

Increased Cancer-Related Mortality for Patients With Type 2 Diabetes Who Use Sulfonylureas or Insulin

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OBJECTIVE — Numerous studies have identified an increased risk of cancer in type 2 diabetes. We explored the association between antidiabetic therapies and cancer-related mortality in patients with type 2 diabetes, postulating that agents that increase insulin levels might promote cancer.

RESEARCH DESIGN AND METHODS — This was a population-based cohort study using administrative databases from Saskatchewan Health. Cancer-related mortality was compared among inception cohorts of metformin users and sulfonylurea monotherapy users. Multivariate Cox regression was used to estimate the hazard ratio (HR) of cancer-related mortality, after adjusting for age, sex, insulin use, and chronic disease score. All statistical tests were two-sided.

RESULTS — We identified 10,309 new users of metformin or sulfonylureas with an average follow-up of 5.4 ± 1.9 years (means \pm SD). The mean age for the cohort was 63.4 ± 13.3 years, and 55% were men. Cancer mortality over follow-up was 4.9% (162 of 3,340) for sulfonylurea monotherapy users, 3.5% (245 of 6,969) for metformin users, and 5.8% (84 of 1,443) for subjects who used insulin. After multivariate adjustment, the sulfonylurea cohort had greater cancer-related mortality compared with the metformin cohort (adjusted HR 1.3 [95% CI 1.1–1.6]; $P = 0.012$). Insulin use was associated with an adjusted HR of cancer-related mortality of 1.9 (95% CI 1.5–2.4; $P < 0.0001$).

CONCLUSIONS — Patients with type 2 diabetes exposed to sulfonylureas and exogenous insulin had a significantly increased risk of cancer-related mortality compared with patients exposed to metformin. It is uncertain whether this increased risk is related to a deleterious effect of sulfonylurea and insulin or a protective effect of metformin or due to some unmeasured effect related to both choice of therapy and cancer risk.

Diabetes Care 29:254–258, 2006

A number of epidemiologic studies have identified an increased risk of development of 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 hyperinsulin-

emia, insulin resistance, and a predilection to type 2 diabetes (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). Thus, 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 role is particularly noteworthy because 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. (26), using a case-control design, recently observed a 23% reduced risk of cancer in patients with type 2 diabetes taking metformin compared with those taking sulfonylureas.

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 with people with type 2 diabetes who were exposed to therapies that are known to decrease circulating insulin levels (i.e., metformin).

RESEARCH DESIGN AND METHODS

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 ~1 million) (27,28). Individuals not covered by Saskatchewan Health include those with federally funded health care,

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Received for publication 18 August 2005 and accepted in revised form 22 October 2005.

Abbreviations: CDS, chronic disease score.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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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 a sulfonylurea from 1 January 1991 through 31 December 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 before 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 1 January 1991 through 31 December 1996 and no prescription claims for any antidiabetic agent for 1 year before the index date. Patients were excluded if they 1) had gestational diabetes mellitus or 2) were new users of oral antidiabetic drugs who had <1-year supply of drug therapy dispensed. To ensure ongoing drug exposure, we also excluded subjects who had <1 year of drug exposure after 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; thus, all patterns of addition of sulfonylurea to metformin and vice versa were included. 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 31 December 1999, providing a maximum follow-up of 9 years.

Table 1—Patient characteristics stratified by drug exposure

	Metformin cohort	Sulfonylurea cohort
<i>n</i>	6,969	3,340
Age (years)		
Means \pm SD	61.8 \pm 13.1	66.9 \pm 13.1*
Median (range)	62.3 (30.0–105.3)	68.1 (30.0–100.2)
Sex (male)	3,727 (53.5)	1,956 (58.6)†
Insulin exposure	1,137 (16.3)†	306 (9.2)
Duration of follow-up (years)	5.6 \pm 1.9*	5.0 \pm 2.0
Mean person-years of follow-up	39,026	16,700
CDS	8.0 (2–26)	8.0 (2–22)
Overall mortality	245 (3.5)	162 (4.9)‡

Data are means \pm SD, median (range), or *n* (%). *n* = 10,309. **P* < 0.0001 for ANOVA; †*P* < 0.0001 for χ^2 ; ‡*P* = 0.001 for χ^2 test.

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 (κ 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 a univariate ANOVA for continuous variables and χ^2 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 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 been proven to be 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.

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 <1-year drug therapy exposure after 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 \pm SD age for the cohort was 63.4 \pm 13.3, and 55% were men. The duration of follow-up was 5.4 \pm 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 whereas the metformin cohort had a longer duration of therapy and was more likely to be receiving 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

Table 2—Cancer mortality and adjusted HR from multivariate Cox regression

	Total n	Cancer deaths	Cancer mortality rate (per 1,000 person-years) (%)	Adjusted HR (95% CI)*
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 (years)				
≤53.9	2,578	16 (0.6)	1.1	1.0†
54.0–64.3	2,578	75 (2.9)	6.0	5.0 (2.9–8.6)
64.4–73.3	2,576	127 (4.9)	8.9	8.9 (5.3–15.0)
≥73.4	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)

Data are n (%) unless otherwise indicated. *Adjusted for all other covariates in the table. †Reference category for HR.

162 (4.9%) cancer-related deaths in the sulfonylurea cohort ($P = 0.001$) (Table 1). This translates to a cancer-related mortality rate (per 1,000 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) (95% CI) for cancer-related mortality was 1.6 (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 with patients not receiving 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 with an adjusted HR of 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 HR of cancer-related mortality of 1.9 (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).

CONCLUSIONS— 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. (26) recently reported a similar difference in risk for patients exposed to metformin compared with sulfonylureas. This case-control study used population-based sampling from a clinical database of diabetic patients in Scotland, allowing adjustment for smoking, BMI, 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, whether the use of insulin was excluded or controlled for 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 adjustment 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 HbA_{1c}), weight or 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 than users of sulfonylureas. Interestingly, Evans et al. (26) observed a similarly reduced risk of cancer incidence for metformin users, both before and after adjusting for BMI.

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 drugs 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.

Although 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 have a beneficial effect not only 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.

Acknowledgments— This study was funded in part by the Alliance for Canadian Health Outcomes Research in Diabetes NET grant sponsored by the Canadian Diabetes Association; the Heart and Stroke Foundation of Canada; The Kidney Foundation of Canada; the Canadian Institutes for Health Research (CIHR) Institute of Nutrition, Metabolism and Diabetes; and the CIHR Institute of Circula-

tory and Respiratory Health. S.R.M. and P.V. hold New Investigator Awards from the CIHR. S.R.M. is a Population Health Investigator with the Alberta Heritage Foundation for Medical Research (AHFMR). J.A.J. is a Health Scholar with AHFMR and holds a Canada Research Chair in Diabetes Health Outcomes.

The authors thank Mary Rose Stang, PhD, from Saskatchewan Health for her help in compiling the datasets and for comments on an earlier draft of this manuscript.

This study is based on de-identified data provided by the Saskatchewan Department of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Department of Health.

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