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ARTICLE

Glucose-lowering agents and cancer mortality rates in type 2 diabetes: assessing effects of time-varying exposure

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Abstract
Aims/hypothesis We explored the relationship between glucose-lowering agents and cancer mortality rates in type 2 diabetes patients, hypothesising a decreased risk of cancer mortality with metformin use and a dose–risk gradient for insulin therapy.
Methods This was a population-based cohort study using administrative data from Saskatchewan Health, Canada. We identified new users of metformin or sulfonylureas from 1 January 1991 to 31 December 1996, with follow-up until death, departure from the province or 31 December 1999. Cox regression analyses were used to estimate the HR of death from cancer, accounting for time-varying exposure to metformin, sulfonylurea, and exogenous insulin therapy.
Results We identified 10,309 new users of metformin or sulfonylurea. The average follow-up was 5.4 (1.9) years, during which 407 (4.0%) cancer deaths occurred. Adjusting for age, sex and chronic disease score, the adjusted HR for metformin use was 0.80 (95% CI 0.65–0.98) compared with sulfonylurea monotherapy users. Adjusted HRs for subsequent insulin use were 2.22 (0.99–5.00), 3.33 (2.26–4.89) and 6.40 (4.69–8.73) for <3, 3 to 11 and ≥12 insulin dispensations/year, respectively, compared with patients not on insulin. We observed a similar risk gradient among the sub-cohort of new insulin users.
Conclusions/interpretation Our results support previous reports of a decreased risk of cancer outcomes associated with metformin use relative to sulfonylurea monotherapy. We also provide new evidence of a gradient of cumulative insulin dispensations and cancer mortality rates.

Keywords Cancer mortality · Glucose-lowering agents · Insulin therapy · Time-varying exposure · Type 2 diabetes

Abbreviation
CDS Chronic disease score

Introduction

There is substantial evidence indicating that patients with type 2 diabetes have an increased risk of cancer and cancer mortality [1–6]. The relationship between type 2 diabetes and various forms of cancer is biologically plausible, with insulin resistance, hyperinsulinaemia and elevated levels of IGF-1 in patients with type 2 diabetes involved in promotion of tumour cell growth [7, 8].

Increasing evidence also supports the possibility that glucose-lowering agents play a role in the relationship between type 2 diabetes and cancer. Treatments such as metformin, which decrease insulin resistance, are thought to reduce the risk of tumour development [9–14]. On the other hand, treatments that increase circulating insulin levels, such as sulfonylureas and exogenous insulin, are thought to increase the risk of cancer [15, 16]. Of particular interest, is the recent epidemiological evidence surrounding different types of insulin and the different mitogenic potencies of insulin analogues [17]. However, the available epidemiological and trial evidence suggests that risk from analogues is no greater than from regular human insulin [18–22]. Limitations of these previous studies are that: (1) they

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included type 1 and type 2 diabetes; and (2) they analysed prevalent, rather than new insulin use.

In a previous study [23], we used a time-fixed Cox regression to evaluate the relationship between glucose-lowering agents and cancer mortality rates. We observed a significantly increased risk of cancer mortality associated with sulfonylurea monotherapy use compared with metformin use (alone or in combination with sulfonylurea), as well as an increased risk of cancer mortality associated with insulin use. Certain biases are inherent in not considering changes in therapy exposures over time, and these may have led to under- or overestimation of the underlying degree of association in our previous study [24–26]. The most common bias associated with such time-independent analyses is survival (or immortal time) bias, which we recognise as being a likely factor in our previous study [23]. We therefore extended our analyses, by classifying time-varying exposure of metformin, sulfonylureas and insulin therapy. This allowed us to obtain more precise risk estimates and examine more closely the dose–response effect of insulin use on cancer mortality rates. We were also interested in the independent effect of new insulin use in patients previously exposed to oral glucose-lowering agents.

