The Use of Glyburide Compared With Other Sulfonylureas and the Risk of Cancer in Patients With Type 2 Diabetes

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OBJECTIVE

To determine whether the use of glyburide is associated with an increased risk of cancer compared with the use of other second-generation sulfonylureas among patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

The U.K. Clinical Practice Research Datalink was used to conduct a cohort study among 52,600 patients newly prescribed glyburide or other second-generation sulfonylureas between 1 January 1988 and 31 July 2013. A time-dependent Cox proportional hazards model was used to estimate adjusted hazard ratios (HRs) and 95% CIs of any cancer associated with the use of glyburide compared with the use of second-generation sulfonylureas. Secondary analyses were conducted to determine whether the association varied with cumulative duration of use and cumulative dose (expressed as defined daily dose [DDD]).

RESULTS

During 280,288 person-years of follow-up, 4,105 patients were given a new diagnosis of cancer (incidence rate 14.6 per 1,000 person-years). Overall, when compared with the use of other second-generation sulfonylureas, the use of glyburide was associated with a nonsignificant increased risk of any cancer (HR 1.09 [95% CI 0.98–1.22]). In secondary analyses, duration- and dose-response relationships were observed, with longer cumulative durations and cumulative doses associated with an increased risk of any cancer (>36 months: HR 1.21 [95% CI: 1.03–1.42]; >1,096 DDDs: HR 1.27 [95% CI 1.06–1.51]).

CONCLUSIONS

In this population-based cohort study, longer cumulative durations and higher cumulative doses of glyburide were associated with an increased risk of cancer.

Sulfonylureas are among the oldest drug classes available for the treatment of type 2 diabetes. Despite their popularity, these drugs have been associated with elevated all-cause and cardiovascular mortality (1). In addition, several observational studies have associated their use with an increased risk of cancer incidence and cancer-related mortality compared with other oral antidiabetic agents (2–11). However, the findings of some of these studies have suggested that this increased risk may not be equivalent with all sulfonylureas (2,12,13). Indeed, in some observational studies, the risk was particularly elevated with glyburide (also known as

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glibenclamide) (2,6,13). These findings are supported by biological evidence, as glyburide seems to cause the production of reactive oxygen species (ROS), which is a well-known pro-oncogenic factor (14). In particular, this activity appears specific to glyburide and not to other sulfonylureas (15).

To date, the few observational studies that have specifically assessed the association between glyburide and cancer risk had a number of methodological shortcomings, such as time-related biases (2,13,16) and confounding by indication (17). Thus, given the widespread use of glyburide and continued concerns regarding its safety, we conducted a population-based cohort study to determine whether the use of glyburide compared with other second-generation sulfonylureas is associated with an increased risk of cancer in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Data Source

This study was conducted using the U.K. Clinical Practice Research Datalink (CPRD), which contains complete primary care medical records for >13 million people enrolled in >680 general practices (18). The Read code classification is used to record medical diagnoses and procedures, and prescription drugs written by general practitioners are coded using the U.K. Prescription Pricing Authority dictionary. The CPRD collects information on anthropometric variables, such as BMI, and lifestyle variables, such as smoking and excessive alcohol use. Data collected in the CPRD have been previously validated and demonstrated to be of high quality (19). The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol 15_126) and by the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

Study Population

For the purposes of this study, we first assembled a base cohort comprising all patients newly prescribed a noninsulin antidiabetic drug between 1 January 1988 and 31 July 2013. All patients were required to be at least 40 years of age and to have at least a 1-year medical history in the CPRD before that first prescription. Patients initially treated with insulin were not included in the cohort because they likely represent those with an advanced form of type 2 diabetes.

From the base cohort, we identified all patients who were newly prescribed a second-generation sulfonylurea during the study period (glyburide, gliclazide, gliquidone, glimepiride, glipizide). The study cohort entry date was defined as the date of the first prescription of a second-generation sulfonylurea. We excluded all patients with any cancer (other than nonmelanoma skin cancer identified based on Read codes) at any time before study cohort entry and those with <1 year follow-up after study cohort entry. The latter criterion was necessary for latency considerations. Thus, follow-up started the year after study cohort entry until a first-ever diagnosis of any cancer (other than nonmelanoma skin cancer) or censored upon death from any cause, end of registration with the general practice, or end of the study period (31 July 2014), whichever occurred first.

