome. Both insulin resistance and beta-cell dysfunction (insulin

secretory defect) play a role in the transition from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT) and then to type 2 diabetes.[6] The metabolic syndrome is present in almost one half of older individuals and may be associated with dyslipidemia, hypertension, insulin resistance/ hyperinsulinemia, and adiposity.[7] The resulting clinical syndrome is represented by obesity, diabetes and cardiovascular disease.

An understanding and extension of the metabolic syndrome suggest the relationship between type 2 diabetes and cancer is also biologically plausible. Insulin is a growth-promoting hormone with mitogenic effects.[8] Several animal studies, complemented by case studies in humans, have demonstrated the critical role of insulin-like growth factor (IGF) in all stages of mammalian growth.[9] IGF binding protein-1 (IGF-1) is suppressed by high insulin levels, such as in hyperinsulinemia, and this increases the levels of bioavailable IGF-1.[10] As such, it has been proposed that hyperinsulinemia combined with insulin resistance promotes carcinogenesis.[11-19] In fact, hyperinsulinemia may underlie the associations of several risk factors for cancer, such as high waist circumference, visceral fat, waist-to-hip ratio, body mass index (BMI), sedentary lifestyle, and energy intake.[20,21] Several recent epidemiologic studies have identified associations between diabetes and specific forms of cancer in various populations.

Overall Cancer Mortality

IGT has been identified as an independent predictor for cancer mortality, after adjusting for age, sex, race, education, smoking, alcohol intake, physical activity, BMI, systolic blood pressure, and high-density lipoprotein cholesterol.[22] Another study observed an increased risk of overall cancer mortality for male and female diabetic patients, compared to non-diabetic patients.[23] More recently Coughlin et al confirmed these findings, and concluded that diabetes was an independent predictor of cancer mortality of the colon, pancreas, and breast in women, and of the liver and bladder in men.[24] Interestingly, their findings were not explained by a high BMI. Larsson et al also found that diabetes was associated with a significantly increased risk of colorectal cancer mortality.[25]

Breast Cancer

In the Nurses' Health Study, women with self-reported diabetes had a small but significantly elevated risk of breast cancer compared with women without diabetes. This finding was independent of age, obesity, family history of breast cancer, history of benign breast disease, reproductive factors, physical activity, and alcohol consumption.[26] The data from the Nurses' Health Study provide the largest population with the longest follow-up in assessing the association between diabetes and breast cancer. A meta-analysis of 5 case-control studies and 15 cohort studies confirmed that diabetes was associated with an increased risk of breast cancer (summary RR: 1.20; 95% CI: 1.12-1.28).[27]

Endometrial Cancer

A recent meta-analysis looked at the association between diabetes (largely type 2) and risk of endometrial cancer.[28] The analysis included 16 case-control and 3 cohort studies, with over 96,000 participants and nearly 7,600 cases of endometrial cancer. The results support a strong relationship between diabetes and risk of endometrial cancer (summary RR: 2.10; 95% CI: 1.75-2.53).[28] In their conclusions, the authors acknowledge that future studies need to examine the role of different antidiabetic therapies when assessing this association.

Pancreatic Cancer

The positive association between diabetes and pancreatic cancer has been consistently observed in numerous studies. Huxley et al performed a meta-analysis looking at type 2 diabetes and pancreatic cancer.[29] The authors included 36 studies (17 case-control and 19 cohort studies) from 1966 to 2005, with information on over 9,000 people with pancreatic cancer. Their results support a strong association between type 2 diabetes and pancreatic cancer (summary OR: 1.82; 95% CI: 1.66-1.89).

Colorectal Cancer

A meta-analysis of diabetes and the risk of colorectal cancer included 15 studies (6 case-control and 9 cohort studies), with nearly 2,600,000 participants.[25] The authors found that diabetes was associated with an increased risk of colorectal cancer, compared to individuals without diabetes (summary RR: 1.30; 95% CI: 1.20-1.40).[25] Importantly, a positive association between diabetes and risk of colorectal cancer remained when only including studies that controlled for two potentially important confounders, physical activity and BMI.[25]

Bladder Cancer

A meta-analysis evaluating the association between diabetes and the risk of bladder cancer included 16 studies (7 case-control studies, 3 cohort studies, and 6 cohort studies of patients hospitalized with type 2 diabetes). Studies of type 1 diabetes were not included. Diabetes was associated with a modestly increased risk of bladder cancer, compared with no diabetes (summary RR: 1.24; 95% CI: 1.08-1.42).[30]

Prostate Cancer

In contrast to other types of cancer, there appears to be an inverse relationship between diabetes and prostate cancer. This inverse association may be explained by the cancer-promoting role of endogenous testosterone, which is lower in people with type 2 diabetes.[31] Bonovas et al conducted a meta-analysis of 14 studies, and reported a negative association of diabetes and prostate cancer, in both random effects and fixed effects models (summary RR: 0.91; 95% CI: 0.88-0.94).[32] A more recent meta-analysis included 19 studies, published between 1971 and 2005, observing a statistically significant decreased risk of prostate cancer associated with diabetes (summary RR:0.84; 95% CI: 0.76-0.93).[33]

1.1.2 Antidiabetic Agents and Cancer Outcomes

Antidiabetic Agents

It is common for patients to start drug therapy shortly after a diagnosis of type 2 diabetes (i.e. within 6 months). While the guidelines still emphasize lifestyle and behaviour modification, the treatment goal is to achieve hemoglobin A1c levels of <7.0%.[34-36] Lowering A1c levels or below or around 7.0% has been shown to reduce microvascular and neuropathic complications of type 2 diabetes.[35]

There are several oral antidiabetic agents currently used in the pharmacologic management of type 2 diabetes, including metformin, sulfonylureas, and the glitazones. In addition to these oral antidiabetic agents, is exogenous insulin, which is often added on to the oral therapy regimen in patients with type 2 diabetes. These antidiabetic agents act by either reducing insulin resistance or directly increase circulating insulin levels in the body. Metformin is the most commonly prescribed drug to treat diabetes in Canada and around the world, and is the initial recommended treatment for diabetes according to national and international guidelines.[34,37] Metformin acts to decrease insulin resistance in the body, and thus, it is often referred to as an insulin sensitizer. The glitazones, also known as thizolidinediones (TZDs), are a newer class of oral antidiabetic therapies that became widely available in Canada in 2000, and are approved for use as second line therapy in combination with, or in patients intolerant to, metformin.[38] Similar to metformin, the glitazones act to reduce insulin resistance by improving insulin sensitivity in the peripheral tissues.[39] On the other hand, sulfonylureas and exogenous insulin therapy act to increase circulating insulin levels in the body.

Metformin and Cancer Outcomes

There are several cellular and animal models that suggest a metformin-mediated reduction in insulin resistance is associated with a reduction in the risk

of tumor development.[40-43] The cellular mechanism of action of metformin is to decrease insulin resistance by activating AMP-activated protein kinase. This results in insulin-mediated glucose uptake into the cell (i.e., its intended antidiabetic action). Activation of AMPK also increases concentrations of LKB1, which is known to be a potent tumour suppressor.[44] This may be the mechanism responsible for the proposed association between metformin use and lower risk of cancer in patients with type 2 diabetes.

Very few epidemiologic studies have examined the effect of metformin on cancer outcomes. In a case-control study, Evans et al observed a 23% reduced risk of cancer in patients with type 2 diabetes taking metformin compared to sulfonylureas.[45] Similarly, another case-control study found that metformin use was associated with a significantly reduced risk of pancreatic cancer in diabetic patients, compared to those not taking metformin.[46] Interestingly, the potential antineoplastic effects of metformin have also sparked interest for its potential use as adjuvant therapy in breast cancer patients.[47,48]

Glitazones and Cancer Outcomes

The glitazones are peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists that activate PPAR-γ receptors in the body, and reduce insulin resistance by improving insulin sensitivity in the peripheral tissues.[39] Thus, similar to metformin, the glitazones are thought to reduce the risk of tumour development. The glitazones and PPAR signaling are thought to play a role in the regulation of cancer cell growth.[49] Specifically, PPAR agonists have been shown to inhibit cell growth by inhibiting microtubulin assembly and tubulin polymerization in the cell.[50-52]

Consistent with the proposed biologic mechanism, recent epidemiologic studies examining the effect of glitazones have observed a reduced risk of cancer outcomes.[53-56] Only one study observed a positive association between rosiglitazone and cancer, although this was simply a cross-sectional association.[57]

Interestingly, there is only one large randomized clinical trial in patients with type 2 diabetes that has evaluated cancer risk as a secondary outcome measure.[58] In this study, patients were randomized to pioglitazone or placebo, which was added to their ongoing antidiabetic therapies. The authors concluded there was no difference in the risk of cancer between the two groups.[59,60] However, this comparison of pioglitazone versus placebo may have been confounded by use of other antidiabetic agents that have also been independently associated with cancer outcomes. This draws attention to the need of considering concurrent antidiabetic therapies, in establishing the relative effect of different antidiabetic therapies on cancer outcomes.

Sulfonylureas and Insulin and Cancer Outcomes

On the other hand, sulfonylureas and exogenous insulin are drugs used in type 2 diabetes which increase circulating insulin levels in the body, and as such, they are thought to accelerate tumour growth.[61,62] Two recent epidemiologic studies have explored the association between exogenous insulin therapy and colorectal cancer. Both studies found that chronic insulin therapy in type 2 diabetes was associated with a significantly increased risk of colorectal cancer.[63,64] Monami et al conducted a matched case-control study to examine the incidence of cancer in patients with type 2 diabetes treated with different sulfonylureas.[65] The authors found that use of glibenclamide for greater than 36 months was associated with a significantly increased risk of malignancies.[65] These authors also conducted a retrospective cohort study looking at insulin secretagogues and exogenous insulin therapy and cancer mortality. They found that both drugs were associated with an increased risk of cancer mortality, after adjusting for multiple confounders.[66]

1.2 Summary

In summary, IGT and type 2 diabetes are clearly associated with cancer, likely due to a common role of insulin resistance. Despite the growing evidence of this association, there are few epidemiologic studies specifically examining the

role of antidiabetic therapies in the relationship between type 2 diabetes and cancer outcomes. It is important when evaluating this relationship to compare the relative harm or benefit of the various antidiabetic therapies to one another.

1.3 Objectives

The objective of this program of research was to evaluate the effect of antidiabetic therapies on cancer mortality in patients with type 2 diabetes. We sought to determine whether antidiabetic agents that reduce insulin resistance, such as metformin and the glitazones, would have a beneficial effect on cancer mortality relative to antidiabetic agents that directly increase circulating insulin levels in the body, such as exogenous insulin and sulfonylureas. Another objective was to explore an advanced survival analysis method that uses time-varying methodology to define drug exposures in order to obtain more precise estimates of effect.

1.4 Program of Research

This program of research consisted of four papers to address the study objectives. We conducted four population-based retrospective cohort studies, using the administrative databases of Saskatchewan Health. Three different datafiles were used for the purposes of these analyses: the health registration file, the outpatient prescription drug file, and the vital statistics file. All of these datafiles are linkable on personal health number.

The first study (Chapter 2) focused on the older antidiabetic agents metformin and sulfonylureas and cancer mortality in type 2 diabetes. The analyses used a time-fixed Cox regression to define drug exposures. The second study (Chapter 3) looked more closely at the effect of metformin and sulfonylurea, and improved on a key limitation from the first study, by using a time-varying Cox regression analysis to define drug exposures. By using a time-varying approach we were able to obtain more precise estimates of effect and assess a dose-response gradient for insulin exposure. The third study (Chapter 4) specifically

examined the effect of exogenous insulin therapy and used a time-varying Cox regression analysis to estimate the hazard ratio of cancer mortality. In the final study (Chapter 5) we focused on the newer class of drugs, the glitazones, and cancer mortality.

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CHAPTER 2: INCREASED CANCER-RELATED MORTALITY FOR PATIENTS WITH TYPE 2 DIABETES WHO USE SULFONYLUREAS OR INSULIN*

2.1 Introduction

A number of epidemiologic studies have identified an increased risk of developing cancer in people with type-2 diabetes.[1-14] The association appears to be mediated through the metabolic syndrome (also known as the insulin resistance syndrome). The metabolic syndrome is present in almost one half of all older individuals and is a condition associated with hyperinsulinemia, insulin resistance and a predilection to type 2 diabetes mellitus.[15]

There is also evidence that impaired glucose tolerance and insulin resistance may lead to an increased risk of cancer.[16] Insulin is a growth-promoting hormone with mitogenic effects.[17,18] Several animal studies, complemented by case studies in humans, have demonstrated the critical role of insulin-like growth factor in all stages of mammalian growth.[19] As such, it has been suggested that hyperinsulinemia combined with insulin resistance might promote carcinogenesis.[16,20-23]

Despite the recognition of the potential link between type 2 diabetes and cancer, very little is known about the role that antidiabetic therapies might have on this relationship. This is particularly noteworthy since there are treatments for diabetes that increase circulating insulin levels (e.g., sulfonylureas and exogenous insulin) as well as treatments that reduce insulin resistance (e.g., metformin and glitazones). Indeed, some cellular and animal models suggest that a metformin-mediated reduction in insulin resistance is associated with a reduction in the risk of tumor development.[24,25] Furthermore, Evans et al, using a case-control design, recently observed a 23% reduced risk of cancer in patients with type 2 diabetes taking metformin compared to sulfonylureas.[26]

A version of this chapter has been published. Bowker 2006. Diabetes Care. 29: 254-8.