Methods

Study design The dataset used for this study has been described in detail previously [23]. 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 1 January 1991 to 31 December 1996. Patients had to be at least 30 years old on the index date (i.e. date of the first claim for an oral glucose-lowering agent 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 patients who had less than 1 year of drug exposure following their index date. Patients with gestational diabetes were also excluded. All study participants were followed prospectively from their index date until death, termination of coverage (e.g. departure from the province) or 31 December 1999, providing a maximum follow-up of 9 years. The primary outcome measure for this study was death from cancer, 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 10 ml vial or 3 ml 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 cohort entry. Participants were grouped according to glucose-lowering agent use as metformin users (alone or in combination with sulfonylurea) or sulfonylurea monotherapy users [23]. 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 χ^2 square tests for categorical variables.

We completed two analyses for the purpose of this study. Our primary analysis looked at cancer mortality rates among new users of metformin or sulfonylureas (new oral user cohort). Among this new oral user cohort, we then identified a subset who subsequently started using insulin therapy (new insulin user cohort). In this new insulin user cohort, all participants had previous exposure to metformin, sulfonylurea or a combination of both, but no prior record of insulin use. The new insulin user cohort was examined in our secondary analysis, mainly to evaluate the dose–response relationship between insulin and risk of death from cancer, given that these patients had started insulin therapy. Because insulin use occurs only if the patient survives and his/her disease progresses to the stage where insulin therapy is necessary, non-insulin use periods in the primary analysis are subject to potential 'survival bias', namely the potential bias between patients who survive and progress to receive insulin therapy and patients who do not survive and progress to receive insulin. The purpose of the secondary analysis was to alleviate this bias in evaluating the effects of increasing insulin exposure.

In both cohorts, we performed Cox regression analysis to evaluate the relationship between glucose-lowering agents and cancer mortality rates. In the analysis of the new oral user cohort, time zero was set at the start of oral drug use (i.e. metformin or sulfonylurea), while in the analysis of the new insulin user cohort, time zero was set at the start of insulin use. The time-varying nature and definitions (see below) of metformin, sulfonylurea and insulin use variables were the same in both analyses, the only difference between the two cohorts being the difference in start time. For both cohorts, our a priori hypotheses were that: (1) a decreased risk of death from cancer is associated with metformin use;

and (2) a gradient in risk of death from cancer is associated with insulin exposure, with patients exposed to more insulin therapy having an increased risk of cancer mortality.

Time-varying exposure to metformin and sulfonylureas was defined by the use of that agent (i.e. dichotomous yes/no exposure) within 1-year time windows. For insulin use, we calculated the 'average 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 1-year time window from the insulin index date. The cumulative sum of insulin exposures for each 1-year time window was then divided by the number of person-years that a patient was on insulin up to the end of the respective time window, thus arriving at the time-varying 'average cumulative insulin exposure per year' for each individual. Therefore, the value for cumulative insulin exposure varied for each 1-year time window after insulin index. For both cohorts, the cumulative insulin exposure per year variable was stratified into the following categories: (1) no exposure to insulin (reference group for new oral user cohort); (2) less than three cumulative insulin dispensations/year (reference group for new insulin user cohort); (3) 3 to 11 cumulative insulin dispensations/year; and (4) ≥12 cumulative insulin dispensations/year.

In addition to time-varying exposure to metformin, sulfonylurea and insulin use, in both analyses we included several potential confounding variables in the Cox regression. In the new oral user cohort, we included age at oral medication index, sex and chronic disease score (CDS), and in the new insulin user cohort, we included age at insulin index, sex, CDS and duration of oral therapy prior to start of insulin use. These potential confounding variables were all entered as time-fixed variables in both models. The CDS uses pharmacy dispensation information for specific drug classes to estimate the burden of comorbidities and has proven valid in predicting hospitalisation, health resource utilisation and mortality rates [23, 27]. The CDS is the sum of all chronic diseases identified from drug therapies over the full follow-up period. For example, all study participants had a minimum CDS of 2.0 because they were using oral glucose-lowering agents. The proportional hazards assumption was assessed graphically for all time-fixed covariates, by comparing the log (−log [survival]) vs log of survival time plots. SPSS 17.0 (SPSS, Chicago, IL, USA) was used for all analyses.