Exposure Definition

A time-dependent exposure definition was used to classify the use of glyburide during follow-up. Specifically, patients were considered unexposed to glyburide until the time of the first prescription and considered exposed until the end of follow-up after lagging the exposure by 1 year. Based on this time-dependent exposure definition, it was possible for individual patients to contribute both an unexposed and an exposed person-time. The 1-year lag period was necessary to taking into account a latency time window because short exposure durations are unlikely to be associated with cancer incidence.

From the exposure definition, the use of glyburide was expressed according to three approaches. The first approach compared the use of glyburide with other second-generation sulfonylureas (gliclazide, gliquidone, glimepiride, glipizide) up until the time of the event. The second and third approaches assessed duration- and dose-response relationships in terms of glyburide cumulative duration and cumulative dose and cancer incidence. Cumulative duration of use was defined, in a time-dependent fashion, as the total number of months of glyburide exposure, calculated by summing the durations of all prescriptions received between cohort entry and the time of the event. This variable was then classified into the following four categories: <12 months, 12–24 months, 24–36 months, and >36 months of use. Similarly, for cumulative dose, use of glyburide was further classified according to defined daily dose (DDD), which is a validated measure from the World Health Organization. Cumulative dose was then calculated by summing all DDDs up until the date of the event. This variable was classified into the following four categories: <365, 365–730, 731–1,096, and >1,096 DDDs.

Statistical Analysis

Descriptive statistics were used to summarize the characteristics of glyburide and other second-generation sulfonylureas (gliclazide, gliquidone, glimepiride, glipizide) users at cohort entry. Crude incidence rates of cancer, with 95% CIs based on the Poisson distribution, were calculated by dividing the number of patients with cancer by the person-time at risk.

Time-dependent Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) and 95% CIs of cancer incidence associated with the use of glyburide compared with second-generation sulfonylureas (primary analysis). We conducted three secondary analyses. The first two assessed for duration- and dose-response relationships on the basis of the cumulative duration of use and cumulative dose categories previously described. Linear trend was assessed by considering these covariates as continuous variables in the models. In the third analysis, the primary analysis was repeated separately for each of the four most common cancer types (breast, prostate, colorectal, and lung). All models accounted for competing risks due to death from any cause using the model proposed by Fine and Gray (20) because glyburide was previously associated with an increased risk of death compared with other sulfonylureas (21).

All models were adjusted for the following potential confounders measured at study cohort entry: year of cohort entry (to control for secular trends in prescribing patterns and variations in the incidence of cancer during the study period), age, sex, BMI, smoking status, excessive alcohol use, glycated hemoglobin A_{1c} (HbA_{1c}) (last laboratory result before study cohort entry), duration of treated diabetes before study cohort entry (defined as the time between base cohort entry and study cohort entry),

ever use of other antidiabetic drugs before study cohort entry (metformin, first-generation sulfonylureas, thiazolidinediones, incretin-based drugs, insulin, and other oral hypoglycemic drugs, all entered individually as non–mutually exclusive variables in the models), and ever use of statins, aspirin, and other nonsteroidal anti-inflammatory drugs before study cohort entry. Finally, the models were adjusted for the use of antidiabetic drugs (metformin, thiazolidinediones, incretin-based drugs, insulin, and other oral hypoglycemic drugs) during follow-up. These drug exposures were entered in the models as nonmutually exclusive variables and defined in exactly the same fashion as glyburide (i.e., as time-dependent variables lagged by 1 year for latency considerations). Variables with missing information (i.e., BMI, smoking, HbA_{1c}) were coded with an unknown category.

For the analyses by cancer type, the models were additionally adjusted for potential confounders, as measured at study cohort entry, specific to each cancer type. For prostate cancer, the model was additionally adjusted for prostate-specific antigen testing in the year before cohort entry; for breast cancer, ever use of oral contraceptives and previous mammography screening in the year before cohort entry; for lung cancer, history of tobacco-related conditions (chronic obstructive pulmonary disease, ischemic heart disease, and vascular diseases), history of lung diseases (pneumonia, tuberculosis, and history of chronic lung disease), and factors associated with sex hormone disorders (hypothalamic, pituitary, testis, ovarian, and adrenal gland); and for colorectal cancer, cholecystectomy, inflammatory bowel disease (Crohn's disease and ulcerative colitis), and history of polyps.

