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ORIGINAL ARTICLE

Initial metformin or sulphonylurea exposure and cancer occurrence among patients with type 2 diabetes mellitus

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Aim: This was a retrospective cohort study of type 2 diabetes patients, to evaluate the association between initial metformin or sulphonylurea treatment and cancer incidence.

Methods: Patients identified in the UK Clinical Practice Research Datalink (CPRD), previously General Practice Research Database, during 1995–2008 who were initially stabilized on OHA monotherapy, including metformin, sulphonylurea, thiazolidinediones (TZDs) or meglitinides, were included in the cohort. New diagnoses of cancer, including malignant solid tumours and haematological malignancies, occurring during the follow-up were identified from the cohort. Age-standardized incidence rates were estimated and compared between metformin and sulphonylurea exposure groups.

Results: The age standardized incidences of cancer were 7.5 and 8.5 per 1000 person-years for the metformin and sulphonylurea exposure groups, respectively. After adjusting for potential confounders, the hazard ratios (HR) for malignant solid tumours and haematological malignancies were 1.06 (95% CI: 0.98, 1.15) and 0.98 (95% CI: 0.67, 1.43) for sulphonylurea group as compared to the metformin group, respectively. For individual cancers, the HRs were 1.17 (95% CI: 0.95, 1.44), 1.04 (95% CI: 0.83, 1.31) and 0.88 (95% CI: 0.71, 1.11) for colorectal cancer, breast cancer and prostate cancer, respectively.

Conclusion: This study provides evidence that cancer incidence in the first few years after starting metformin or sulphonylurea therapy in type 2 diabetes patients is not much affected by choice of hypoglycaemic drug class.

Keywords: antidiabetic drug, diabetes complications, diabetes mellitus

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A number of studies [1–3] have found that diabetes mellitus is associated with increased risks for one or more malignancies, including colorectal cancer, breast cancer and pancreatic cancer. The mechanisms explaining the increased risks of cancer among diabetics may be related to the effects of insulin and insulin-like growth factors (IGFs) on cellular growth.

If hyperinsulinaemia plays a role in increasing cancer risk in diabetic patients, it is reasonable to expect that oral hypoglycaemic agents (OHAs) that increase endogenous insulin (sulphonylurea) may be risk factors for cancer development, and in contrast, those treatments that decrease endogenous insulin (metformin) may not be risk factors or even play protective roles in cancer occurrence among diabetics.

A systematic review [4] of observational studies showed that metformin was associated with a 30% lower cancer incidence in individuals with type 2 diabetes compared with other diabetic treatments. Jiralerspong et al. [5] observed that diabetic breast cancer patients treated with metformin experienced a threefold greater pathologic complete response (pCR) rates with neoadjuvant chemotherapy than those treated with other antidiabetic medications. In other studies, metformin was associated with decreased cancer mortality [6] and sulphonylurea was associated with increased cancer morbidity and mortality [7,8].

Although it is generally agreed that patients with type 2 diabetes have an increased risk of cancer, the evidence supporting the role of OHAs in promoting carcinogenesis is inconsistent. We conducted a retrospective cohort study to compare cancer incidence among type 2 diabetes patients who were newly exposed to metformin or sulphonylurea monotherapy.

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Research Design and Methods

Data source

The UK Clinical Practice Research Datalink (CPRD), previously General Practice Research Database, is one of the world's largest electronic medical record (EMR) databases of anonymized longitudinal clinical primary care records. It contains population-based data collected prospectively in primary care settings. The large size of the database with several years of longitudinal data recording enables the study of uncommon outcomes, including those with substantial latency periods. The comprehensiveness and quality of the CPRD provide a

rich resource for studying the frequency of diseases in the community as well as the natural history, prognosis and secular trends [9–12]. Diagnostic outcomes are captured as Read codes and validation of these codes has shown excellent agreement between the recorded diagnoses and the information on paper-based medical records, including the diagnoses of colorectal cancer and diabetes mellitus [9,13,14]. Most prescriptions cover 30-day medications in the UK. Prior studies using the database have also found complete agreement between prescription information received from the general practitioners (GPs) and that recorded in the database [13,15,16].