Results

New oral user cohort There were 12,272 participants who met the inclusion criteria and were identified as new users of oral glucose-lowering agents from 1991 to 1996. From this group, 1,963 (16.0%) participants had less than 1 year drug therapy exposure following the index date and were excluded. This left an inception cohort of 10,309 participants who used oral glucose-lowering agents 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 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. Sulfonylurea monotherapy users were significantly older and more likely to be men, while metformin users had a longer duration of therapy and a higher CDS (Table 1).

There were 407 (3.9%) cancer deaths in the whole cohort throughout the follow-up period, of which 245 (3.5%) were among metformin users and 162 (4.9%) in the sulfonylurea monotherapy group (Table 2). 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).

In multivariable Cox regression analyses, the adjusted HR for metformin use, relative to sulfonylurea monotherapy use, was 0.80 (95% CI 0.65–0.98; $p=0.03$). The adjusted HRs (95% CI) for insulin use compared with participants not exposed to insulin 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 fewer than three, 3 to 11 and 12 or more cumulative insulin dispensations per year, respectively (Table 2).

New insulin user cohort Among the oral glucose-lowering agent user cohort, we identified a subset of 1,443 patients who subsequently went on to become new users of insulin (Table 3). The mean (SD) duration of insulin use was 2.5 (2.0) years and mean (SD) age at insulin index was 63.0 (14.7) years. Among our new insulin users, there were 1,137 (78.8%) metformin users (i.e. metformin alone or in combination) and 306 (21.2%) sulfonylurea monotherapy users. Among the metformin users at time of insulin start, 1,058 (93.1%) were 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 in the whole new insulin user cohort throughout the follow-up period (Table 4). In multivariable Cox regression analyses, the adjusted HRs (95% CI) for insulin use compared with the reference group were 1.35 (0.56–3.28) and 2.47 (1.05–5.84; $p\leq0.05$) for 3 to 11 and 12 or more cumulative insulin dispensations per year, respectively (Table 4).

Table 1 Patient characteristics of new oral glucose-lowering agent user cohort stratified by drug exposure group

Variable	New oral users	
	Metformin (alone or with sulfonylurea)	Sulfonylurea monotherapy
n	6,969	3,340
Age at oral index (years), mean (SD)	61.8 (13.1)	66.9 (13.1)*
Age at oral index (years), median (range)	62.3 (30.0–105.3)	68.1 (30.0–100.2)
Men, *n* (%)	3,727 (53.5)	1,956 (58.6)**
Insulin exposure, *n* (%)	1,137 (16.3)**	306 (9.2)
Duration of follow-up (years), mean (SD)	5.6 (1.9)*	5.0 (2.0)
Follow-up in total person-years	38,999	16,749
CDS, mean (SD)	8.7 (4.2)*	8.4 (4.1)
Cancer mortality, *n* (%)	245 (3.5)	162 (4.9)

*$p<0.0001$ by *t* test; **$p<0.0001$ by χ^2 test

Discussion

Our results provide further support for the notion that glucose-lowering agents may play a role in the relationship between type 2 diabetes and cancer outcomes. In our cohort of new users of oral medications for type 2 diabetes, exposure to metformin therapy, relative to sulfonylurea monotherapy, was associated with a significant 20% reduction in cancer mortality rates. We also observed a strong gradient of cumulative insulin dispensations and cancer mortality rates in this population. Compared with patients not exposed to insulin therapy, we observed a significantly increased risk of death from cancer associated with increases in cumulative exogenous insulin exposure. These results were confirmed in our cohort of new insulin users, where patients exposed to more insulin had a higher risk of death from cancer. Interestingly, our cohort of patients pre-dated the clinical use of insulin analogues and therefore insulin usage refers to human insulin.

Our findings are in line with those of several other epidemiological studies [28–32]. An earlier case–control study by Evans et al. found that metformin was associated with a statistically significant 23% reduction in the risk of cancer compared with sulfonylurea therapy among patients with type 2 diabetes, after adjusting for various clinical factors [28]. In a follow-up cohort study using the same clinical database from Tayside Scotland, these investigators further replicated these findings of a protective effect of metformin and an increased risk of cancer associated with insulin exposure [29]. These observational studies are also consistent with the findings from the UKPDS 34, which showed a decreased risk of cancer mortality associated with metformin use [33].