Sensitivity Analyses

We conducted two sensitivity analyses to assess the robustness of the findings. First, the primary analysis was repeated after excluding patients entering the cohort with gliclazide and censoring upon initiation during follow-up because some studies reported that this sulfonylurea may decrease the risk of cancer (16,22). Second, given uncertainties related to the latency time window, we repeated the primary analysis by varying the lag period to 2 and 3 years. All analyses were conducted with SAS 9.4 statistical software (SAS Institute, Cary, NC).

RESULTS

A total of 52,600 patients met the study inclusion criteria (Fig. 1), which included 3,413 patients initially prescribed glyburide and 49,187 patients initially prescribed other second-generation sulfonylureas. Overall, the prescribing rate of glyburide was high in the early years of the study period and then declined. In contrast, the prescribing rate of other second-generation sulfonylureas gradually increased during the study period (Supplementary Fig. 1). The cohort was followed for a mean (SD) of 5.3 (4.2) years, generating 280,288 person-years of follow-up. A total of 4,105 patients were given a new diagnosis of any cancer during follow-up, yielding a crude incidence rate of 14.6 (95% CI 14.2–15.1) per 1,000 person-years.

Table 1 presents the baseline characteristics of the cohort. Users of glyburide were less likely to have a BMI above the obese range and ever smoked and were generally healthier compared with users of other second-generation sulfonylureas. In addition, users of glyburide had a shorter duration of treated diabetes and were less likely to have previously used other antidiabetic drugs compared with other second-generation sulfonylureas.

Table 2 presents the results of the primary and secondary analyses. Overall, compared with the use of other second-generation sulfonylureas, the use of glyburide was associated with a nonsignificant increased risk of any cancer (14.6 vs. 15.1 per 1,000 person-years, respectively, HR 1.09 [95% CI 0.98–1.22]). Similar results were observed when varying the lag period to 2 and 3 years (1.09 [0.97–1.22] and 1.07 [0.95–1.21],

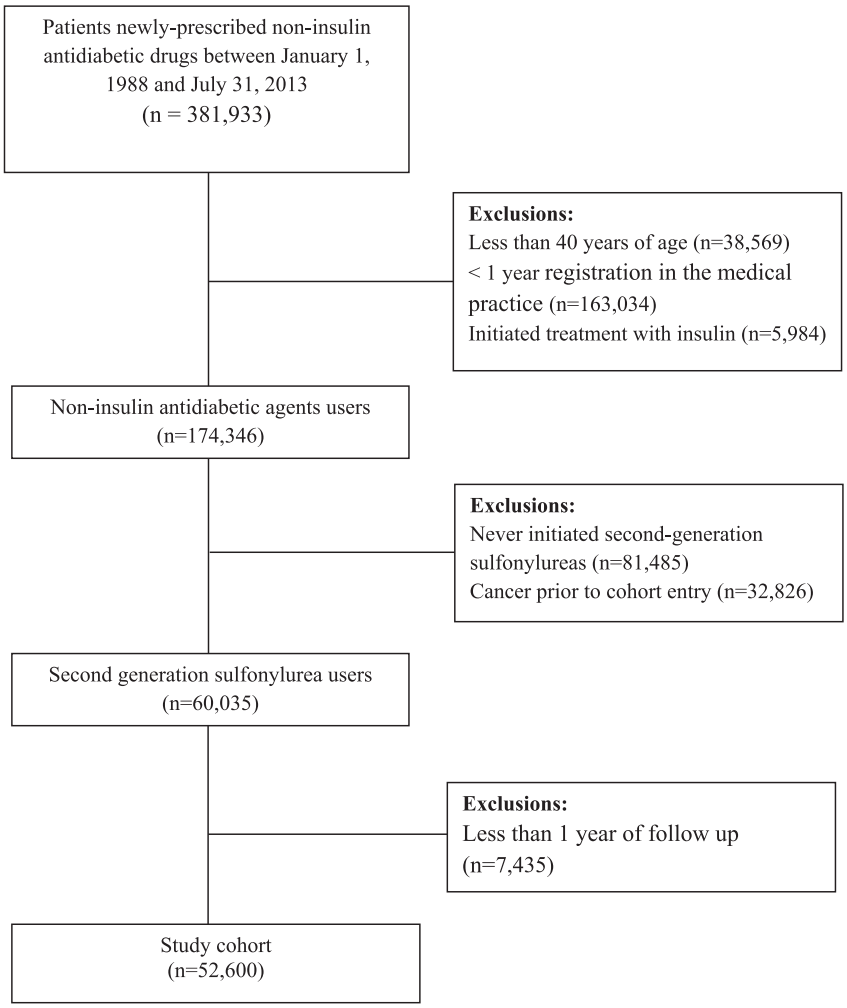

Figure 1—Study flowchart of patients initiating second-generation sulfonylureas between 1988 and 2013.