Study Cohort

The study population was drawn from patients registered to the GPs contributing to the CPRD. The cohort was assembled starting with a pool of 180 406 patients who initiated OHA therapy during the period 1 January 1995 through 31 December 2008 (figure 1). The diagnosis of type 2 diabetes was determined from the clinical diagnoses using Read codes and related supporting evidence, including age at diagnosis and types of treatment. This was done using a set of all possible diabetes-related Read codes from which irrelevant codes (e.g. diabetes insipidus, gestational diabetes, child with diabetes etc.) were excluded.

Only patients initially stabilized with OHA monotherapy, which was defined as at least six sequential prescriptions of the same OHA monotherapy, were included. The earliest OHA with at least six sequential prescriptions was set as the primary exposure. After the set of exclusions shown in figure 1, 56 844 diabetic patients were retained in the cohort who were diagnosed of diabetes between the ages of 35 and 80, were started and stabilized on OHA monotherapy (six sequential prescriptions), and who had no diagnosis of cancer prior to starting OHA or in the first year of follow-up.

Exposures

Exposures were measured by the presence of antidiabetic prescription records using the British National Formulary (BNF) codes. Prescription dates were captured from the therapy data. The primary exposures were classified as metformin, sulphonylurea, thiazolidinediones (TZDs) or meglitinides. The first prescription date of the primary exposure was set as the OHA index date.

Outcomes

Cancer cases were defined by the presence of a Read code indicating an invasive solid tumour (other than non-melanoma skin cancer) or a haematological malignancy first diagnosed at least 1 year after the OHA index date.

As cancer cases that occurred within 1 year after the OHA index date were not included in the study, the follow-up period for the main analysis started 1 year after the OHA index date and continued until a new diagnosis of cancer, registration end date, or 31 December 2008, whichever occurred first. Cancers were divided into cancer subtypes as malignant solid tumours and haematological malignancies. Among the malignant solid tumours, colorectal cancer, breast cancer and prostate cancer were also identified and analysed individually. For cancer subtypes, the date of a new diagnosis was defined as the earliest diagnosis of a cancer within that subtype (haematological, solid tumour and specified individual cancer). Patients with more than one cancer subtypes would have different follow-up durations for each cancer subtype. Age-standardized incidences of overall cancer, as well as incidences of cancer subtypes were estimated for each exposure group. The incidences were also compared between metformin and sulphonylurea exposure groups.

In addition, for sensitivity analyses, an alternate duration of follow-up (duration of the primary exposure), was defined from 1 year after the OHA index date to (i) the first date of a new therapeutic regimen plus 6 months or (ii) the end of the cohort follow-up, whichever occurred first. New therapeutic regimens include other mono or combination therapies or the addition of another antidiabetic medication to the primary exposure (add on).

Demographic and Baseline Characteristics

Multiple demographic and baseline characteristics were considered as potential confounding variables in the cohort. The baseline period was defined as starting 1 year prior to the OHA index date. Because of the potential for non-linearity of the association between cancer risk and continuous variables, these covariates were set as categorical variables in the analyses. These categories were defined prior to examining any associations with cancer risk.

Each patient's gender and age at the OHA index date were used as covariates. The highest value of HbA1c during the entire baseline period was used as the baseline HbA1c. Abnormal HbA1c was defined as a value $\geq$7%. Body mass indices (BMIs) were calculated when height and weight recordings were available. The greatest value of weight during the baseline period was used to calculate BMI. The range 20–24 kg/m^2 was considered normal. Smoking status was assessed at baseline. Patients were categorized as non-smokers, current smokers, ex-smokers or unknown based on the smoking entry closest to the OHA index date.

Cancer screening tests/procedures were also considered as potential confounding factors. Patients who had a mammogram (for women) or a prostate-specific antigen (PSA) (for men) at baseline or a colonoscopy within 10 years prior to the OHA index date were considered as having cancer screening measurement. However, the purposes of these tests (screening or rule-out diagnosis) were unknown.

The chronic disease score (CDS) is an aggregate co-morbidity measure based on medication use. It is calculated from prescription information for specific drug classes and the scores are summed from these classes [17]. It has been shown to be valid in predicting hospitalization, health resource utilization and mortality. Prescription information at baseline was used to calculate the CDS.