Given the aforementioned epidemiologic links between cancer and diabetes and the presence of a biologically plausible mechanism whereby metformin might reduce the risk of cancer in people with type-2 diabetes, we undertook the present observational study to explore the association between antidiabetic therapies and cancer-related mortality in patients with type-2 diabetes. We hypothesized that people with type 2 diabetes exposed to sulfonylureas and exogenous insulin would have an increased risk of cancer-related mortality compared to people with type 2 diabetes who were exposed to therapies which are known to decrease circulating insulin levels (i.e. metformin).

2.2 Methods

Study Design

This was a population-based retrospective cohort study, using the administrative databases of Saskatchewan Health. These databases include information on 99% of residents of the province of Saskatchewan (population approximately 1 million).[27,28] Individuals not covered by Saskatchewan Health include those with federally-funded health care, such as members of the Royal Canadian Mounted Police and Canadian Forces.[27] About 90% of the covered population is eligible for prescription drug benefits. Those ineligible include registered Indians who receive prescription benefits through a federal program. Data from three different data files were used in this study: the health registration file, the outpatient prescription drug file, and vital statistics. These data files are linkable based on personal health numbers and provide demographic information, prescription drug usage, and diagnostic codes for cause of death, respectively.

We identified new users of metformin or sulfonylurea from January 1, 1991 – December 31, 1996 using the computerized Saskatchewan Prescription Drug Plan database. We included patients if they: 1) were new users of oral antidiabetic drugs, 2) were registered and eligible for prescription drug benefits during the study period, 3) were at least 30 years old on the index date (i.e. date of the first claim for an oral antidiabetic drug in the index period), and 4) had

continuous drug coverage for at least 1 year prior to the index date. New users of oral antidiabetic drugs and insulin were identified as patients who had a prescription claim for a sulfonylurea, metformin, or insulin during the index period of January 1, 1991 – December 31, 1996 and no prescription claims for any antidiabetic agent for one year prior to the index date. Patients were excluded if they: 1) had gestational diabetes, or 2) were new users of oral antidiabetic drugs who had less than a one year supply of drug therapy dispensed. To ensure ongoing drug exposure, we also excluded subjects who had less than 1 year of drug exposure following the index date.

Subjects were grouped according to their antidiabetic drug use as exposed to sulfonylureas alone or to metformin. The latter group consisted of metformin monotherapy users and people who were exposed to combination therapy with sulfonylurea and metformin at some point; this included all patterns of addition of sulfonylurea to metformin and vice versa. Patients in either inception cohort who had insulin added to their oral therapy regimens were identified, and insulin use was entered as a covariate into our multivariate models. All study subjects were followed prospectively from their index date until death, termination of coverage (e.g. departure from the province), or December 31, 1999, providing a maximum follow-up of 9 years.

The primary outcome for this study was cancer-related mortality. Cause of death was ascertained through the computerized vital statistics file of Saskatchewan Health.[27] The agreement between cancer registry and hospital charts or death registrations in Saskatchewan databases has been previously reported as excellent (kappa: 0.93; 95% CI: 0.89 – 0.97), with 91% of those with cancer having the same neoplasm recorded in their chart or death registration as in the registry.[29] Furthermore, the databases of Saskatchewan Health have, in general, been widely recognized for their comprehensiveness and quality.[27]

Statistical Analysis

Descriptive analyses were stratified by drug exposure group. Comparisons between groups were evaluated using univariate analysis of variance (ANOVA)

for continuous variables and Chi square tests for categorical variables; all tests of statistical significance were two-sided. Cox proportional hazard models were then used to evaluate the relationship between drug exposure (metformin or sulfonylurea cohorts) and time to first event (cancer-related mortality). In all Cox models, the metformin cohort served as the reference group. In multivariate Cox models, the following potential confounding variables were included: age, sex, insulin use, and the Chronic Disease Score (CDS). The CDS uses pharmacy dispensation information for specific drug classes to estimate the burden of comorbidities, and has proven valid in predicting hospitalization, health resource utilization, and mortality.[30] The CDS is the sum of all chronic diseases identified from drug therapies over the full follow-up period. For example, all study subjects had a minimum CDS of 2.0 because they were using oral antidiabetic drugs. Both age and CDS variables were collapsed into quartiles for the Cox regression. Final models met the proportional hazards assumptions. Interaction terms between each variable in the model and drug exposure group were also examined. None of these interaction terms were statistically significant (at the $p < 0.10$ level), however, so no interaction terms were included in the final model.

2.3 Results

A total of 12,272 subjects met the inclusion criteria and were identified as new users of oral antidiabetic drugs from 1991 to 1996. From this group, 1,963 (16.0%) subjects had less than a 1-year drug therapy exposure following the index date and were excluded. This left an inception cohort of 10,309 subjects who used oral antidiabetic drugs for >1 year. The mean (standard deviation, SD) age for the cohort was 63.4 (13.3) and 55% were men. The mean (SD) duration of follow-up was 5.4 (1.9) years. The median (range) CDS for the whole cohort was 8.0 (2-26). We identified 6,969 patients in the metformin cohort and 3,340 patients in the sulfonylurea cohort. Within the metformin cohort, 5,740 (82.4%) patients eventually used a combination of sulfonylurea and metformin therapy. The two groups were generally comparable, although the sulfonylurea cohort was

significantly older and had more men while the metformin cohort had a longer duration of therapy and was more likely to be on insulin (Table 1).

Over the 5 years of follow-up there were 40 (3.3%) cancer deaths in metformin monotherapy users and 205 (3.6%) in combination therapy users, for 245 (3.5%) cancer-related deaths in the metformin cohort overall, compared with 162 (4.9%) cancer-related deaths in the sulfonylurea cohort ($p = 0.001$) (Table 1). This translates to a cancer-related mortality rate (per 1000 person years of follow-up) of 6.3 and 9.7 for the metformin and sulfonylurea cohorts, respectively (Table 2). The unadjusted hazard ratio (HR) and 95% confidence intervals (95% CI) for cancer-related mortality was 1.6 (95% CI 1.3 – 1.9) for the sulfonylurea cohort compared with the metformin cohort ($p < 0.0001$). Insulin users had a similarly higher incidence of cancer-related mortality compared to patients not on insulin (9.9 vs. 6.8, respectively; Table 2).

In multivariate Cox regression analyses adjusted for age, sex, insulin use, and comorbidity, the sulfonylurea cohort had significantly greater cancer-related mortality compared with the metformin cohort (adjusted HR: 1.3, 95% CI: 1.1 – 1.6; $p=0.012$; Table 2). Of note, insulin use (irrespective of any other antidiabetic treatments) was associated with an adjusted hazard of cancer-related mortality of 1.9 (95% CI: 1.5 – 2.4; $p<0.0001$). Older age and male sex were associated with a significantly increased risk of cancer-related mortality (Table 2).

2.4 Discussion

In an inception cohort of 10,309 people newly treated for type 2 diabetes and followed for about 5 years, we found that people exposed to sulfonylureas or exogenous insulin (agents that increase circulating insulin levels) were significantly more likely to have a cancer-related death than people exposed to metformin (which does not increase insulin levels). Despite the increasing recognition of the link between type 2 diabetes and cancer, possibly through a common mechanism of insulin resistance, very little is known about the possible effect of various antidiabetic therapies on cancer-related mortality. The

pharmacologic effects of these treatments on circulating insulin levels may play an important role in this comorbidity relationship.

Insulin is known to have mitogenic properties.[17,18] Metformin appears to have pleiotropic mechanisms of action, including reduced hepatic glucose production and increased peripheral insulin sensitivity.[31] It has also been shown to reduce hyperglycemia, without an increased risk of hypoglycemia, and to produce modest improvements in lipid profiles while promoting weight loss.[31-33] On the other hand, sulfonylureas promote increases in circulating insulin levels in the body and exogenous insulin use in type 2 diabetes would be expected to directly increase insulin levels. Consistent with these biologic mechanisms, we found that the risk of cancer-related mortality was even greater for insulin exposure (90% relative increase) than for sulfonylurea exposure (30% relative increase). Evans et al recently reported a similar difference in risk for patients exposed to metformin compared to sulfonylureas.[26] This case-control study used population-based sampling from a clinical database of diabetic patients in Scotland, allowing for adjustment for smoking, body mass index, and blood pressure. The results suggested a dose-response relationship, with greater risk reduction associated with greater exposure to metformin. It is not clear, however, if the use of insulin was excluded or controlled in their analyses. The authors suggested a more rigorous cohort study to add support for the hypothesized relationship. One previous study evaluated insulin exposure and the incidence of colorectal cancer.[34] Although this study did not examine mortality as an outcome, the authors found that chronic insulin therapy significantly increased the risk of colorectal cancer among patients with type 2 diabetes, after adjusting for potential confounders.[34]

Similar to other studies that are based on administrative databases, there are several inherent limitations that need to be acknowledged. First, we lacked important clinical information such as glycemic control (e.g. fasting blood glucose or A1c), weight or body mass index (BMI), or smoking status. These variables may be potential confounders in the relationship between choice of drug

therapy and cancer-related mortality in people with type 2 diabetes. We have no reason to believe, however, that such clinical characteristics would be differentially distributed across groups, except for BMI. Weight is known to increase with sulfonylurea or insulin exposure and decrease with metformin exposure.[32] Metformin is more likely to be used in overweight individuals and, in turn, overweight individuals are also more likely to get cancer or die from cancer.[35] It would follow, therefore, that users of metformin would have an increased risk of cancer and cancer-mortality. Yet, in our data, metformin users were less likely to die of cancer compared to users of sulfonylureas. Interestingly, Evans et al observed a similarly reduced risk of cancer incidence for metformin users, both before and after adjusting for BMI.[26]

Given the available data, we only examined cancer-related mortality and did not look at the development of various types of nonfatal cancers. Further, we recognize that cancer mortality will depend on the type and aggressiveness of the cancer, and the effectiveness of cancer treatments. If the difference in mortality rates is attributable to the diabetes treatments, then the effect may have been on the later progression of the cancer, or on the response to cancer treatment. We have no reason to believe, however, that use of antidiabetic drug would be associated with the choice of cancer therapy, or aggressiveness of cancer (other than our hypothesized relationship); these do not seem to be plausible confounders. Nonetheless, we recognize it would be helpful to determine the association between antidiabetic drug exposure and the incidence of cancer in a similar cohort design.

Finally, our analyses were based on only 407 cancer-related deaths. This small number of events precludes us from separating the two exposure groups into more refined categories that might allow for examination of dose-response relationships and graded insulin exposures. Our results are certainly an underestimate of the possible deleterious association between sulfonylurea or insulin exposure and cancer-related mortality.

While our results are intriguing, they should only be considered hypothesis-generating. Nevertheless, from a public health perspective, the impacts of type 2 diabetes and cancer are both substantial. Both are costly chronic diseases with a relatively long duration. A better understanding of the relationship between diabetes and its treatments and cancer has many important implications for prevention and management. Pharmacologic therapies that increase insulin sensitivity in type 2 diabetes, such as metformin, may not only have a beneficial effect on diabetes outcomes, but also on cancer-related mortality. It is still uncertain, based on our data and previous reports,[17,18,26,36,37] whether the observed increased risks of cancer-related mortality are related to a protective effect of metformin or deleterious effects of sulfonylurea and insulin.

Table 2.1. Patient Characteristics Stratified by Drug Exposure (N = 10309).

	Metformin Cohort	Sulfonylurea Cohort
N	6969	3340
Age (Years)		
Mean (Standard Deviation, SD)	61.8 (13.1)	66.9 (13.1)*
Median (Range)	62.3 (30.0-105.3)	68.1 (30.0-100.2)
Men, (%)	3727 (53.5%)	1956 (58.6%)†
Insulin Exposure, (%)	1137 (16.3%)†	306 (9.2%)
Duration of follow-up (Years), Mean (SD)	5.6 (1.9)*	5.0 (2.0)
Mean Person Years of Follow-up	39026	16700
Chronic Disease Score, Median (Range)	8.0 (2-26)	8.0 (2-22)
Overall Mortality, (%)	245 (3.5%)	162 (4.9%)‡

*P <0.0001 for Analysis of Variance (ANOVA)

†P <0.0001 for Chi-square test

‡P=0.001 for Chi-square test

Table 2.2. Cancer Mortality and Adjusted Hazard Ratio (HR) (95% CI) from multivariate Cox regression

	Total N	Cancer Deaths N (%)	Cancer Mortality Rate (/1000 P-Yr)	Adjusted* HR
Oral Antidiabetics				
Metformin	6,969	245 (3.5)	6.3	1.0†
Sulfonylurea	3,340	162 (4.9)	9.7	1.3 (1.1 – 1.6)
Insulin Use				
No Insulin Use	8,866	323 (3.6)	6.8	1.0†
Insulin Use	1,443	84 (5.8)	9.9	1.9 (1.5 – 2.4)
Age				
≤53.9 years old	2,578	16 (0.6)	1.1	1.0†
54.0-64.3 years old	2,578	75 (2.9)	6.0	5.0 (2.9 – 8.6)
64.4-73.3 years old	2,576	127 (4.9)	8.9	8.9 (5.3 – 15.0)
≥73.4 years old	2,577	189 (7.3)	15.6	16.9 (10.0 – 28.3)
Sex				
Female	4,626	162 (3.5)	6.5	1.0†
Male	5,683	245 (4.3)	8.0	1.5 (1.2 – 1.8)
Comorbidity				
CDS ≤6	3,181	102 (3.2)	6.0	1.0†
CDS 7-8	2,210	84 (3.8)	7.0	0.9 (0.7 – 1.2)
CDS 9-11	2,513	103 (4.1)	7.5	0.9 (0.7 – 1.2)
CDS ≥12	2,405	118 (4.9)	9.0	1.0 (0.8 – 1.3)

*Adjusted for all other covariates in the table.