Similarly, Li et al. found that insulin and insulin secretagogue use were associated with an increased risk of pancreatic cancer, whereas metformin use was associated with a reduced risk of pancreatic cancer [30]. 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; this increased risk of colorectal cancer was relative to non-insulin users, many of whom were on metformin. The age- and sex-adjusted hazard ratio for colorectal cancer was 2.1 for ≥1 year of

Table 2 Cancer mortality rates and adjusted HR from time-varying multivariable Cox regression among new oral glucose lowering agent user cohort

Variable	Time at risk (person-days)	Cancer deaths, *n* (%)	Cancer mortality (/1000 person-years)	Adjusted HR (95% CI)[a]
Oral glucose-lowering agents				
Sulfonylurea monotherapy	16,737	162 (4.9)	9.7	1.0[b]
Metformin	38,973	245 (3.5)	6.3	0.80 (0.65–0.98)*
Insulin use (dispensations/year)[c]				
No insulin ever	52,131	323 (3.6)	–	1.0[b]
<3	400	6 (3.8)	–	2.22 (0.99–5.00)*
3 to 11	1,543	29 (5.0)	–	3.33 (2.26–4.89)**
≥12	1,636	49 (7.0)	–	6.40 (4.69–8.73)**

[a] Adjusted for age, sex and CDS

[b] Reference category for HR

[c] Specific mortality rates cannot be estimated for insulin exposure categories because of the time-varying nature of exposure. Cancer deaths were calculated on the basis of insulin category at the time of cancer death

*$p\leq0.05$; **$p<0.0001$

Table 3 Patient characteristics of new insulin user cohort

Variables	New insulin users
n	1,443
Age at insulin index (years), mean (SD)	63.0 (14.7)
Age at insulin index (years) median (range)	64.0 (30.9–102.0)
Men, *n* (%)	729 (50.5)
Oral agents use at insulin index	
Sulfonylurea monotherapy, *n* (%)	306 (21.2)
Metformin (alone or with sulfonylurea), *n* (%)	1,137 (78.8)
Duration of treatments	
Oral agent use at insulin index (years), mean (SD)	3.4 (2.2)
Insulin use (years), mean (SD)	2.5 (2.0)
Follow-up in total person-years	3,579.17
CDS, mean (SD)	9.2 (4.5)
Cancer mortality, *n* (%)	84 (5.8)

insulin use. Moreover, the authors observed an adjusted odds ratio of 1.2 for colorectal cancer for each incremental year of insulin therapy [31]. More recently, Chung et al. confirmed these findings that chronic insulin therapy was associated with an increased risk of colorectal adenoma in people with type 2 diabetes [32].

The role of insulin in the relationship between type 2 diabetes and cancer mortality rates is supported by a biologically plausible mechanism. Insulin is a growth hormone and is known to have arthrogenic and mitogenic properties [34–36]. Specifically, it is suggested that hyperinsulinaemia and elevated levels of IGF-1 promote tumour cell growth in patients with type 2 diabetes [7, 8]. Patients with type 2 diabetes are known to be hyperinsulinaemic, at least early in the course of their disease, and sulfonylureas and exogenous insulin increase circulating insulin levels in the body even further. The biological mechanism suggests that insulin does not necessarily cause the associated risk of death from cancer in type 2 diabetes patients, but that, rather, it is more likely to accelerate this outcome.

This study has several key strengths, particularly in the methodology. To our knowledge, none of the epidemiological research on this topic has used a time-varying approach in analyses of the effect of glucose-lowering agents in the relationship between type 2 diabetes and cancer outcomes. By applying a time-varying exposure definition for glucose-lowering agents, we were able to obtain more precise risk estimates and to refine our categories of insulin exposure by examining the risk gradient for insulin use. This enabled us to address some of the survival bias and confounding by duration, which are inherent in studies not employing such methodology. However, we do recognise the possibility of residual survival bias and other unknown biases. Due to this time-varying methodology, our findings also provide the first evidence of a risk gradient for insulin exposure and death from cancer in patients with type 2 diabetes.