Duration of diabetes prior to the OHA index date was calculated using the earliest diagnosis date of diabetes. Although there was no missing value of date of diabetes, the duration of diabetes was set as missing if the earliest diagnosis date of diabetes was later than the OHA index date.

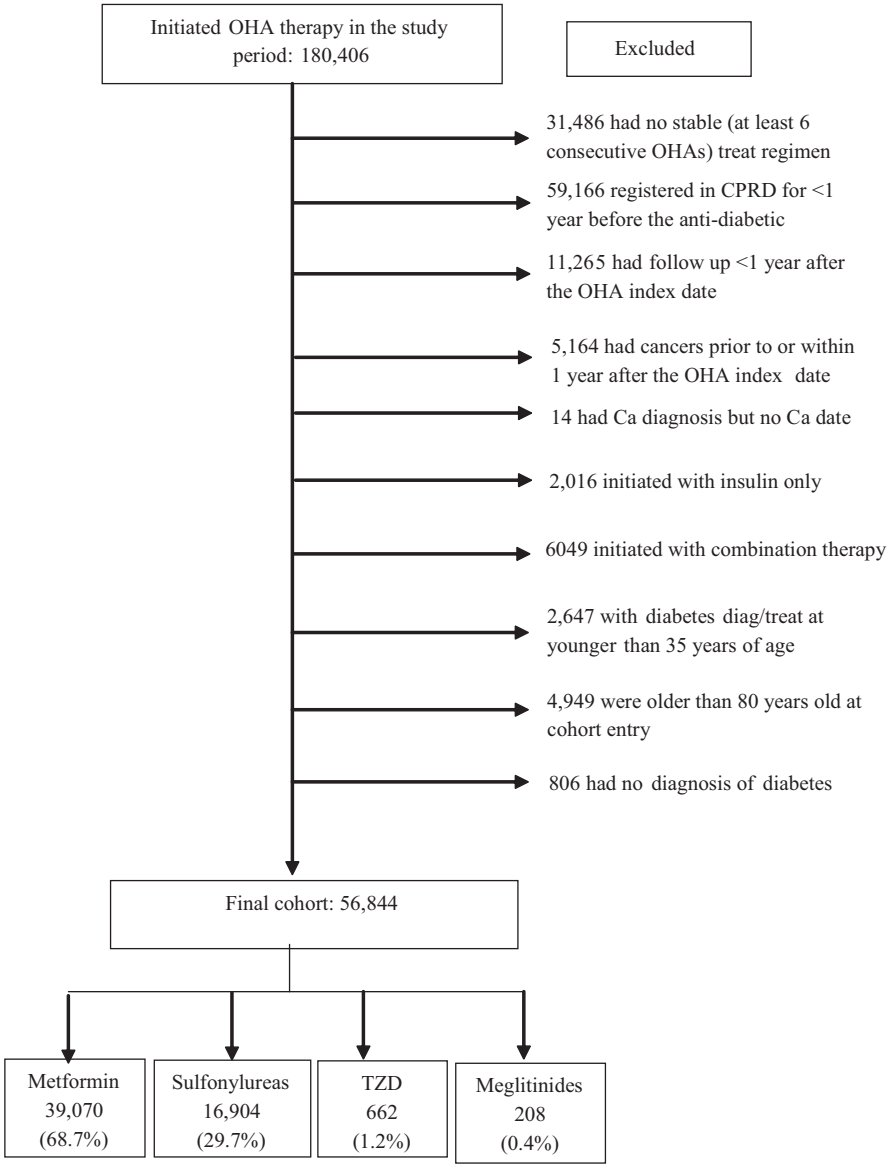

Figure 1. Cohort selection.

In addition, hospitalization (yes vs. no) and year of the OHA index date were considered as potential confounding variables in the analyses.

Statistical Analyses

Descriptive analyses of demographic and baseline characteristic were performed for each exposure group. Cancer incidences and their 95% confidence intervals (CIs), both overall and for specific cancer, were estimated and age standardized for the metformin and sulphonylurea exposure groups. The incidences were compared using Cox proportional-hazards regression models before and after adjusting for important prognostic covariates. Hazard ratios (HRs) and their 95% CIs were estimated. Patients who did not meet the case criteria in the cohort were censored at the end of their registration in a CPRD practice or 31 December 2008, whichever occurred first. Owing to limited sample size, the resulting lack of precision, and different baseline characteristics of the TZD and meglitinides exposure groups, incidences of cancers were not estimated and comparative analyses were only performed between these exposure groups.