†Reference category for hazard ratio

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CHAPTER 3: ANTIDIABETIC THERAPIES AND CANCER MORTALITY IN TYPE 2 DIABETES: ASSESSING TIME-VARYING EXPOSURE

3.1 Introduction

Hyperinsulinemia plays a central role in morbidity and mortality associated with diabetes, particularly cardiovascular disease.[1] There is also substantial evidence that supports the biologically plausible link between diabetes and various forms of cancer. It is suggested that hyperinsulinemia and elevated levels of insulin-like growth factor 1 (IGF-1) in patients with type 2 diabetes promotes tumour cell growth.[2-5] For the most part, the evidence suggests that patients with type 2 diabetes have an increased risk of cancer, including endometrial cancer,[6,7] breast cancer,[8,9] colorectal cancer,[8,10,11] pancreatic cancer,[8,10,12] and liver cancer.[8,10,13] However, patients with type 2 diabetes have been found to have a significantly decreased risk of prostate cancer.[14,15]

There is also increasing evidence supporting a role of antidiabetic therapies in the relationship between diabetes and cancer. Treatments such as metformin, which decrease insulin resistance, are thought to reduce the risk of tumour development.[16-20] The accumulated evidence has led to suggestions that clinical trials be considered to evaluate the role of metformin as an adjuvant therapy for treatment of breast cancer.[21]

An extension of this evidence would suggest that treatments which increase circulating insulin levels, such as exogenous insulin and sulfonylureas, might accelerate tumour growth. Several epidemiologic studies have corroborated this theory. A case-control study by Evans et al., found that metformin was associated with a statistically significant 23% reduction in the risk of cancer compared to sulfonylurea therapy among patients with type 2 diabetes, after adjusting for various clinical factors.[22] Yang et al. found that chronic exogenous insulin therapy was associated with a significantly increased risk of colorectal cancer among patients with type 2 diabetes. The age- and sex-adjusted

hazard ratio for colorectal cancer was 2.1 for ≥1 year of insulin use, and the authors observed an adjusted odds ratio of 1.2 for colorectal cancer for each incremental year of insulin therapy.[23]

In a previous study, we also observed a significantly increased risk of cancer mortality associated with sulfonylurea monotherapy use compared to metformin use (alone or in combination with sulfonylurea), as well as an increased risk of cancer mortality associated with insulin use.[24] We employed multivariable time-independent Cox analyses to determine the effect of metformin, sulfonylurea, and exogenous insulin therapy, after adjusting for several potential confounding covariates.[24] There are certain biases inherent in not considering changes in therapy exposures over time, which may have underestimated or overestimated the underlying degree of association.[25-27] The most common bias associated with such time-independent analyses is survival- (or immortal-time) bias, which we recognize was likely a factor in our previous study.[24] For example, insulin therapy subsequent to oral therapy can only be applied to patients who survive long enough to receive it, which leads to their "immortal time", the time period between the index date and the start of the insulin therapy when these patients cannot die (otherwise they would not be labelled as insulin users). Such immortal time would underestimate the time-independent insulin effects on mortality due to the existence of the immortal time for the exposed. Therefore, we re-analyzed our data using Cox regression with time-varying exposure to insulin, by specifying one year time window after insulin index. This time-varying approach will allow us to obtain more precise estimates of risk for subsequent insulin exposure and examine more closely the dose-response effect of insulin use on cancer mortality.

To our knowledge, there is no study which has considered time-varying exposures for insulin therapy and its effects on cancer outcomes in type 2 diabetes. We hypothesized a decreased risk of cancer mortality associated with metformin use and a dose-response gradient for insulin exposure, whereby patients exposed to higher levels of insulin therapy would have an increased risk of cancer mortality.

3.2 Methods

Study Design

The dataset used for this study has been described in detail in our previous manuscript.[24] Briefly, this was a population-based retrospective cohort study, using the administrative databases (i.e. health registration file, outpatient prescription drug file, and vital statistics) of Saskatchewan Health, Canada. We identified new users of metformin or sulfonylurea during the index period of January 1, 1991 – December 31, 1996. Patients had to be at least 30 years old on the index date (i.e. date of the first claim for an oral antidiabetic drug in the index period) and had to have continuous drug coverage for at least 1 year prior to the index date to be included in the study. To ensure ongoing drug exposure, we excluded subjects who had less than 1 year of drug exposure following the index date. Patients with gestational diabetes were also excluded. All study subjects were followed prospectively from their index date until death, termination of coverage (e.g. departure from the province), or December 31, 1999, providing a maximum follow-up of 9 years. The primary outcome measure for this study was cancer mortality, which was determined from the vital statistics file of Saskatchewan Health. Ethics approval for this study was obtained from the Health Research Ethics Board at the University of Alberta.

The information available on insulin use in the outpatient prescription drug file included date of dispensation and total number of dispensations throughout the follow-up period. Unfortunately, the type of insulin or the product dispensed (e.g., whether it was a 10mL vial or 3mL cartridge) were not recorded in the drug file. However, regardless of the product dispensed, each mL contains 100 units of insulin. Information available on metformin and sulfonylurea use included date of dispensation and total number of dispensations.

Statistical Analysis

Descriptive analyses were stratified according to the new user drug exposure category at the cohort entry. Consistent with our previous analyses, subjects were grouped according to their antidiabetic drug use as metformin users

(alone or in combination with sulfonylurea) or sulfonylurea monotherapy users.[24] Combination therapy users included all patterns of addition of sulfonylurea to metformin and vice versa. Comparisons between groups were evaluated using two-sample t-test for continuous variables and Chi square tests for categorical variables.

We performed Cox regression analysis to evaluate the relationship between antidiabetic therapies and cancer mortality. To remain consistent with our previous analyses, we compared metformin users (i.e. alone or in combination with sulfonylurea) to sulfonylurea monotherapy users.[24] For insulin use, we calculated the "cumulative insulin exposure per year" as follows. First, a total count of the number of insulin dispensations for each 1-year time window after insulin index was assessed. We then calculated a cumulative sum of insulin dispensations up to the end of each one year time window from the insulin index date. The cumulative sum of insulin exposures for each one year time window was then divided by the number of person years a patient was on insulin up to the end of the respective time window, to arrive at the time-varying "cumulative insulin exposure per year" for each subject. Therefore, the value for the cumulative insulin exposure varies for each one year time window after insulin index. By not including the person years prior to insulin use as person years of insulin users, we accounted for survival bias. For the purposes of the analyses, the cumulative insulin exposure per year was stratified into the following categories: 1) No exposure to insulin (reference group), 2) >0 to <3 cumulative insulin dispensations/year, 3) ≥3 to <12 cumulative insulin dispensations/year, and 4) ≥12 cumulative insulin dispensations/year.

In addition to oral antidiabetic exposure (i.e. metformin and/or sulfonylurea use) and time-varying exposure to insulin, we included the following potential confounding variables into the Cox regression as time-independent variables: age at oral medication index, sex, and chronic disease score (CDS). The CDS uses pharmacy dispensation information for specific drug classes to estimate the burden of comorbidities, and has proven valid in predicting hospitalization, health resource utilization, and mortality.[24,28] The CDS is the sum of all chronic

diseases identified from drug therapies over the full follow-up period. For example, all study subjects had a minimum CDS of 2.0 because they were using oral antidiabetic drugs. For the time-varying Cox regression analyses, age was collapsed into 5-year age groups, and the CDS was collapsed into quartiles. The proportional hazards assumption was met for age at oral medication index, sex, and CDS by comparing the hazard curves for each variable over time.

3.3 Results

There were 12,272 subjects that met the inclusion criteria and were identified as new users of oral antidiabetic drugs from 1991 to 1996. From this group, 1,963 (16.0%) subjects had less than one year drug therapy exposure following the index date and were excluded. This left an inception cohort of 10,309 subjects who used oral antidiabetic drugs for >1 year. The mean (SD) duration of follow-up was 5.4 (1.9) years in the whole cohort.

We identified 6,969 metformin users (i.e. metformin monotherapy users or combination therapy users) and 3,340 sulfonylurea monotherapy users. Among metformin users, 5,740 (82.4%) patients eventually used a combination of sulfonylurea and metformin therapy. There were 1,443 (14.0%) patients in the whole cohort who had insulin added on to their oral therapy regimen, with 1,137 (16.3%) among metformin users and 306 (9.2%) among sulfonylurea monotherapy users. The mean (SD) length of time before addition of insulin was 3.6 (2.2) years for metformin users and 2.4 (2.1) years for sulfonylurea monotherapy users. Sulfonylurea monotherapy users were significantly older and were more likely to be male, while metformin users had a longer duration of therapy and a higher CDS (Table 1). Overall mortality was also significantly higher in the sulfonylurea monotherapy group (25.5%) compared to the metformin group (14.5%) ($p<0.0001$; Table 1).

There were 407 (3.9%) cancer deaths in the whole cohort throughout the follow-up period, with 245 (3.5%) cancer deaths among metformin users and 162 (4.9%) cancer deaths in the sulfonylurea monotherapy group (Table 1). This

translates to a cancer mortality rate (per 1,000 person years of follow-up) of 6.3 for the metformin group and 9.7 for the sulfonylurea monotherapy group (Table 2). The unadjusted hazard ratio (HR) and 95% confidence interval (CI) for cancer mortality was 0.63 (95% CI: 0.51 – 0.77) for metformin users compared to those on sulfonylurea monotherapy ($p < 0.0001$), and 2.07 (0.92 – 4.65; $p=0.08$), 2.57 (1.75 – 3.78; $p<0.0001$), and 4.10 (3.01 – 5.56; $p<0.0001$) for >0 to <3, ≥3 to <12, and ≥12 cumulative insulin dispensations per year, respectively, compared to those not using insulin.

In multivariable Cox regression analyses, the adjusted HR for metformin use was 0.80 (95% CI: 0.65 – 0.98; $p=0.03$). The adjusted HRs (95% CI) for insulin use were 2.22 (0.99 – 5.00; $p=0.05$), 3.33 (2.26 – 4.89; $p<0.0001$), and 6.40 (4.69 – 8.73; $p<0.0001$) for >0 to <3, ≥3 to <12, and ≥12 cumulative insulin dispensations per year, respectively, compared to those not exposed to insulin. We observed a consistent monotonic relationship between increasing age and an increased hazard of cancer mortality. Male sex was also associated with a significantly increased risk of cancer mortality, while CDS was not.

3.4 Discussion

Our results provide further support that antidiabetic therapies may play a role in the relationship between type 2 diabetes and cancer outcomes. In our cohort of new users of oral medications (i.e. metformin or sulfonylureas) for type 2 diabetes, exposure to metformin therapy, relative to sulfonylurea monotherapy, was associated with a 20% reduction in cancer mortality ($p=0.03$), which can be considered clinically important. The small number of cancer deaths (N=407) in this particular cohort, however, limited the power for this analysis.

The previously published case-control study by Evans et al found very similar results to ours, observing a 23% decreased risk of cancer in patients with type 2 diabetes taking metformin compared to sulfonylureas.[22] Their results also supported a dose-response gradient, whereby patients with greater exposure to metformin had a greater reduction in the risk of cancer.[22]

We also observed a strong dose-response gradient for insulin exposure and cancer mortality in this population. Compared to those not exposed to insulin therapy, we observed a significantly increased risk of cancer mortality associated with increases in cumulative exogenous insulin exposure. Specifically, we found that subjects with >0 to <3, ≥3 to <12, and ≥12 cumulative insulin dispensations per year after insulin index had adjusted HRs for cancer mortality of 2.22, 3.33, and 6.40, respectively. These current results, along with our previous study,[24] where we used a time-fixed survival analysis and observed a 90% relative increased risk of cancer mortality among insulin users, add strength to the evidence of association between exogenous insulin use and cancer mortality among those with type 2 diabetes. To our knowledge, there is no research available that has used a time-varying approach in their analyses when looking at the relationship between insulin exposure in type 2 diabetes and cancer outcomes. There is only one other study that has looked at the effect of cumulative insulin exposure and incidence of colorectal cancer.[23] These authors also observed a significantly increased risk of colorectal cancer associated with chronic insulin therapy in type 2 diabetes, after adjusting for potential confounders.[23]

The role of insulin in the relationship between type 2 diabetes and cancer mortality is supported by a biologically plausible mechanism. Insulin is growth hormone and is known to have arthrogenic and mitogenic properties.[1,29,30] Specifically, it is suggested that hyperinsulinemia and elevated levels of insulin-like growth factor 1 (IGF-1) promotes tumour cell growth in patients with type 2 diabetes.[2-5] Patients with type 2 diabetes are known to be hyperinsulinemic, at least early in the course of their disease, and exogenous insulin therapy directly increases circulating insulin levels. A recent report from the Wisconsin Epidemiologic Study of Diabetic Retinopathy cohort suggests that hyperinsulinemia in patients with late onset diabetes is associated with increased cardiovascular morbidity and mortality.[1] In the multivariable regression models of that study, exogenous insulin was also associated with a nonsignificant increased risk of cardiovascular events.[1]

There are some limitations in our study. Firstly, as noted above, we had a relatively small number of cancer deaths (N=407), thereby limiting the power for our analyses, particularly with the point estimate for metformin use. Secondly, since we used administrative data, we lacked information on potentially important clinical covariates, such as smoking status, weight or body mass index (BMI), glycemic control (i.e. A1c levels), and alcohol consumption. These are all potential confounders in the relationship between choice of drug therapy and cancer mortality in patients with type 2 diabetes. Nonetheless, as we noted in our previous analysis,[24] we feel the relationships are robust to these excluded data, particularly given the consistent results to those of others when such potential confounders have been included.[22,23] Finally, we looked at the outcome of cancer mortality as opposed to cancer incidence, and there are many intervening events which may determine the risk of cancer mortality.