In this study, we were also able to look at the effect of glucose-lowering agents on cancer mortality rates in a cohort of new oral glucose-lowering agent users and a cohort of new insulin users. The inception cohorts of new oral agent and new insulin users in this study ensure that all patients are at a similar point in the course of their diabetes. Our results were similar among both cohorts, a fact that further strengthens our findings. Only one other study looking at glucose-lowering agents and cancer outcomes has incorporated a new user design in its analyses [29]. Another study by Yang et al did not use a new user design for insulin use, and the authors acknowledge that the

Table 4 Cancer mortality rates and adjusted HR from time-varying multivariable Cox regression among new insulin user cohort

Variable	Time at risk (person-days)	Cancer deaths *n* (%)	Cancer mortality (/1,000 person-years)	Adjusted HR (95% CI)[a]
Insulin use (dispensations/year)[b]				
<3	400	6 (3.8)	–	1.0[c]
3 to 11	1,543	29 (5.0)	–	1.35 (0.56–3.28)
≥12	1,636	49 (7.0)	–	2.47 (1.05–5.84)*
Oral glucose-lowering agents				
Sulfonylurea monotherapy	1,648	23 (7.5)	25.2	1.0[c]
Metformin use	6,804	61 (5.4)	22.9	1.09 (0.66–1.80)

[a] Adjusted for age, sex, CDS and duration of oral therapy prior to insulin use

[b] Specific mortality rates cannot be estimated for insulin exposure categories because of the time-varying nature of exposure. Cancer deaths were calculated on the basis of insulin category at the time of cancer death

[c] Reference category for HR

*$p \leq 0.05$

association observed by them may have been due to severity of diabetes rather than a true effect of insulin [31]. Therefore, we can be more confident about our observed associations between exogenous insulin therapy and cancer mortality rates. A final strength of our research 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 [23, 37–39].

On the other hand, there are some limitations in our study. First, as noted above, we had a relatively small number of cancer deaths in the new oral glucose-lowering agent user cohort (n=407) and particularly in the new insulin user cohort (n=84), thereby limiting the power of our analyses. Another limitation is the confounding by indication, where the choice of glucose-lowering agents was not based on random assignment, but rather on clinical decisions by the patient and treating physician. Since we used administrative data, we lacked information on potentially important clinical covariates, such as smoking status, weight or BMI, glycaemic control (i.e. HbA_{1c} levels) and alcohol consumption. These are all potential confounders in the relationship between choice of drug therapy and cancer mortality rates in patients with type 2 diabetes. As Pocock and Smeeth recently pointed out, clinical decisions that determine each patient's treatment regimen are not random and patients are prescribed different treatment regimens for health-related reasons [40]. Thus, despite adjusting for potential confounders, residual selection bias remains likely, and this may have distorted any effect of differences between treatment regimens [40]. Nonetheless, we feel the evaluation of the relationships is informative. Robustness in relation to the excluded data in our analysis may be inferred in comparisons with the consistency of results of other studies when such potential confounders were included [28, 31]. We also lacked control for the underlying risk of cancer in type 2 diabetes. Another important limitation relates to the time-varying methodology employed in this analysis. This method assesses the association between the value of the therapy variable in the same time window of the event occurrence, not with the values in prior time windows. Indeed, this was why we conceived of the time-varying nature of insulin as a variable representing cumulative dispensations. Finally, we looked at cancer mortality as opposed to the more proximal outcome of cancer incidence. We recognise that many intervening events may alter the risk of cancer mortality once a diagnosis of cancer has been established.

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 gradient of cumulative insulin dispensations and cancer mortality rates. A better understanding of the relationship between both type 2 diabetes and its treatments, and cancer would have many important implications for prevention and management of both conditions. Therefore, until we have more evidence of the effects of insulin on long-term outcomes, we should be cautious with earlier initiation and aggressiveness of insulin therapy in patients with type 2 diabetes. It would, of course, 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. Future studies should consider more refined drug therapy groups, including the various types of insulin, sulfonylureas and thiazolidinediones, as well as paying particular attention to the time-varying nature of glucose-lowering therapy for type 2 diabetes patients.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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