Table 1—Baseline characteristics of patients starting second-generation sulfonylureas

Characteristic	Glyburide (*n* = 3,413)	Other second-generation sulfonylureas (*n* = 49,187)	Standardized difference
Male sex	2,265 (66.4)	36,044 (73.3)	0.15
Age (years)	64.0 (11.9)	64.0 (12.5)	0.01
BMI (kg/m^2)			
Median (IQR)	28.1 (25.0–31.3)	29.2 (26.0–33.2)	0.24
<25	628 (18.4)	8,227 (16.7)	0.04
25–30	1,059 (31.0)	16,791 (34.1)	0.07
≥30	873 (25.6)	20,291 (41.3)	0.34
Unknown	853 (25.0)	3,878 (7.9)	0.47
Smoking			
Ever	1,288 (37.7)	28,147 (57.2)	0.40
Never	1,398 (41.0)	18,469 (37.6)	0.07
Unknown	727 (21.3)	2,571 (5.2)	0.49
Excessive alcohol use	202 (5.9)	5,758 (11.7)	0.20
HbA_{1c} (%) [mmol/mol]			
Median (%; mmol/mol) (IQR)	8.7; 71.6 (7.5–10.4; 58.5–90.2)	8.5; 69.4 (7.6–10.0; 59.6–85.8)	0.05
≤7 [53]	180 (5.3)	3,824 (7.8)	0.10
7.1–8.0 [54–64]	220 (6.5)	9,759 (19.8)	0.40
>8 [65]	730 (21.4)	22,595 (45.9)	0.54
Unknown	2,283 (66.9)	13,009 (26.5)	0.89
Duration of treated diabetes (years)	0.3 (0.9)	1.3 (2.0)	0.64
Comedications			
Statins	409 (12.0)	24,898 (50.6)	0.92
Aspirin	590 (17.3)	17,635 (35.9)	0.43
Other NSAIDs	537 (15.7)	5,635 (11.5)	0.13
Use of other antidiabetic drugs*			
Metformin	547 (16.0)	26,427 (53.7)	0.86
First-generation sulfonylureas	39 (1.1)	378 (0.8)	0.04
Thiazolidinediones	28 (0.8)	2,628 (5.3)	0.26
Incretin-based drugs	0 (0.0)	1,084 (2.2)	0.21
Insulin	1 (0.0)	117 (0.2)	0.06
Other oral hypoglycemic drugs	18 (0.5)	357 (0.7)	0.03

Data are *n* (%) or mean (SD) unless otherwise indicated. IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug. *Not mutually exclusive.

respectively) as well as excluding and censoring upon initiation of gliclazide (1.04 [0.86–1.27]). In secondary analyses, a duration-response relationship was observed, with the risk gradually increasing with longer cumulative durations of use. Specifically, the use of glyburide for at least 36 months was associated with a 21% increased risk of cancer (1.21 [1.03–1.42]) (Table 2). Similarly, a dose-response relationship was observed, where a cumulative dose of at least 1,096 DDDs was associated with a 27% increased risk of cancer (1.27 [1.06–1.51]) (Table 2).

Table 2—Crude and adjusted HRs for the association between the use of glyburide and the risk of cancer

Exposure	Events	Person-years	Incidence rate[a] (95% CI)	Crude HR	Adjusted HR (95% CI)[b]
Other second-generation sulfonylureas	3,650	250,219	14.6 (14.1–15.1)	1.00	1.00 (reference)
Glyburide	455	30,069	15.1 (13.8–16.6)	1.03	1.09 (0.98–1.22)
Duration of glyburide use (months)					
<12	121	9,100	13.3 (11.0–15.9)	0.90	0.98 (0.81–1.19)
12–24	73	5,739	12.7 (10.0–16.0)	0.87	0.92 (0.72–1.18)
24–36	70	4,041	17.3 (13.5–21.9)	1.20	1.26 (0.98–1.63)
>36	191	11,189	17.1 (14.7–19.7)	1.14	1.21 (1.03–1.42)
Dosage of glyburide use (DDD)					
<365	169	12,253	13.8 (11.8–16.0)	0.94	1.00 (0.85–1.18)
365–730	74	5,086	14.5 (11.4–18.3)	0.98	1.03 (0.80–1.31)
730–1,096	50	3,364	14.9 (11.0–19.6)	0.99	1.07 (0.80–1.44)
>1,096	162	9,367	17.3 (14.7–20.2)	1.17	1.27 (1.06–1.51)

[a]Per 1,000 person-years. [b]Adjusted for variables listed in Table 1 and for the use of antidiabetic drugs (metformin, thiazolidinediones, incretin-based drugs, insulin, and other oral hypoglycemic drugs) during follow-up as non–mutually exclusive time-dependent variables.