On the other hand, we do feel there are several strengths in the present study, particularly with the methodology. While we used a new user design for assessing the association with oral antidiabetic therapy, there was likely a substantial survival bias in our previous assessment of insulin use, where we used a simple time-fixed exposure variable.[24] By applying the time-varying exposure definition for insulin use in this current analysis, we were able to obtain more precise risk estimates, and refine our categories of insulin exposure by examining the dose-response gradient for insulin use. In this manner, we were able to overcome some of the survival bias and confounding by duration inherent in our previous results.[24] We do recognize the possibility of residual survival bias and other unknown biases in our current research. Most importantly, however, by using this time-varying methodology, our findings provide the first evidence of a dose-gradient for insulin exposure and cancer mortality in patients with type 2 diabetes. Confounding by indication may play a role in the dose-gradient with increasing insulin use being associated with greater level of hyperglycemia, which may be associated with cancer mortality, although we saw the risk estimates increase when potential confounding variables were controlled for in the multivariable regression models. Therefore, we believe the magnitude of the risk

estimates for the higher insulin exposure levels would likely exceed the strength of any relationship between hyperglycemia alone and cancer mortality.

In conclusion, we provide additional evidence supporting previous reports of a decreased risk of cancer outcomes associated with metformin use. We also provide preliminary evidence of a strong dose-response gradient for insulin exposure and cancer mortality. A better understanding of the relationship between type 2 diabetes and its treatments and cancer has many important implications for prevention and management of both conditions.[21,22,24] Therefore, until we have more evidence of the effects of insulin on long-term outcomes, we should be cautious in earlier initiation and aggressiveness of insulin therapy in type 2 diabetes. Nonetheless, it will be helpful to confirm our results in a larger cohort study, with a longer duration of follow-up, a non-diabetes control group, and using cancer incidence as the outcome measure.

Table 3.1. Patient Characteristics Stratified by Drug Exposure Group (N = 10309)

	Metformin Users (Alone or in Combination With Sulfonylurea)	Sulfonylurea Monotherapy Users
N	6,969	3,340
Age (Years)		
Mean (Standard Deviation, SD)	61.8 (13.1)	66.9 (13.1)*
Median (Range)	62.3 (30.0-105.3)	68.1 (30.0-100.2)
Men, (%)	3,727 (53.5%)	1,956 (58.6%)†
Insulin Exposure, (%)	1,137 (16.3%)†	306 (9.2%)
Duration of follow-up (Years), Mean (SD)	5.6 (1.9)*	5.0 (2.0)
Total Person Years of Follow-up	38,999	16,749
Chronic Disease Score, Mean (SD)	8.7 (4.2)*	8.4 (4.1)
Cancer Mortality, (%)	245 (3.5%)	162 (4.9%)
Overall Mortality, (%)	1,013 (14.5%)	852 (25.5%)

*P <0.0001 by t-test

†P <0.0001 by Chi-square test

Table 3.2. Cancer Mortality and Adjusted Hazard Ratio (HR) (95% CI) from time-varying multivariable Cox regression

	Total N	Cancer Deaths N (%)	Cancer Mortality Rate (/1000 P-Yr)	Adjusted* HR (95% CI)
Oral Antidiabetics				
Sulfonylurea Monotherapy	3,340	162 (4.9)	9.7	1.0**
Metformin Use	6,969	245 (3.5)	6.3	0.80 (0.65 – 0.98) †
Insulin Use (Insulin Dispensations/Year) ‡				
No Insulin Use Ever	52131	323 (3.6)	-	1.0**
>0 to <3	400	6	-	2.22 (0.99 – 5.00) †
≥3 to <12	1543	29	-	3.33 (2.26 – 4.89) §
≥12	1636	49	-	6.40 (4.69 – 8.73) §
Age				
<45 years old	1,050	3 (0.3%)	0.5	1.0†
45-49.9 years old	794	6 (0.8%)	1.3	3.24 (0.81 – 12.97)
50.0-54.9 years old	984	11 (1.1%)	2.0	5.22 (1.45 – 18.75) ‡
55.0-59.9 years old	1,105	33 (3.0%)	5.3	14.11 (4.31 – 46.16) §
60.0-64.9 years old	1,429	47 (3.3%)	5.8	14.96 (4.64 – 48.23) §
65.0-69.9 years old	1,450	77 (5.3%)	9.5	27.29 (8.56 – 86.98) §
70.0-74.9 years old	1,337	69 (5.2%)	9.6	27.84 (8.71 – 89.02) §
75.0-79.9 years old	1,056	82 (7.8%)	15.4	46.33 (14.54 – 147.68) §
80.0-84.9 years old	689	50 (7.3%)	16.2	52.24 (16.15 – 169.02) §
85.0-89.9 years old	309	22 (7.1%)	17.8	59.13 (17.55 – 199.28) §
≥90.0 years old	106	7 (6.6%)	19.7	65.20 (16.74 – 253.94) §
Sex				
Female	4,626	162 (3.5)	6.5	1.0†
Male	5,683	245 (4.3)	8.0	1.50 (1.23 – 1.84) §
Comorbidity				
CDS ≤6	3,181	102 (3.2)	6.0	1.0†
CDS 7-8	2,210	84 (3.8)	7.0	0.92 (0.69 – 1.24)
CDS 9-11	2,513	103 (4.1)	7.5	0.92 (0.69 – 1.21)
CDS ≥12	2,405	118 (4.9)	9.0	0.95 (0.72 – 1.24)

*Adjusted for all other covariates in the table; **Reference category for hazard ratio; †p≤0.05; ‡Specific rates cannot be estimated for insulin exposure categories, because of the time-varying nature of exposure. Cancer deaths are calculated based on the insulin category at the time of cancer death, and the total N is time at risk in each insulin category; §p<0.0001

3.5 References

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CHAPTER 4: INCREASED RISK OF CANCER MORTALITY ASSOCIATED WITH EXOGENOUS INSULIN THERAPY FOR TYPE 2 DIABETES

4.1 Introduction

There is a substantial amount of evidence linking type 2 diabetes to various types of cancer in the epidemiologic literature. Type 2 diabetes is associated with an increased risk of pancreatic cancer[1], endometrial cancer[2,3], colorectal cancer[4], breast cancer[5], bladder cancer[6], liver cancer[7-9], and overall cancer mortality.[7] On the other hand, patients with type 2 diabetes have a decreased risk of prostate cancer, as a result of the protective effect of lower testosterone levels in men with diabetes.[10,11]

The association between type 2 diabetes and cancer is biologically plausible. Most patients with type 2 diabetes have the metabolic syndrome, which is associated with insulin resistance and hyperinsulinemia.[12] Endogenous insulin is considered to be a growth-promoting hormone with mitogenic effects[13], and in fact, the hyperinsulinemia in type 2 diabetes may underlie the associations of several risk factors for cancer, such as a high waist circumference and a high body mass index (BMI).[14,15]

Type 2 diabetes is characterized by initial relative hepatic and peripheral insulin resistance and compensatory hyperinsulinemia, followed by progressive loss of beta-cell mass and a fall-off of endogenous insulin production.[16] In addition to initially elevated levels of endogenous insulin, many patients with type 2 diabetes subsequently receive exogenous insulin for glycemic control.[17] The expected physiologic or therapeutic effect of either endogenous or exogenous insulin is to interact with insulin receptors (IR) on the cell membrane to activate glucose transporters for glucose uptake into the cell. There are also closely related insulin-like growth factor receptors (IGF-1R) on the cell, which are a major factor in the control of cell proliferation.[18] As such, insulin-like growth factor (IGF-1) and IGF-1R have been implicated in many cancers.[18] The IGF-1R is suppressed by insulin; therefore, at higher concentrations of circulating insulin, such as in

hyperinsulinemia, there are higher levels of circulating bioavailable IGF-1, which in turn stimulates cell growth.[19,20] Therefore, it is suggested that hyperinsulinemia, combined with elevated levels of insulin like growth factor (IGF-1) in type 2 diabetes, promotes tumour cell growth.[21-25]

There is growing evidence for the role of antidiabetic therapies in the relationship between type 2 diabetes and cancer outcomes.[26-28] In a previous study, we found that time-independent exposure to sulfonylurea monotherapy, which increases circulating insulin levels, was associated with a 30% increased risk of cancer mortality, when compared to metformin use.[27] Incidentally, we also observed a substantially increased risk of cancer mortality associated with time-independent exposure to insulin therapy (HR: 1.9, 95%CI: 1.5-2.4).[27] Yang et al found that exposure to exogenous insulin therapy for at least 1 year in type 2 diabetes was associated with a similarly increased risk of colorectal cancer (HR: 2.1, 95%CI: 1.03-1.42).[28] The authors also observed a strong dose-response gradient, whereby people exposed to higher levels of insulin therapy had a higher risk of colorectal cancer.[28]

The objectives of the current study were to explore the relationship between exposure to exogenous insulin therapy in type 2 diabetes and cancer mortality. To our knowledge, there are no studies that have looked at new insulin users to assess the time-varying exposure of insulin therapy on cancer outcomes in type 2 diabetes. We hypothesized a dose-response gradient with insulin exposure, where patients with increasing levels of exposure to insulin therapy would have a higher risk of cancer mortality.

4.2 Methods

Study Design

The dataset used for this study has been previously described in detail.[27] Briefly, this was a population-based retrospective cohort study, using the linkable administrative databases (i.e. health registration file, outpatient prescription drug file, hospital separation file, and vital statistics) of Saskatchewan Health, Canada. A cohort of new users of oral antidiabetic agents during January 1991 to

December 1996 was identified.[27] Patients had to be at least 30 years old at oral agent index (i.e. date of the first claim for oral agent therapy) and had to have continuous drug coverage for at least 1 year prior to the oral agent index date to be included in the study. They also had to have a minimum of 1 year of drug exposure after their oral index date.

Among this cohort, we identified new users of insulin therapy; all subjects therefore had previous exposure to metformin, sulfonylurea, or their combination, but no prior record of insulin use. For this analysis, all subjects were followed prospectively from insulin index until death, termination of coverage (e.g. departure from the province), or December 31, 1999. Patients with gestational diabetes and Registered Indian status were excluded from the analysis. The primary outcome measure for this study was cancer mortality, which was determined from the cause of death on record in the vital statistics file of Saskatchewan Health.

Information available on metformin, sulfonylurea, and insulin use in the outpatient prescription drug file included the date of dispensation and the total number of dispensations throughout the follow-up period. The type of insulin or the product dispensed (e.g., whether it was a 10mL vial or 3mL cartridge) were not recorded in the drug file. However, regardless of the product dispensed, each mL contains 100 units of insulin. Similarly, information on directions for individual prescriptions (i.e. the number of times/day a person is taking metformin or sulfonylurea) was not available.

Statistical Analyses

We performed Cox regression analysis to evaluate the relationship between insulin therapy and cancer mortality. Time-varying exposure to insulin therapy was calculated as the cumulative insulin exposure per one year time window after insulin index. We first defined 1-year time windows, beginning with insulin index date. A total count of the number of insulin dispensations for each 1-year time window after insulin index was assessed. We then calculated the cumulative sum of insulin dispensations for each one year time window after

insulin index. The cumulative sum of insulin exposures was then divided by the number of person years on insulin, to arrive at the time-varying cumulative insulin exposure per one year time window for each subject. We stratified cumulative insulin exposure per year into the following categories: 1) ≤30 days of insulin exposure, or <9 insulin dispensations/year (reference group), 2) 9 to <15 insulin dispensations/year, and 3) ≥15 insulin dispensations/year.

Use of oral antidiabetic agents was classified at time of insulin index as either metformin use (alone or in combination with sulfonylurea) or sulfonylurea monotherapy. Combination therapy included all patterns of addition of sulfonylurea to metformin and vice versa. Time-varying exposure to metformin was defined by use of that agent (i.e., dichotomous yes/no exposure) within each 1 year time window after insulin index. We compared metformin users (i.e. alone or in combination with sulfonylurea) to sulfonylurea monotherapy users because of the small number of events in the metformin monotherapy group.

We also included the following potential confounding variables into the Cox regression as time-independent variables: age at insulin index, sex, chronic disease score (CDS), and duration of oral therapy prior to start of insulin use. The CDS uses pharmacy dispensation information for specific drug classes to estimate the burden of comorbidities, and has proven valid in predicting hospitalization, health resource utilization, and mortality.[27,29] The CDS is the sum of all chronic diseases identified from drug therapies over the full follow-up period. For the Cox regression analyses, age at insulin index, CDS, and duration of oral therapy prior to start of insulin use were collapsed into quartiles. The proportional hazards assumption was met for age at insulin index, sex, CDS, and duration of oral therapy prior to start of insulin use by comparing the hazard curves for each variable over time.

Finally, in a sensitivity analysis, we repeated the above Cox regression model including only those subjects who had at least one year of exposure to insulin after insulin index.

4.3 Results

There were 10,309 subjects identified as new users of oral antidiabetic agents during the study period.[27] Among this cohort, we identified the subset of 1,443 patients that were subsequently new users of insulin (Table 1). The mean (standard deviation, SD) duration of insulin use for the whole cohort was 2.5 (2.0) years and the mean (SD) age at insulin index was 63.0 (14.7). The mean (SD) CDS for the whole cohort was 9.2 (4.5) and 51% were men. Among our new insulin users, there were 1,137 (78.8%) metformin users (i.e. metformin monotherapy users or combination therapy users) and 306 (21.2%) sulfonylurea monotherapy users. Among the metformin users at time of insulin start, there were 1,058 (93.1%) patients on a combination of metformin and sulfonylurea therapy. The mean (SD) duration of oral agent use prior to insulin index was 3.4 (2.2) years.