In the adjusted models, age, gender, baseline HbA1c, BMI, smoking status, CDS, year of OHA index date, number of OHA prescriptions prior to the OHA index date, hospitalization, use of cancer screening tests and duration of diabetes prior to OHA index date were initially considered. Age and gender were always retained in the final models.

Potential confounders were tested one-by-one by generating two models for each confounder. One model contained the exposure factor only, that is, calculating an unadjusted HR, and the other contained the exposure factor and the tested

confounder (adjusted HR). Only patients who had a non-missing value for the tested confounder were included in these two models. The confounders were retained in the final model only if their inclusion, in a model containing the single covariate and the OHA exposure variable, changed the HR for the OHA exposure variable by 10% or more, relative to the unadjusted HR for the OHA exposure (i.e. adjusted HR/unadjusted HR is either >1.10 or <0.90), the so-called 'change in estimate' criterion [18].

Three sensitivity analyses were performed utilizing the same Cox proportional-hazard regression models. The first sensitivity analysis was to investigate the influence of missing values for each covariate on estimating the HR of cancers. For each tested covariate (HbA1c, BMI, duration of diabetes to OHA start date, cardiovascular disease, OHA index year, hospitalization, CDS, cancer screening and smoking status), an unadjusted model was fit including only patients who had non-missing values of the tested covariate. The HR estimated from this test model was compared to the unadjusted HR from the model with all patients included (with or without a missing value for the tested covariate), to separate out the effect of limiting the dataset to those with non-missing covariate values from the effect of adjusting for covariates. The second sensitivity analysis compared the incidence of cancers based on the primary exposure follow-up period. Only cancers that occurred during the primary exposure follow-up period (from the OHA index date to the day before the new therapeutic regimen + 6 months or the end of cohort follow-up, whichever occurred first) were considered as cases. Follow-up was censored at this time point. The third sensitivity analysis was to assess the influence of prevalent diabetic patients who registered with the CPRD after the onset of diabetes. Patients who had a diabetes diagnosis date prior to the CPRD registration date were excluded from these sensitivity analyses. Patients whose earliest diabetes dates were within 1 year after the CPRD registration date were also excluded, because these patients were likely to have developed diabetes prior to entering the CPRD. All analyses were conducted using SAS version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Results

Baseline Characteristics

The final cohort contained 56 844 qualified patients (figure 1). In this cohort, 39 070 (68.7%) patients were initially stabilized on metformin, 16 904 (29.7%) on sulphonylurea, 662 (1.2%) on TZDs and 208 (0.4%) on meglitinides.

Table 1 shows the demographic and baseline characteristics of the cohort. The TZD group had the lowest proportion (51%) of males. Over one half of individuals in the sulphonylurea group were over 65 years old, while only about one third of the other exposure groups were in this older category. The sulphonylurea group was leaner with 28% having a BMI <25 compared to 7% in the metformin group. Conversely, 28% of the sulphonylurea group was obese (BMI ≥30) as compared to 65% of the metformin group. The mean baseline HbA1c values for all exposure groups were above the normal limit defined as 7%, with the sulphonylurea group having the highest HbA1c, with 92% above the normal limit. The minimum CDS was 2, which indicated that antidiabetic treatment was the only treatment for chronic disease at baseline. The sulphonylurea and meglitinides groups had similar proportions (27 and 26%, respectively) in this low CDS category. Conversely, the metformin and TZD groups had lower proportions (11 and 19%, respectively) in this minimum chronic disease category. The duration of diabetes prior to cohort entry was shorter in the metformin and sulphonylurea groups compared to the TZD and meglitinides groups. The proportions of patients with recent cancer screening and smoking status were similar across the exposure groups. In early study years, patients were more likely to initiate OHA therapy with sulphonylurea. More than half of the metformin group initiated OHA after 2003. There was no TZD therapy prior to 2000 and no meglitinide use prior to 1999, because these classes are newer OHAs. The mean follow-up duration is similar for subjects on sulphonylureas and meglitinides (5 years), while it was shorter in the metformin group (3.4 years) and the TZD group (2.6 years).