When the primary analysis was repeated separately for each of the four major cancers, no single cancer type was statistically associated with an increased risk, although the HR for breast cancer was numerically elevated (HR 1.19 [95% CI 0.78–1.79]). The HR for lung cancer was under the null and statistically significant (0.93 [0.88–0.99]) (Table 3).

CONCLUSIONS

To our knowledge, this study is the largest to have specifically assessed the association between the use of glyburide and cancer incidence in patients with type 2 diabetes. The use of glyburide was associated with an overall nonsignificant 9% increased risk of cancer. In secondary analyses, we observed duration- and dose-response relationships, supporting the hypothesis that the use of glyburide may be associated with an increased risk of cancer. The analysis of the association between glyburide and site-specific cancers generated heterogeneous findings, ranging from a mild protective effect of 7% for lung cancer to a nonsignificant increased risk of 19% for breast cancer.

Although several observational studies have investigated the association between sulfonylureas and cancer incidence or cancer-related mortality (3–11,16,17,22,23), only five focused on glyburide and cancer-related outcomes (2,6,13,16,17). Overall, these studies produced conflicting findings, with three reporting increased risks ranging from 150 to 250% (2,6,13) and two reporting decreased risks ranging from 20 to 50% (16,17). The discrepancy between these studies is likely due to important methodological shortcomings. Specifically, in one study, the use of glyburide compared with gliclazide was associated with an increased risk of cancer mortality (odds ratio 3.6 [95% CI 1.1–11.9]). However, this observed increased risk may have been exaggerated by time-lag bias (24) because glyburide users had longer diabetes duration than gliclazide users (13.2 vs. 7.7 years, respectively) (2). Similarly, time-lag bias was likely present in another study reporting strong decreased risks with gliclazide and tolbutamide compared with glyburide (13). As for the studies reporting decreased risks, the use of glyburide in one was associated with a 17% decreased risk of prostate cancer, with similar decreased risks observed with all other antidiabetic drugs (17). However, these findings are likely the result of confounding by indication because type 2 diabetes has been associated with a decreased risk of prostate cancer (25). In the second study reporting a decreased risk, immortal time bias was introduced by considering exposure to glyburide after cohort entry in a non–time-dependent fashion. Thus, the time between cohort entry and the first glyburide prescription was misclassified as exposed as well as immortal because, by definition, no events could have occurred (16).

Overall, the study findings suggest that glyburide may be associated with an increased risk of cancer. Biologically, animal models have ruled out direct tumorigenic activity of glyburide and, conversely, supported an antiproliferative effect of all sulfonylureas (26–30). On the other hand, the current findings are consistent with an ROS-inducing effect that seems to pertain to glyburide (14) and not to other sulfonylureas, which in turn appear to exert a protective activity against ROS (31,32). Because it is well known that in diabetes chronic hyperglycemia can trigger cellular proliferation by generating ROS with subsequent intracellular signaling pathway impairment and DNA damage (33), this ROS scavenging effect of other sulfonylureas together with the oxidative stress induced by glyburide could explain the unbalanced risk of cancer we observed. This hypothesis would also be consistent with the observed time- and dose-dependent tumorigenic effect.

Although our analysis confirms that the use of glyburide declined progressively over the years in the U.K. (34), glyburide remains widely used in other countries, such as the U.S. where it is the initial treatment drug for 15% of patients (35). Thus, given the growing prevalence of type 2 diabetes worldwide and the relatively high prevalence of patients exposed to glyburide, the current findings raise concerns that need to be corroborated in other well-designed studies.