There were 84 (5.8%) cancer deaths among the whole new insulin user cohort throughout the follow-up period. The unadjusted hazard ratio (HR) and 95% confidence interval (CI) for cancer mortality was 1.29 (0.74-2.26) and 2.04 (1.21-3.46; p=0.008) for 9 to <15 and ≥15 cumulative insulin dispensations per year, respectively, compared to those with ≤30 days of exposure to insulin or <9 cumulative insulin dispensations per year (reference group).

In multivariable Cox regression analyses, the adjusted HRs (95% CI) for insulin use were 0.88 (0.51 – 1.51) and 1.36 (0.80 – 2.33) for 9 to <15 and ≥15 cumulative insulin dispensations per year, respectively, compared to those with ≤30 days of exposure to insulin or <9 cumulative insulin dispensations per year (reference group) (Table 2). Metformin use was associated with a 41% decreased risk of cancer mortality, although this was not statistically significant in this cohort (adjusted HR: 0.59, 95%CI: 0.33-1.09). Increasing age and male sex were associated with a significantly increased hazard of cancer mortality.

In the sensitivity analysis restricted to insulin users with at least 1 year of exposure to insulin (n=1,017), we also observed a nonsignificant dose response gradient with insulin exposure and cancer mortality, although statistical power remained limited (data not shown).

4.4 Discussion

In this cohort of new insulin users for type 2 diabetes, we observed a dose-response gradient for the unadjusted risk of cancer mortality with increasing insulin exposure. However, after adjustment for important covariates, the risk remained elevated only for those with the highest level of insulin exposure. Specifically, we found that subjects with 9 to <15, and ≥15 cumulative insulin dispensations/year after insulin index had adjusted HRs for cancer mortality of 0.88 and 1.36, respectively, compared to the reference group of individuals treated with oral agents, but with little or no exogenous insulin exposure. We observed similar results when we limited the analyses to individuals who had at least 1 year of exposure to insulin therapy. Of note, concurrent metformin use was associated with a 41% reduction in cancer mortality, compared to sulfonylurea monotherapy use. Duration of oral therapy prior to start of insulin therapy was not associated with cancer mortality.

There are several key strengths to the current research. Firstly, the inception cohort of new insulin users in this study ensures that all patients are at a similar point in the course of their diabetes. Therefore, this minimizes the confounding associated with both duration and severity of type 2 diabetes, and any associated survival biases. The study by Yang et al did not use a new user design for insulin use, and the authors acknowledge that their observed association may be due to a severity of diabetes rather than a true effect of insulin.[28] Therefore, we can be more confident in our observed association between cancer mortality and exogenous insulin. We do acknowledge, however, that there may be some residual survival bias and other unknown biases, which may be present.

Another strength to this study is that we employed a time-varying approach when looking at the effects of antidiabetic therapies. By using a time-varying approach for looking at the effects of insulin and oral antidiabetic therapies, we were able to obtain a more precise estimate of effect compared to an analysis which uses a time-independent approach. To our knowledge, there are no

studies which have assessed the time-varying effects of exogenous insulin therapy on cancer outcomes in a cohort of new insulin users in type 2 diabetes. A final strength is the accuracy and comprehensiveness of the linked Saskatchewan Health databases, which have been used in many studies of health outcomes in type 2 diabetes.

On the other hand, there are some limitations to the present study. The main limitation is the confounding by indication, where the choice of antidiabetic therapy was not based on random assignment, but rather on clinical decisions by the patient and treating physician. Since we used administrative data, we lacked potentially important clinical information on variables such as body mass index (BMI), smoking status, hemoglobin A1c levels, and physical activity level. These variables are all potential confounders in the relationship between choice of drug therapy and cancer mortality in type 2 diabetes. Nonetheless, as we noted in our previous study[27], we feel the relationships are robust to these excluded data, particularly given the consistent results to those of others when such potential confounders have been included.[26,28] Furthermore, our design of comparing high to low exposure among new users of exogenous insulin reduces the likelihood of confounding by indication, as the decision to begin insulin therapy itself would likely be the greatest confounder, rather than the actual amount of insulin subsequently used.

Another limitation is the small number of cancer deaths in this new insulin user cohort, which limited the power of our analyses. We also lacked control for the underlying risk of cancer in type 2 diabetes. Finally, we examined cancer mortality as opposed to the more proximal outcome of cancer incidence. We do recognize that there are many intervening events which may alter the risk of cancer mortality once a diagnosis of cancer has been established.

Nonetheless, these findings add evidence supporting previous reports of an increased risk of cancer outcomes associated with exogenous insulin therapy in type 2 diabetes.[27,28] In a nested case-control study by Yang et al, the authors observed evidence of an increased risk of colorectal cancer associated with longer duration of insulin therapy, after adjusting for potential confounding variables.[28]

Similarly, in a previous study, where we used a time-independent Cox analysis and looked at new users of oral antidiabetic therapies, we observed a 90% increased risk of cancer mortality associated with exogenous insulin therapy, after adjusting for potential confounding variables.[27] Importantly, however, those previous analyses did not consider the time-varying nature of antidiabetic agent use or increasing insulin exposure.

Our findings also support the proposition that insulin, IGF and their receptors play an important role in progression of cancer. The biologically plausible mechanism has lead to the suggestion of using drug therapies which interact with these receptors as adjuvant therapy for breast cancer.[21] By extension, this same biologic plausibility should alert the diabetes community to the risk of long-term adverse outcomes associated with treatments which affect insulin concentration or action at the cellular level. The biologic mechanism suggests that insulin is not necessarily causing the associated risk of cancer mortality in type 2 diabetes; rather, it is more likely accelerating this outcome. Furthermore, recent large randomized trials suggest aggressive glycemic control is not without risk.[30,31] Therefore, until we have more evidence of the effects of insulin on other long-term outcomes, we should be cautious in earlier initiation and aggressiveness of insulin therapy in type 2 diabetes.

In conclusion, we observed an unadjusted dose-response gradient for insulin exposure and cancer mortality in type 2 diabetes. After adjustment for important covariates, the increased risk of cancer mortality remained only for those subjects with the highest use of exogenous insulin. Nonetheless, it will be helpful to confirm our results in a larger cohort study, with a longer duration of follow-up, a non-diabetes control group, and using cancer incidence as the outcome measure.

Table 4.1. Patient Characteristics Among New Insulin Users (N = 1,443)

	Insulin Users
N	1,443
Age at Insulin Index (Years)	
Mean (Standard Deviation, SD)	63.0 (14.7)
Median (Range)	64.0 (30.9-102.0)
Men, N (%)	729 (50.5)
Oral Agents Use at Insulin Index, N (%)	
Sulfonylurea Monotherapy	306 (21.2%)
Metformin Use (Alone or in Combo SU)	1,137 (78.8%)
Duration of Oral Agent Use at Insulin Index, Mean (SD)	3.4 (2.2)
Duration of Insulin Use (Years), Mean (SD)	2.5 (2.0)
Total Person Years of Follow-up	3579.17
Chronic Disease Score, Mean (SD)	9.2 (4.5)
Cancer Mortality, N (%)	84 (5.8)
Overall Mortality, N (%)	321 (22.2)

Table 4.2. Cancer Mortality and Adjusted Hazard Ratio (HR) (95% CI) From Time-Varying Multivariable Cox Regression

	Total N	Cancer Deaths N (%)	Cancer Mortality Rate (/1000 P-Yr)	Adjusted* HR (95% CI)
Insulin Use (Insulin Dispensations/Year)				
≤30 Days Exposure to Insulin or <9	1190.2	12 (5.4)	-	1.0**
9 to <15	3399.5	29 (5.0)	-	0.88 (0.51 – 1.51)
≥15	3862.0	43 (6.7)	-	1.36 (0.80 – 2.33)
Oral Antidiabetics				
Sulfonylurea Monotherapy	1647.7	23 (7.5)	25.2	1.0**
Metformin Use	6804.0	61 (5.4)	22.9	0.59 (0.33 – 1.09)
Age, Quartiles				
≤51.4 years old	359	4 (1.1%)	3.5	1.0**
51.5-64.0 years old	359	17 (4.7%)	18.2	6.63 (2.19 – 20.06)†
64.1-74.5 years old	365	28 (7.7%)	31.8	13.00 (4.44 – 38.09)†
≥74.6 years old	360	35 (9.7%)	55.3	24.78 (8.36 – 73.44)†
Sex				
Female	714	30 (4.2)	16.8	1.0**
Male	729	54 (7.4)	30.1	2.21 (1.40 – 3.49)†
Comorbidity, Quartiles				
CDS ≤5	326	22 (6.7)	22.9	1.0**
CDS 6-8	341	13 (3.8)	16.7	0.42 (0.21 – 0.84)‡
CDS 9-11	340	24 (7.0)	30.6	0.76 (0.42 – 1.39)
CDS ≥12	435	25 (5.7)	23.6	0.52 (0.29 – 0.94)§
Duration Oral Therapy Prior to Insulin, Quartiles				
≤554 days	360	32 (8.9)	21.7	1.0**
555-1166 days	361	21 (5.8)	21.0	0.62 (0.35 – 1.08)
1167-1872 days	361	20 (5.5)	29.5	0.84 (0.47 – 1.51)
≥1873 days	360	11 (3.1)	25.6	0.53 (0.26 – 1.09)

*Adjusted for all other covariates in the table; **Reference category for hazard ratio; †p=0.001; ‡p=0.01; §p≤0.05

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CHAPTER 5: DECREASED CANCER MORTALITY ASSOCIATED WITH GLITAZONE USE IN TYPE 2 DIABETES

After successful completion and defense of this PhD Thesis, we were made aware of a data quality issue, that pertains specifically to the dataset used for Chapter 5. This data quality issue requires further investigation and analyses, that will take some time to resolve. Results from this chapter should therefore not be quoted for future reference. For further clarification, contact the author or supervisor.

5.1 Introduction

Patients with type 2 diabetes have an increased risk of various types of cancer and cancer mortality.[1-10] Evidence has accumulated supporting the biologically plausible link between type 2 diabetes and cancer outcomes, with the most likely link being hyperinsulinemia and elevated levels of insulin-like growth factor 1 (IGF-1) in patients with type 2 diabetes, both of which promote tumour cell growth.[11-16]

There is also growing evidence for the moderating role of antidiabetic therapies in the relationship between type 2 diabetes and cancer outcomes. Given the biologically plausible link between diabetes and cancer, drugs which reduce insulin resistance, such as metformin and the glitazones, might reduce the risk of tumour development. Several observational studies have supported this hypothesis for metformin use.[9,17,18] There is also evidence supporting the use of metformin as potential adjuvant therapy for breast cancer.[19]

The glitazones, also known as thiazolidinediones (TZDs), are a newer class of oral antidiabetic therapies that became widely available in the past decade. The glitazones are peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists that activate PPAR-γ receptors, and reduce insulin resistance by improving insulin sensitivity in the peripheral tissues.[20] It has been suggested that the glitazones and PPAR signaling may play a role in the regulation of cancer cell growth.[21] Specifically, PPAR agonists have been shown to inhibit cell growth

by inhibiting microtubulin assembly and tubulin polymerization in the cell.[22-24] Glitazones also activate AMP-protein kinase, a downstream target for LKB1, which is known as a potent tumour suppressor.[22-23] Therefore, in addition to being a therapeutic option in type 2 diabetes, PPAR-γ agonists are currently being investigated as a novel therapeutic approach for cancer treatment.[22-23] There are currently two clinical trials underway to evaluate the role of pioglitazone for the prevention or treatment of lung cancer.[25]

Several recent epidemiologic studies have examined the association between glitazone use and cancer incidence in people with type 2 diabetes. Consistent with the proposed biologic mechanism, these studies have generally observed a reduced risk of cancers of the lung, prostate or colon.[26-29] One population-based study did observe a positive association between rosiglitazone and cancer, although this was simply a cross-sectional association.[30]

The two currently marketed glitazones (pioglitazone and rosiglitazone) became available in Canada in 2000, and are approved for use as second line therapy in combination with, or in patients intolerant to, metformin.[31] The objectives of the current study were to explore the relationship between glitazones and cancer mortality in type 2 diabetes. We hypothesized a decreased risk of overall cancer and lung cancer mortality associated with glitazone use (in combination with metformin) compared to people on sulfonylurea monotherapy.

5.2 Methods

Study Design

This was a retrospective, population-based cohort study, using the administrative databases of Saskatchewan Health, Canada. We used three different datafiles for the purposes of these analyses: the health registration file, the outpatient prescription drug file, and vital statistics. These datafiles are linkable on personal health number, and provide demographic information, prescription drug usage, and diagnostic codes for cause of death, respectively. These databases include information on 99% of the residents in the province of Saskatchewan, which has a population of approximately 1 million.[32-33]

Individuals not covered by Saskatchewan Health include those with federally-funded health care, such as members of the Royal Canadian Mounted Police and Canadian Forces.[32] About 90% of the covered population is eligible for prescription drug benefits. Those ineligible include the registered Indians who receive prescription drug benefits through a federal program. Ethics approval for this study was obtained from the Health Research Ethics Board at the University of Alberta.