There were 20 932 (36.8%) subjects with missing baseline HbA1c. Notably, the proportions with missing baseline HbA1c were significantly different across exposure groups. Half of the sulphonylurea group had a missing baseline HbA1c, compared with about one third of the metformin group. The TZD group had the lowest proportion (13%) of missing HbA1c values. This trend of missing values was similar across other baseline characteristics, including BMI, smoking status and duration of diabetes prior to the OHA index date. In further exploration, it was found that this trend of missing baseline characteristics was explained mainly by the difference in the OHA index year. Patients entering treatment in the early years were more likely to be started on sulphonylurea, whereas metformin became the dominant initial therapy in the later years. HbA1c was not systematically measured among diabetes patients in earlier years, so it was missing more often in the sulphonylurea group. The rates of missing HbA1c decreased by year for all groups. There were more than 60% of subjects with missing HbA1c before 2000 and more than half were missing between 2000 and 2001. The rate of missing HbA1c dropped to around one third between 2002 and 2003. After 2004, this rate stabilized at around 20%. The rates of missing HbA1c values were similar across exposure groups, except for the TZD group, when examined within each specific calendar year. Other missing baseline characteristics had similar distributions and were similar across exposure groups by year (data not shown).

Exposures and Cancer Risk

During the cohort follow-up of the metformin and sulphonylurea exposure groups, a malignancy developed in 2554 subjects (4.6%). Among these cases, 2372 were malignant solid tumours and 198 were haematological malignancies. Sixteen subjects developed both a malignant solid tumour and a haematological malignancy.

Table 2 shows the person-years of follow-up (started from 1 year after the OHA index date) and the unadjusted and age standardized [based on UK 2001 Census [19]] incidence rates of overall cancers, as well as of malignant solid tumours

Table 1. Demographic and baseline characteristics of the cohort.