This study has a number of strengths. First, we assembled one of the largest population-based cohorts of patients treated with second-generation sulfonylureas,

Table 3—Crude and adjusted HRs for the association between the use of glyburide and the risk of site-specific cancers

Exposure	Events	Person-years	Incidence rate[a] (95% CI)	Crude HR	Adjusted HR (95% CI)[b]
Prostate cancer					
Other second-generation sulfonylureas	586	181,455	3.2 (3.0–3.5)	1.00	1.00 (reference)
Glyburide	70	20,026	3.5 (2.7–4.4)	1.01	1.11 (0.84–1.47)
Breast cancer					
Other second-generation sulfonylureas	211	68,764	3.1 (2.7–3.5)	1.00	1.00 (reference)
Glyburide	35	10,043	3.5 (2.4–4.8)	1.12	1.19 (0.78–1.79)
Lung cancer					
Other second-generation sulfonylureas	472	250,219	1.9 (1.7–2.1)	1.00	1.00 (reference)
Glyburide	51	30,069	1.7 (1.3–2.2)	0.87	0.93 (0.88–0.99)
Colorectal cancer					
Other second-generation sulfonylureas	456	250,219	1.8 (1.7–2.0)	1.00	1.00 (reference)
Glyburide	59	30,069	2.0 (1.5–2.5)	1.04	1.11 (0.82–1.51)

[a]Per 1,000 person-years. [b]Adjusted for variables listed in Table 1 and for the use of antidiabetic drugs (metformin, thiazolidinediones, incretin-based drugs, insulin, and other oral hypoglycemic drugs) during follow-up as non–mutually exclusive time-dependent variables. For prostate cancer, the model is additionally adjusted for prostate-specific antigen screening; for breast cancer, ever use of oral contraceptives and hormone replacement therapy and previous mammography screening; for lung cancer, history of tobacco-related conditions (chronic obstructive pulmonary disease, ischemic heart disease, and vascular diseases), history of lung diseases (pneumonia, tuberculosis, and history of chronic lung disease), factors associated with sex hormone disorders (hypothalamic, pituitary, testis, ovarian, and adrenal gland); and for colorectal cancer, cholecystectomy, inflammatory bowel disease (Crohn's disease and ulcerative colitis), and history of polyps.

followed for up to 27 years (1988–2014). Thus, the size and long-term follow-up of the cohort have enabled the identification of a substantial number of cancer cases. Second, the inclusion of new users eliminated biases related to prevalent users (36). Third, the choice of second-generation sulfonylureas as an active comparator likely minimized potential confounding by indication and time-lag bias (24). Fourth, the use of glyburide was defined as a time-varying variable, allowing patients to move from period of exposure to period of nonexposure. This time-dependent approach eliminated immortal time bias (37). Finally, all analyses took into account competing risks due to death from any cause, an important consideration given the previously reported association between glyburide and mortality (1,2).

This study has some limitations. First, drug information in the CPRD represents prescriptions written by general practitioners. Therefore, it is unknown whether prescriptions were actually filled at the pharmacy and whether patients adhered to the treatment regimen. Such misclassifications are likely nondifferential, thus biasing the point estimates toward the null. Second, CPRD lacks information on certain cancer risk factors, including diet, physical activity, family history of cancer, and race/ethnicity. However, because the reference category for all analyses comprised patients using other second-generation sulfonylureas, we do not expect the distribution of these unmeasured variables to be differential between the exposure groups, thereby not affecting the validity of the study. Third, users of glyburide were more likely to have missing information on smoking status, BMI, and HbA_{1c} levels than users of other second-generation sulfonylureas. It is possible that this is because glyburide was predominantly used in the earlier years of the study period, a time that preceded the Quality and Outcomes Framework implemented in the U.K. (2004). The Quality and Outcomes Framework provides monetary incentives to general practitioners with the goal of improving the recording of certain patient characteristics, such as smoking status, blood pressure, and cholesterol levels (38). As such, we do not believe that missing information among glyburide users was related to the outcome. Fourth, our outcome definition was based on cancer diagnoses recorded in general practice medical records and is thus prone to misclassifications. Reassuringly, cancer diagnoses recorded in the CPRD have been shown to be highly concordant with those recorded in the U.K. National Cancer Data Repository (39). In addition, the overall cancer rate estimated in the current study (14.6 per 1,000 patients) is highly consistent with U.K. cancer statistics for a population at least 65 years of age (incidence rates 12.7–21.4 per 1,000) (40). Finally, residual confounding needs to be considered given the observational nature of the study, although adjustment for >20 potential confounders did not have an important impact on the point estimates.

In conclusion, the findings of this population-based study indicate that the use of glyburide is associated with an increased risk of cancer in a duration- and dose-dependent fashion. Additional studies are needed to replicate the findings and assess whether glyburide is associated with an increased risk of a specific cancer.

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