We identified a cohort of new users of metformin or sulfonylurea from January 1, 2000 to December 31, 2005, using the computerized Saskatchewan Prescription Drug Plan database. Patients were included if they: 1) were new users of oral antidiabetic therapies, 2) had continuous drug coverage for at least 1 year prior to their index date, and 3) were at least 30 years of age on their index date (i.e. the date of their first claim for an oral antidiabetic drug). New users of oral antidiabetic drugs and insulin were identified as patients who had prescription claims for sulfonylurea, metformin, glitazones, or insulin during the index period of January 1, 2000 – December 31, 2005 and no prescription claims for any antidiabetic agent for one year prior to the index date. Of note, this index period coincided with when glitazones became available in Canada. We excluded patients with gestational diabetes, and to ensure ongoing drug exposure, we also excluded subjects who had less than 1 year of drug exposure following their index date.

All study subjects were followed prospectively from their index date until death, termination of coverage (e.g. departure from the province), or December 31, 2006, providing a maximum follow-up of 7 years. The primary outcome measure for this study was overall cancer mortality. As a secondary outcome measure, we looked specifically at lung cancer mortality. We chose lung cancer mortality because of the large number of deaths in this cancer subtype and because of the recent clinical trials that are currently underway looking at glitazones as possible lung cancer treatment and chemoprevention.[25] The outcome measures were determined as the underlying cause of death recorded in the vital statistics file of Saskatchewan Health.

The information available on oral antidiabetic therapy use in the outpatient prescription drug file included the date of dispensation and the total number of dispensations throughout the follow-up period. The information available on insulin use included the date of dispensation and total number of dispensations, and the type of insulin (i.e. human biosynthetic or analog). For the purposes of these analyses, all insulin users were grouped together.

Statistical Analyses

Descriptive analyses were stratified according to the drug exposure category. Subjects were grouped into the following cohorts, according to oral antidiabetic drug use over the full follow-up period, as: 1) sulfonylurea monotherapy users, 2) metformin and sulfonylurea combination users, 3) metformin monotherapy users, and 4) metformin and glitazone users. The metformin and sulfonylurea combination therapy users included all patterns of use (i.e. addition of sulfonylurea to metformin and vice versa). Under the Saskatchewan Prescription Drug Plan, glitazones are approved for use only as second line therapy and in combination with metformin.[34] As such, the metformin and glitazone therapy cohort included only a very small percentage of subjects (<1%) who had sulfonylurea therapy dispensation at any point in the index period. The sulfonylurea monotherapy cohort served as the reference group in all analyses. Comparisons between drug exposure groups were evaluated using analysis of variance (ANOVA) for continuous variables and Chi square tests for categorical variables.

We performed a time-varying Cox regression analysis to evaluate the relationship between antidiabetic therapies and cancer mortality, using the above drug exposure groups. Time-varying exposure to metformin, sulfonylurea, and glitazones was defined by the use of that agent (i.e., dichotomous yes/no exposure) within 1 year time windows after oral index. For time-varying exposure to insulin, we calculated the "cumulative insulin exposure per year" as follows. First, a total count of the number of insulin dispensations for each 1-year time window after insulin index was assessed. We then calculated a cumulative

sum of insulin dispensations up to the end of each one year time window. The cumulative sum of insulin exposures for each one year time window was then divided by the number of person years a patient was on insulin up to the end of the respective time window, to arrive at the time-varying "cumulative insulin exposure per year" for each subject. For the purposes of the analyses, the cumulative insulin exposure per year was stratified into the following categories: 1) No exposure to insulin (reference group), 2) <12 cumulative insulin dispensations/year, and 3) ≥12 cumulative insulin dispensations/year.

In addition to time-varying exposure to oral antidiabetic therapies (i.e. metformin, sulfonylurea, and/or glitazone use) and insulin, we included the following potential confounding variables into the Cox regression as time-independent variables: age at oral medication index, sex, and chronic disease score (CDS). The CDS uses pharmacy dispensation information for specific drug classes to estimate the burden of comorbidities, and has proven valid in predicting hospitalization, health resource utilization, and mortality.[9,35] The CDS is the sum of all chronic diseases identified from drug therapies over the full follow-up period. For example, all study subjects had a minimum CDS of 2.0 because they were using oral antidiabetic drugs. Both age and the CDS were collapsed into quartiles. Proportional hazards assumption was met for age, sex, and CDS by comparing the hazard curves for each variable over time.

The same analytic approach was applied to the primary outcome of overall cancer mortality and for our secondary outcome of lung cancer mortality. As noted above, our primary analyses were based on cohorts with a minimum of 1-year drug exposure after the index date. In a sensitivity analysis, we repeated the time-varying Cox regression including patients who had a minimum of 6 months drug exposure following their index date. All analyses were completed using SPSS 17.0 (SPSS Inc 2009, Chicago, Illinois).

5.3 Results

There were 20,448 subjects who met the inclusion criteria and were identified as new users of oral antidiabetic therapies during the index period

January 1, 2000 to December 31, 2005. From this group, 910 (4.5%) subjects had less than one year drug therapy exposure following their index date and were excluded, leaving an inception cohort of 19,538 subjects who used oral antidiabetic drugs for >1 year. The mean (SD) duration of follow-up was 3.6 (1.7) years in the whole cohort.

There were 1,331 (6.8%) sulfonylurea monotherapy users, 4,586 (23.5%) sulfonylurea and metformin combination therapy users, 10,282 (52.6%) metformin monotherapy users, and 3,339 (17.1%) metformin and glitazone combination therapy users. There were 1,300 (6.7%) patients in the whole cohort who had insulin added on to their oral therapy regimen at some point during the follow-up period. Sulfonylurea monotherapy users were significantly older, more likely to be male, and had a higher CDS (Table 1). On the other hand, the glitazone (plus metformin) cohort had a longer duration of therapy and were more likely to start insulin (Table 1).

Among the 1,581 total deaths in the whole cohort, there were 412 (26.1%) overall cancer mortalities and 85 (5.4%) lung cancer mortalities across all drug exposure groups throughout the follow-up period. Overall cancer and lung cancer mortality were highest in the sulfonylurea monotherapy group (4.6% and 1.3%, respectively; $p<0.0001$) (Table 1).

The overall cancer mortality rate (per 1,000 person years of follow-up) was 11.8 in the sulfonylurea monotherapy group, 7.1 in the sulfonylurea and metformin combination group, 5.4 in the metformin monotherapy group, and 2.8 in the metformin and glitazone group (Table 2). The unadjusted hazard ratio (HR) and 95% confidence interval (CI) for overall cancer mortality was 0.53 (95% CI: 0.35–0.80) for glitazone (plus metformin) users compared to those on sulfonylurea monotherapy ($p=0.003$). In multivariable Cox regression analyses, the adjusted HR for overall cancer mortality was 0.74 (95% CI: 0.49–1.12) for glitazone (plus metformin) users. The adjusted HRs (95% CI) for insulin use were 1.67 (1.02–2.72; $p\leq0.05$) and 6.89 (4.89–9.71; $p<0.0001$) for <12 and ≥12 cumulative insulin dispensations per year, respectively, compared to those not exposed to insulin.

The lung cancer mortality rate was highest in the sulfonylurea monotherapy group (3.3 per 1,000 person years of follow-up). This is in comparison to a rate of 0.5 per 1,000 person years of follow-up in the glitazone (plus metformin) group (Table 3). In multivariable Cox regression analyses, the adjusted HR for glitazone (plus metformin) users was 0.40 (95% CI: 0.15–1.07). The adjusted HRs (95% CI) for insulin use were 2.37 (0.95–5.92) and 5.07 (2.17–11.87; $p<0.0001$) for <12 and ≥12 cumulative insulin dispensations per year, respectively, compared to those not exposed to insulin.

In a sensitivity analysis, we looked at patients who had a minimum of 6 months of drug exposure after oral index (N=19,915). Similar to our primary analyses, sulfonylurea monotherapy users were older, more likely to be male, had a higher CDS, and a higher overall cancer and lung cancer mortality. This is in comparison to the glitazones (plus metformin) cohort, which was more likely to start insulin and had a longer duration of follow-up (Appendix A, Table A1). Overall cancer mortality and lung cancer mortality continued to be lowest among the glitazone (plus metformin) users (adjusted HR: 0.71, 95%CI: 0.48-1.04 and adjusted HR: 0.47, 95% CI: 0.19-1.17, respectively), compared to those on sulfonylurea monotherapy (Table A2 and Table A3).

5.4 Discussion

In this retrospective population-based cohort study of new users of oral antidiabetic therapies, we observed a consistently decreased risk of overall cancer and lung cancer mortality associated with glitazone (plus metformin) use. While the confidence intervals for the risk estimates are wide and cross 1.0, this is largely an issue of statistical power, and we believe the consistency in the HR provides further evidence supporting a moderating role for antidiabetic therapies in the relationship between type 2 diabetes and cancer outcomes. These findings are consistent with the proposed biologic mechanism that antidiabetic agents which reduce insulin resistance, such as the glitazones and metformin, are thought to reduce the risk of tumour development and progression.[20-21] Although not formally tested in analyses, the observation of a greater risk reduction when the

two insulin sensitizers were used in combination than when metformin was used as monotherapy may be taken as further support of this hypothesis.

Our findings are in agreement with several other epidemiologic studies that have looked at the effect of glitazones and cancer outcomes in type 2 diabetes. Lewis et al conducted three nested case-control studies within a cohort of patients with diabetes to examine the association between glitazones and risk of colonic neoplasia. The authors found that glitazones were associated with a 27% reduction in the risk of colonic neoplasia.[26] Similarly, another study, in male patients 40 years or older diagnosed with diabetes, used a time-dependent Cox regression to look at glitazones and the risk of lung, prostate, and colon cancer.[27] They found that glitazones were associated with a significant 33% reduction in the risk of lung cancer and a nonsignificant risk reduction for prostate and colorectal cancers.[27] A recent meta-analysis of randomized clinical trials looking at rosiglitazone and risk of cancer found that rosiglitazone was associated with a decreased risk of cancer, although this modification was not statistically significant.[28] On the other hand, Koro et al observed a neutral effect of glitazones on breast, colon, and prostate cancers.[29]

However, these studies have several limitations. One key limitation is that only one of these studies examined the effect of other antidiabetic therapies in comparison to the glitazones.[29] Attention to specific combination of antidiabetic therapies is important in order to determine the relative harm or benefit of glitazones. Another important limitation is a short follow-up, or exposure period to glitazones, in order to properly attribute a protective effect or excess risk of glitazones on cancer outcomes.[27,29] Other studies were limited to select patient populations[27], had relatively small sample sizes[29], and were unable to control for potential confounders.[29] The one observational study reporting a positive association between rosiglitazone and cancer, has several key limitations.[30] It was a cross-sectional analysis of interviewed subjects, and the authors acknowledge that they lacked information on the time relation between onset of cancer and the use of glitazones, as well as on the duration of treatment.[30]

There is only one large randomized clinical trial in patients with type 2

diabetes that has looked at cancer risk as an outcome measure.[36] In this study patients were randomized to pioglitazone or placebo, which were added to their ongoing antidiabetic therapies. The authors concluded there was no difference in the risk of cancer between the two groups.[37-38] However, this comparison of pioglitazone versus placebo may have been confounded by use of other antidiabetic agents that have also been associated with cancer outcomes. At the end of the follow-up period, there were significantly more people on metformin and insulin in the placebo group than in the pioglitazone group. Since both insulin and metformin have been independently associated with cancer outcomes, the net effect of these increases in drug use in the placebo group at the end of the follow-up period would make it more difficult to detect a difference in the risk of cancer between the two groups. This draws further attention to the need of considering concurrent antidiabetic therapies, in establishing the relative effect of glitazones on cancer outcomes.

There are several strengths in the current study. Firstly, the Saskatchewan Health databases are known for their accuracy and comprehensiveness, which have been used in numerous studies of health outcomes in type 2 diabetes. Furthermore, we employed a new user design for oral antidiabetic therapy. This ensures an inception cohort of individuals who are at a similar stage of diabetes, and thus, minimizes possible confounding associated with both duration and severity of disease, and any associated survival biases. We also required patients to have at least 1 year drug exposure, which ensured a minimum induction period for exposure to antidiabetic therapy. In our cohort, patients on glitazone therapy had a mean exposure of 1.2 years on the drug. Another key strength is that we employed a time-varying Cox analysis to define drug exposures. By using a time-varying approach, we were able to obtain more precise estimates of effect than had we used the more traditional time-fixed approach in our analyses.[39-41] The time-varying analysis also overcomes some survival bias and confounding by duration that is present in studies which do not use this methodology.[39-41]

This study also has some limitations. Firstly, we recognize that there is likely a prescription bias, or confounding by indication. It is difficult in

observational studies such as ours, which used an administrative dataset, to fully account for the effect of differences in characteristics of patients when receiving different therapeutic options. Since we used administrative data, we lacked info on potentially important clinical variables, such as hemoglobin A1c, smoking status, body mass index (BMI), and physical activity level. These are all potential confounders in the relationship between choice of drug therapy and cancer mortality in type 2 diabetes. However, we feel that our findings are robust to these excluded data, especially given the consistent results to those of similar studies when such potential confounders have been included.[26-27]

Another limitation is that our study had limited power in the dataset we used to address this question. Despite being a population-based study, there was a relatively small number of events in our analysis, also precluding us from looking more closely at other cancer subtypes. Lung cancer mortality was the only subtype we chose to examine more closely, as it had the largest number of events, but also due to its clinical relevance and ongoing controlled trials.[25] We also lacked control for the underlying risk of diabetes (i.e. a non-diabetes control group) in our study. It would be useful in future studies to have a non-diabetes control group as the reference group. Finally, we examined cancer mortality as our outcome measure, as opposed to the more proximal outcome of cancer incidence. There may be many intervening events, which could possibly alter the risk of cancer mortality once a diagnosis of cancer has been established. Nonetheless, as we have no reason to suspect that management of cancer would differ based on exposure to antidiabetic therapies, it is likely that differences in cancer mortality would be due to difference in the incidence or aggressiveness of the cancer itself.

In summary, we observed a HR consistent with a decreased risk of cancer mortality associated with glitazone and metformin use in a cohort of patients with type 2 diabetes. We believe these findings add further support that antidiabetic therapies may play a moderating role in the relationship between type 2 diabetes and cancer outcomes. These observations require confirmation in larger

prospective studies with adequate power to assess the incidence of various cancer subtypes.

Table 5.1. Patient Characteristics Stratified By Drug Exposure Group (N = 19,538)

	Sulfonylurea Monotherapy	Sulfonylurea and Metformin Combination	Metformin Monotherapy	Metformin and Glitazone Combination
N	1,331	4,586	10,282	3,339
Age at Oral Index (Years)				
Mean (Standard Deviation, SD)	68.3 (13.7)*	61.3 (13.7)	60.6 (14.4)	57.5 (12.7)
Median (Range)	70 (30-107)	61 (30-99)	61 (30-102)	57 (30-98)
Men, N (%)	767 (57.6)†	2,629 (57.3)†	5,260 (51.2)	1,838 (55.0)
Insulin Exposure, (%)	77 (5.8)	512 (11.2)†	325 (3.2)	386 (11.6)†
Duration of Follow-Up (Years), Mean (SD)	3.9 (1.8)	4.2 (1.7)*	3.2 (1.6)	4.2 (1.7)*
Total Person Years of Follow-up	5188.2	19329.0	32551.9	13995.4
Chronic Disease Score, Mean (SD)	6.1 (3.3)*	5.6 (3.3)	5.7 (3.2)	5.6 (3.1)
Overall Cancer Mortality, N (%)	61 (4.6)†	137 (3.0)	175 (1.7)	39 (1.2)
Lung Cancer Mortality, N (%)	17 (1.3)†	24 (0.5)	37 (0.4)	7 (0.2)

*P <0.0001 by ANOVA

†P <0.0001 by Chi-square test

Table 5.2. Overall Cancer Mortality and Adjusted Hazard Ratio (HR) (95% CI) From Time-Varying Multivariable Cox Regression (N=19,538).

	Total N	Overall Cancer Mortality N (%)	Overall Cancer Mortality Rate (/1000 P-Yr)	Adjusted* HR (95% CI)
Oral Antidiabetics				
Sulfonylurea Monotherapy	1,331	61 (4.6)	11.8	1.0
Sulfonylurea and Metformin	4,586	137 (3.0)	7.1	0.96 (0.70-1.30)
Metformin Monotherapy	10,282	175 (1.7)	5.4	0.81 (0.63-1.04)
Metformin and Glitazone	3,339	39 (1.2)	2.8	0.74 (0.49-1.12)
Insulin Use (Cumulative Insulin Dispensations/Year)**				
No Insulin Use Ever	65,285	353 (1.9)	-	1.0
<12	2,958	17	-	1.67 (1.02-2.72)†
≥12	2,821	42	-	6.89 (4.89-9.71)‡
Age				
≤51 years old	5,388	23 (0.4%)	1.1	1.0
52-61 years old	4,764	63 (1.3%)	3.6	3.26 (2.02–5.26)‡
62-72 years old	4,860	134 (2.8%)	7.5	6.63 (4.24–10.38)‡
≥73 years old	4,526	192 (4.2%)	12.5	11.39 (7.31–17.74)‡
Sex				
Female	9,044	163 (1.8)	5.0	1.0
Male	10,494	249 (2.4)	6.5	1.39 (1.14–1.70)§
Comorbidity				
CDS 0-2	4,489	68 (1.5)	3.9	1.0
CDS 3-5	5,841	112 (1.9)	5.2	1.08 (0.80–1.46)
CDS 6-8	5,784	124 (2.1)	6.0	1.03 (0.76–1.39)
CDS ≥9	3,424	108 (3.2)	9.4	1.38 (1.01–1.89)

*Adjusted for all other covariates in the table; **Specific rates cannot be estimated for insulin exposure categories, because of the time-varying nature of exposure. Cancer deaths are calculated based on the insulin category at the time of cancer death, and the total N is time at risk in each insulin category; †$p \leq 0.05$; ‡$p < 0.0001$; §$p = 0.001$

Table 5.3. Lung Cancer Mortality and Adjusted Hazard Ratio (HR) (95% CI) From Time-Varying Multivariable Cox Regression (N=19,538).

	Total N	Lung Cancer Mortality N (%)	Lung Cancer Mortality Rate (/1000 P-Yr)	Adjusted* HR (95% CI)
Oral Antidiabetics				
Sulfonylurea Monotherapy	1,331	17 (1.3)	3.3	1.0
Sulfonylurea and Metformin	4,586	24 (0.5)	1.2	0.69 (0.36-1.30)
Metformin Monotherapy	10,282	37 (0.4)	1.1	0.57 (0.34-0.95)**
Metformin and Glitazone	3,339	7 (0.2)	0.5	0.40 (0.15-1.07)
Insulin Use (Cumulative Insulin Dispensations/Year)†				
No Insulin Use Ever	65,285	74 (0.4)	-	1.0
<12	2,958	5	-	2.37 (0.95-5.92)
≥12	2,821	6	-	5.07 (2.17-11.87)‡
Age				
≤51 years old	5,388	5 (0.1%)	0.2	1.0
52-61 years old	4,764	13 (0.3%)	0.7	3.06 (1.09–8.62)**
62-72 years old	4,860	34 (0.7%)	1.9	7.54 (2.91–19.55)‡
≥73 years old	4,526	33 (0.7%)	2.2	8.65 (3.29–22.72)‡
Sex				
Female	9,044	31 (0.3)	0.9	1.0
Male	10,494	54 (0.5)	1.4	1.51 (0.97–2.37)
Comorbidity				
CDS 0-2	4,489	16 (0.4)	0.9	1.0
CDS 3-5	5,841	23 (0.4)	1.1	0.98 (0.52–1.87)
CDS 6-8	5,784	23 (0.4)	1.1	0.86 (0.45–1.66)
CDS ≥9	3,424	23 (0.7)	2.0	1.37 (0.71–2.66)

*Adjusted for all other covariates in the table; ** p≤0.05; †Specific rates cannot be estimated for insulin exposure categories, because of the time-varying nature of exposure. Cancer deaths are calculated based on the insulin category at the time of cancer death, and the total N is time at risk in each insulin category; ‡p<0.0001

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CHAPTER 6: GENERAL DISCUSSION AND CONCLUSIONS

6.1 Summary of Research

The findings from this program of research provide further evidence of the relationship between antidiabetic therapies and cancer outcomes in type 2 diabetes. Across the four separate analyses, we observed, as hypothesized, an increased risk of cancer mortality associated with antidiabetic therapies that increase circulating insulin levels (i.e. sulfonylureas and exogenous insulin) and a decreased risk of cancer mortality associated with antidiabetic therapies that reduce insulin resistance (i.e. metformin and glitazones). In addition, we observed a dose-response gradient for exogenous insulin use, whereby patients exposed to higher levels of insulin therapy had a higher risk of cancer mortality. Our conclusions of an association between antidiabetic therapies and cancer mortality from this line of research are strengthened by the general agreement with other epidemiologic studies examining these agents[1-8] and the proposed biologic mechanisms for antidiabetic therapies and tumour cell growth[9-17].

6.2 Significance of Research

From a public health perspective, the impact of the combination of type 2 diabetes and cancer is substantial. Both cancer and diabetes are chronic diseases of a long duration, and are increasingly prevalent in the general population.[18-21] The majority of the public health burden attributed to diabetes is a result of the morbidity related to microvascular and macrovascular complications in this patient population. The prevalence of cardiovascular disease is significantly higher in people with diabetes compared to those without.[22] Moreover, cardiovascular disease, including macrovascular complications of type 2 diabetes, and cancer are two of the leading causes of death in Canada.[23-24] Therefore, these chronic diseases place a large economic burden on our health care system, and significantly impact the day-to-day functioning of people with these conditions.[25-29]

We used advanced analytic techniques to answer our research question. By using a time-varying Cox regression to define drug exposures, we were able to obtain more precise estimates of effect and minimize some of the survival biases associated with using a time-fixed survival analysis.[30-32] Other research on this topic has not used a time-varying approach to define drug exposures.[1-3,5,6] Furthermore, this line of research is the first to control for individual drug effects separately. Previous research did not separate drug treatment groups, so it was difficult to determine the relative harms and benefits of the different drugs being studied.[1-6]

Although it is still not widely known in the clinical community, the epidemiologic association between diabetes and cancer has been recognized for some time. This line of research provides additional evidence that there might be some therapeutic benefit associated with antidiabetic therapies that ameliorate insulin resistance (i.e. metformin and glitazones), relative to therapies which increase circulating insulin levels (i.e. sulfonylureas and exogenous insulin).

Given the two conditions that are being considered, this line of research may have implications for the management of either cancer or diabetes. Despite recent evidence of the glitazones being investigated as chemopreventive agents and metformin as an adjuvant therapy in breast cancer, it is unlikely that the findings from this line of research will directly affect clinical practice in the field of oncology.[15,16,33] The findings from this line of research were not intended to answer the question of whether antidiabetic therapies will alter treatment regimens in oncology. If anything, the conclusions herein are hypothesis-generating and will stimulate more research in the area of oncology. For example, research by Goodwin et al examined the insulin-lowering effects of metformin in nondiabetic women with early breast cancer, postulating that if metformin reduces insulin levels in women with breast cancer, it may also improve breast cancer outcomes.[33] Indeed, they found that metformin significantly reduced insulin levels and improved insulin resistance in nondiabetic women with breast cancer, and the authors recommend a phase III randomized trial to evaluate the effects of metformin on breast cancer outcomes.[33] Similarly, biologic evidence of glitazones

reducing cell growth has sparked interest in the field of oncology, and there are currently clinical trials underway examining pioglitazone in the prevention and treatment of lung cancer.[34] However, additional research and consistent evidence on this topic is required before making strong statements regarding therapeutic management in oncology.

On the other hand, awareness of the moderating role of antidiabetic therapies in the relationship between diabetes and cancer outcomes has important implications for prevention and management of type 2 diabetes. The 2008 Canadian Diabetes Association Clinical Practice Guidelines (CDA CPG) suggest adjustment and addition of antihyperglycemic agents in order to attain a target hemoglobin A1c level of 7.0% within 6 to 12 months of diagnosis of type 2 diabetes.[35] Specifically, the guidelines suggest initiating patients with an A1c <9.0% on metformin.[35] It is recommended that patients with an A1c ≥9.0% be initiated on metformin concurrently with another agent from a different class, or insulin.[35] By using metformin as the first line of therapy in patients with type 2 diabetes, the guidelines will drive the positive implications of this line of research. However, in patients with marked hyperglycemia (i.e. A1c ≥9.0%), the positive impacts of using metformin may be outweighed by the negative impacts of adding sulfonylureas or exogenous insulin therapy on to the treatment regimen. Therefore, as an extension of this program of research, perhaps we should focus on managing patients with type 2 diabetes with metformin and glitazones, as a means of attaining target A1c levels, and be cautious in the earlier initiation and aggressiveness of insulin therapy.

6.3 Limitations and Implications for Future Research

Although we were able to add to the growing evidence assessing the moderating role of antidiabetic therapies in the relationship between type 2 diabetes and cancer mortality, there were a number of limitations to our line of research that future studies could address. Firstly, since we used administrative data for our observational cohort studies, we lacked information on several potentially important clinical variables, such as hemoglobin A1c, smoking status,

body mass index (BMI), diet, alcohol intake, and physical activity level. These are all potential confounders in the relationship between choice of drug therapy and cancer mortality in people with type 2 diabetes. However, our results are consistent with other studies that have included information on such clinical covariates.[1,3,4] Nonetheless, it would be useful to have information on such clinical variables in future studies, as a means to confirm and strengthen our findings.

Another limitation is that we lacked control for the underlying risk of diabetes on cancer outcomes, which would have been possible with a non-diabetes control group. It would be useful to have a non-diabetes control group as the reference group in order to more specifically see the relative harms and benefits of different therapeutic options in type 2 diabetes. In our line of research, we compared antidiabetic therapies to one another. Therefore, it was not entirely clear whether the effects we observed were related to a protective effect of metformin and glitazone therapy or a toxic effect of sulfonylureas and exogenous insulin therapy. By having a non-diabetes control group as a reference group, we would be able to more clearly ascertain these effects.

In all of our analyses, the primary outcome of interest was overall cancer mortality. It would be useful in future research to look at the more proximal outcome of different types of cancer incidence, as opposed to cancer mortality, when assessing the effects of different antidiabetic therapies. There may be many intervening events, such as stage or aggressiveness of the cancer, or different types of treatments for cancer, which could potentially alter the risk of cancer mortality once a diagnosis of cancer has been established.

Furthermore, although our outcome measure was overall cancer mortality, the epidemiologic evidence examining the effect of antidiabetic therapies on cancer outcomes has generally focused on one type of cancer.[2,3,4] These observational studies of antidiabetic therapies tended to focus on the incidence of colon, pancreatic, lung, and prostate cancers. Unfortunately, the administrative data we used to address this line of research had limited power to address specific

cancer outcomes. Despite being a population-based study, there was a relatively small number of events in our analysis, which precluded us from looking more closely at different cancer mortality subtypes. This limitation could be overcome in future studies that are powered to specifically address the question of the effect of antidiabetic therapies on the incidence of cancer.

Lastly, it would be worthwhile to look at the different types of insulin, sulfonylureas, and glitazones when examining effects of antidiabetic therapies on cancer outcomes. The mitogenic potency of the newly available insulin analogs has received some attention in the literature. Insulin glargine, a long-acting insulin analog, has the strongest mitogenic potency among insulin analogs, when compared to human synthetic insulin.[36] Therefore, it would be interesting to look at analog versus human biosynthetic insulin or long-acting versus short-acting insulin when exploring their effect on cancer outcomes. Given the evidence of an increased risk of cancer with the sulfonylurea glibenclamide, it would also be useful to look at the effects of all sulfonylureas separately (i.e. gliclazide, glimepiride, glyburide).[5] We were unable to look at the effects of different sulfonylureas, insulins, and glitazones in this line of research because the small number of events in our studies precluded us from having more refined drug exposure categories. Therefore, this is a subject that requires further attention and larger population-based epidemiologic studies in different populations are needed to answer these questions.

6.4 Conclusions

We observed an increased risk of cancer mortality associated with antidiabetic therapies that increase circulating insulin levels (i.e. sulfonylureas and exogenous insulin) and a decreased risk of cancer mortality associated with antidiabetic therapies that reduce insulin resistance (i.e. metformin and glitazones). We also observed a dose-response gradient for exogenous insulin use, whereby patients exposed to higher levels of insulin therapy had a higher risk of

cancer mortality. Further research on this topic is required in larger population-based studies to confirm our findings.

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APPENDICES

Appendix A. Patient Characteristics Stratified By Drug Exposure Group (<6 Months Drug Exposure Excluded, N=19,915).

	Sulfonylurea Monotherapy	Sulfonylurea and Metformin Combination	Metformin Monotherapy	Metformin and Glitazone Combination
N	1,422	4,666	10,473	3,354
Age at Oral Index (Years)				
Mean (Standard Deviation, SD)	68.7 (13.7)*	61.4 (13.8)	60.8 (14.5)	57.6 (12.7)
Median (Range)	71 (30-107)	61 (30-100)	61 (30-102)	57 (30-98)
Men, N (%)	818 (57.5)†	2,675 (57.3)†	5,361 (51.2)	1,846 (55.0)
Insulin Exposure, (%)	81 (5.7)	521 (11.2)†	331 (3.2)	387 (11.5)†
Duration of Follow-Up (Years), Mean (SD)	3.7 (1.9)	4.2 (1.7)*	3.1 (1.6)	4.2 (1.7)*
Total Person Years of Follow-up	5254.8	19390.3	32696.0	14007.7
Chronic Disease Score, Mean (SD)	6.2 (3.4)*	5.6 (3.3)	5.7 (3.2)	5.6 (3.1)
Cancer Mortality, N (%)	84 (5.9)†	156 (3.3)	218 (2.1)	42 (1.3)
Lung Cancer Mortality, N (%)	20 (1.4)†	27 (0.6)	46 (0.4)	8 (0.2)

*P <0.0001 by ANOVA

†P <0.0001 by Chi-square test

Appendix B. Overall Cancer Mortality and Adjusted Hazard Ratio (HR) (95% CI) From Time-Varying Multivariable Cox Regression (<6 Months Drug Exposure Excluded, N=19,915).

	Total N	Overall Cancer Mortality N (%)	Overall Cancer Mortality Rate (/1000 P-Yr)	Adjusted* HR (95% CI)
Oral Antidiabetics				
Sulfonylurea Monotherapy	1,422	84 (5.9)	16.0	1.0
Sulfonylurea and Metformin	4,666	156 (3.3)	8.0	0.94 (0.72-1.24)
Metformin Monotherapy	10,473	218 (2.1)	6.7	0.74 (0.59-0.93)**
Metformin and Glitazone	3,354	42 (1.3)	3.0	0.71 (0.48-1.04)
Insulin Use (Cumulative Insulin Dispensations/Year)†				
No Insulin Use Ever	65,554	433 (2.3)	-	1.0
<12	2,962	18	-	1.61 (1.00-2.60)‡
≥12	2,833	49	-	6.87 (4.94-9.54)§
Age				
≤51 years old	5,435	26 (0.5%)	1.3	1.0
52-61 years old	4,814	72 (1.5%)	4.1	3.21 (2.05–5.04)§
62-72 years old	4,928	160 (3.2%)	8.9	6.75 (4.44–10.27)§
≥73 years old	4,738	242 (5.1%)	15.6	11.82 (7.81–17.88)§
Sex				
Female	9,215	198 (2.1)	6.0	1.0
Male	10,700	302 (2.8)	7.8	1.41 (1.17–1.68)§
Comorbidity				
CDS 0-2	4,539	77 (1.7)	4.4	1.0
CDS 3-5	5,917	128 (2.2)	5.9	1.07 (0.80–1.42)
CDS 6-8	5,898	153 (2.6)	7.4	1.09 (0.82–1.44)
CDS ≥9	3,561	142 (4.0)	12.3	1.53 (1.15–2.04)**

*Adjusted for all other covariates in the table; **p<0.01; †Specific rates cannot be estimated for insulin exposure categories, because of the time-varying nature of exposure. Cancer deaths are calculated based on the insulin category at the time of cancer death, and the total N is time at risk in each insulin category; ‡p≤0.05; §p<0.0001

Appendix C. Lung Cancer Mortality and Adjusted Hazard Ratio (HR) (95% CI) From Time-Varying Multivariable Cox Regression (<6 Months Drug Exposure Excluded, N=19,915).

	Total N	Lung Cancer Mortality N (%)	Lung Cancer Mortality Rate (/1000 P-Yr)	Adjusted* HR (95% CI)
Oral Antidiabetics				
Sulfonylurea Monotherapy	1,422	20 (1.4)	3.8	1.0
Sulfonylurea and Metformin	4,666	27 (0.6)	1.4	0.74 (0.41-1.34)
Metformin Monotherapy	10,473	46 (0.4)	1.4	0.60 (0.37-0.97)**
Metformin and Glitazone	3,354	8 (0.2)	0.6	0.47 (0.19-1.17)
Insulin Use (Cumulative Insulin Dispensations/Year)†				
No Insulin Use Ever	65,554	89 (0.5)	-	1.0
<12	2,962	5	-	2.16 (0.87-5.38)
≥12	2,833	7	-	4.66 (2.00-10.84)‡
Age				
≤51 years old	5,435	5 (0.1%)	0.2	1.0
52-61 years old	4,814	16 (0.3%)	0.9	3.64 (1.33–9.98)§
62-72 years old	4,928	38 (0.8%)	2.1	8.02 (3.12–20.61)‡
≥73 years old	4,738	42 (0.9%)	2.7	10.13 (3.93–26.17)‡
Sex				
Female	9,215	37 (0.4)	1.1	1.0
Male	10,700	64 (0.6)	1.7	1.54 (1.03–2.32)**
Comorbidity				
CDS 0-2	4,539	16 (0.4)	0.9	1.0
CDS 3-5	5,917	28 (0.5)	1.3	1.17 (0.63–2.18)
CDS 6-8	5,898	26 (0.4)	1.3	0.95 (0.50–1.79)
CDS ≥9	3,561	31 (0.9)	2.7	1.78 (0.95–3.32)

*Adjusted for all other covariates in the table; **p≤0.05; †Specific rates cannot be estimated for insulin exposure categories, because of the time-varying nature of exposure. Cancer deaths are calculated based on the insulin category at the time of cancer death, and the total N is time at risk in each insulin category; ‡p<0.0001; §p=0.01

Appendix D. Patient Characteristics for the Whole Cohort Stratified By Drug Exposure Group (No Drug Exposures Excluded, N=20,448).

	Sulfonylurea Monotherapy	Sulfonylurea and Metformin Combination	Metformin Monotherapy	Metformin and Glitazone Combination
N	1,577	4,758	10,755	3,358
Age at Oral Index (Years)				
Mean (Standard Deviation, SD)	69.3 (13.7)*	61.7 (13.9)	61.1 (14.6)	57.6 (12.7)
Median (Range)	71 (30-107)	62 (30-100)	61 (30-102)	57 (30-98)
Men, N (%)	910 (57.7)†	2,726 (57.3)†	5,523 (51.4)	1,847 (55.0)
Insulin Exposure, (%)	90 (5.7)	533 (11.2)†	349 (3.2)	387 (11.5)†
Duration of Follow-Up (Years), Mean (SD)	3.4 (2.1)	4.1 (1.8)*	3.0 (1.6)	4.2 (1.7)*
Total Person Years of Follow-up	5287.8	19412.0	32760.7	14008.7
Chronic Disease Score, Mean (SD)	6.4 (3.4)*	5.7 (3.4)	5.8 (3.3)	5.6 (3.1)
Cancer Mortality, N (%)	154 (9.8)†	192 (4.0)	298 (2.8)	43 (1.3)
Lung Mortality, N (%)	27 (1.7)†	38 (0.8)	67 (0.6)	8 (0.2)

*P <0.0001 by ANOVA

†P <0.0001 by Chi-square test

Appendix E. Overall Cancer Mortality and Adjusted Hazard Ratio (HR) (95% CI) From Time-Varying Multivariable Cox Regression (No Drug Exposures Excluded, N=20,448).

	Total N	Overall Cancer Mortality N (%)	Overall Cancer Mortality Rate (/1000 P-Yr)	Adjusted* HR (95% CI)
Oral Antidiabetics				
Sulfonylurea Monotherapy	1,577	154 (9.8)	29.1	1.0
Sulfonylurea and Metformin	4,758	192 (4.0)	9.9	0.78 (0.63-0.98)**
Metformin Monotherapy	10,755	298 (2.8)	9.1	0.56 (0.47-0.67)†
Metformin and Glitazone	3,358	43 (1.3)	3.1	0.50 (0.35-0.72)†
Insulin Use (Cumulative Insulin Dispensations/Year)‡				
No Insulin Use Ever	65,666	600 (3.1)	-	1.0
<12	2,963	18	-	1.39 (0.87-2.23)
≥12	2,841	69	-	7.828 (5.42-9.77)†
Age				
≤51 years old	5,474	35 (0.6%)	1.7	1.0
52-61 years old	4,871	98 (2.0%)	5.6	3.09 (2.10–4.55)†
62-72 years old	5,046	218 (4.3%)	12.1	6.24 (4.35–8.96)†
≥73 years old	5,057	336 (6.6%)	21.6	10.32 (7.23–14.75)†
Sex				
Female	9,442	270 (2.9)	8.2	1.0
Male	11,006	417 (3.8)	10.8	1.43 (1.23–1.67)†
Comorbidity				
CDS 0-2	4,595	91 (2.0)	5.2	1.0
CDS 3-5	6,016	166 (2.8)	7.7	1.17 (0.91–1.52)
CDS 6-8	6,060	209 (3.4)	10.1	1.25 (0.97–1.60)
CDS ≥9	3,777	221 (5.9)	19.0	1.96 (1.52–2.52)†

*Adjusted for all other covariates in the table; **p≤0.05; †p<0.0001; ‡Specific rates cannot be estimated for insulin exposure categories, because of the time-varying nature of exposure. Cancer deaths are calculated based on the insulin category at the time of cancer death, and the total N is time at risk in each insulin category.

Appendix F. Lung Cancer Mortality and Adjusted Hazard Ratio (HR) (95% CI) From Time-Varying Multivariable Cox Regression (No Drug Exposures Excluded, N=20,448).

	Total N	Lung Cancer Mortality N (%)	Lung Cancer Mortality Rate (/1000 P-Yr)	Adjusted* HR (95% CI)
Oral Antidiabetics				
Sulfonylurea Monotherapy	1,577	27 (1.7)	5.1	1.0
Sulfonylurea and Metformin	4,758	38 (0.8)	2.0	0.93 (0.57-1.54)
Metformin Monotherapy	10,755	67 (0.6)	2.0	0.65 (0.43-0.99)**
Metformin and Glitazone	3,358	8 (0.2)	0.6	0.44 (0.18-1.07)
Insulin Use (Cumulative Insulin Dispensations/Year)†				
No Insulin Use Ever	65,666	124 (0.6)		1.0
<12	2,963	5		1.82 (0.74-4.49)
≥12	2,841	11		5.90 (2.94-11.82)‡
Age				
<45 years old	5,474	6 (0.1%)	0.3	1.0
45-49.9 years old	4,871	20 (0.4%)	1.1	3.73 (1.49–9.31)§
50.0-54.9 years old	5,046	53 (1.1%)	2.9	9.03 (3.84–21.21)‡
55.0-59.9 years old	5,057	61 (1.2%)	3.9	11.25 (4.78–26.49)‡
Sex				
Female	9,442	49 (0.5)	1.5	1.0
Male	11,006	91 (0.8)	2.4	1.69 (1.19–2.39)§
Comorbidity				
CDS ≤6	4,595	21 (0.5)	1.2	1.0
CDS 7-8	6,016	35 (0.6)	1.6	1.09 (0.63–1.89)
CDS 9-11	6,060	31 (0.5)	1.5	0.83 (0.47–1.46)
CDS ≥12	3,777	53 (1.4)	4.6	2.15 (1.27–3.63)§

*Adjusted for all other covariates in the table; **p≤0.05; †Specific rates cannot be estimated for insulin exposure categories, because of the time-varying nature of exposure. Cancer deaths are calculated based on the insulin category at the time of cancer death, and the total N is time at risk in each insulin category; ‡p<0.0001; §p<0.01