	Metformin N = 39 070	Sulphonylurea N = 16 904	TZD N = 662	Meglitinides N = 208
Gender (male)	22 253 (57.0%)	9993 (59.1%)	334 (50.5%)	116 (55.8%)
Age (years) (n = 56844)	39 070	16 904	662	208
35–50	7653 (19.6%)	1978 (11.7%)	104 (15.7%)	40 (19.2%)
51–65	17 486 (44.8%)	6383 (37.8%)	287 (43.4%)	90 (43.3%)
66–75	10 825 (27.7%)	6122 (36.2%)	208 (31.4%)	62 (29.8%)
76–80	3106 (8.0%)	2421 (14.3%)	63 (9.5%)	16 (7.7%)
Median	61.0	66.0	63.0	61.5
Mean (SD)	60.5 (±10.7)	64.2 (±10.4)	62.2 (±10.6)	60.4 (±10.9)
Min–max	35–80	35–80	35-80	35–80
BMI*(n = 43306)	31 397	11 151	598	160
10 to <20	80 (0.3%)	270 (2.4%)	5 (0.8%)	4 (2.5%)
20 to <25	2120 (6.8%)	2891 (25.9%)	67 (11.2%)	29 (18.1%)
25 to <30	10 005 (31.9%)	4826 (43.3%)	217 (36.3%)	68 (42.5%)
30 to <35	10 441 (33.3%)	2120 (19.0%)	163 (27.3%)	30 (18.8%)
≥35	8752 (27.9%)	1047 (9.4%)	146 (24.4%)	29 (18.1%)
Median	5	5	6	5
Mean (SD)	32.5 (±6.2)	28.1 (±5.2)	31.6 (±6.4)	29.6 (±6.1)
Min–max	11.9–79.1	12.2–78.4	18.8–67.8	17.8–47.4
BMI missing	7672 (19.6%)	5750 (34.0%)	64 (9.7%)	48 (23.1%)
HbA1c*(n = 35915)	26 768	8453	577	114
<7	2580 (9.6%)	657 (7.8%)	64 (11.1%)	10 (8.8%)
7 to <9	14 776 (55.2%)	4085 (48.3%)	373 (64.6%)	58 (50.9%)
9 to <12	7573 (28.3%)	2826 (33.4%)	116 (20.1%)	37 (32.5%)
≥12	1839 (6.9%)	885 (10.5%)	24 (4.2%)	9 (7.9%)
Median	8.3	8.7	8.0	8.5
Mean (SD)	8.8 (±1.8)	9.2 (±2.1)	8.4 (±1.6)	8.8 (±1.8)
Min–max	2.9–21.0	2.7–36.0	5.5–16.5	4.9–14.1
HbA1c missing	12 302 (31.5%)	8451 (50.0%)	85 (12.8%)	94 (45.2%)
CDS (n = 56844)	39 070	16 904	662	208
2	7392 (18.9%)	4607 (27.3%)	73 (11.0%)	54 (26.0%)
3–5	12 535 (32.1%)	5029 (29.8%)	219 (33.1%)	65 (31.3%)
6–10	16 514 (42.3%)	6189 (36.6%)	322 (48.6%)	70 (33.7%)
>10	2629 (6.7%)	1079 (6.4%)	48 (7.3%)	19 (9.1%)
Median	31.4	27.2	30.3	28.0
Mean (SD)	5.6 (±3.0)	5.3 (±3.1)	6.2 (±3.0)	5.5 (±3.3)
Min–max	2–19	2–18	2–21	2–16
Duration of diabetes prior to OHA start (months)*(n = 56013)	38 582	16 572	657	202
≤6	12 934 (40.8%)	5578 (39.9%)	166 (27.2%)	55 (29.3%)
7–24	8205 (25.9%)	3219 (23.0%)	197 (32.2%)	51 (27.1%)
25–60	7066 (22.3%)	3002 (21.5%)	173 (28.3%)	49 (26.1%)
>60	3480 (11.0%)	2190 (15.7%)	75 (12.3%)	33 (17.6%)
Median	17.2	18.1	27.2	27.1
Mean (SD)	19.6 (±32.0)	24.6 (±40.5)	25.9 (±32.1)	30.7 (±40.1)
Min–max	0–514.5	0–480.7	0–243.9	0–295.1
Duration missing	488 (1.3%)	332 (2.0%)	5 (0.8%)	6 (2.9%)
Cancer screening	2582 (6.6%)	853 (5.1%)	57 (8.6%)	15 (7.2%)
Smoking status*(n = 53981)	37 753	15 381	655	192
No smoker	15 812 (41.9%)	7197 (46.8%)	276 (42.1%)	93 (48.4%)
Current smoker	13 143 (34.8%)	5133 (33.4%)	218 (33.3%)	70 (36.5%)
Previous smoker	8798 (23.3%)	3051 (19.8%)	161 (24.6%)	29 (15.1%)
Smoking missing	1317 (3.4%)	1523 (9.0%)	7 (1.1%)	16 (7.7%)
Previous prescriptions of OHA	39070	16904	662	208
None	37 503 (96.0%)	14 349 (84.9%)	267 (40.3%)	106 (51.0%)
≤3	1192 (3.1%)	2086 (12.3%)	295 (44.6%)	69 (33.2%)
>3 and ≤6	344 (0.9%)	428 (2.5%)	81 (12.2%)	26 (12.5%)
>6	31 (0.1%)	41 (0.2%)	19 (2.9%)	7 (3.4%)
OHA start year				
1996 to <1998	1116 (2.9%)	2248 (13.3%)	0	0
1998 to <2000	2363 (6.1%)	3511 (20.8%)	0	41 (19.7%)

Table 1. Continued.

	Metformin N = 39 070	Sulphonylurea N = 16 904	TZD N = 662	Meglitinides N = 208
2000 to <2002	5066 (13.0%)	4407 (26.1%)	18 (2.7%)	67 (32.2%)
2002 to <2004	8222 (21.0%)	3137 (18.6%)	110 (16.6%)	72 (34.6%)
≥2004	22 303 (57.1%)	3601 (21.3%)	534 (80.7%)	28 (13.5%)
Follow-up duration (year)†				
Median	2.9	4.9	2.5	5.2
Mean (SD)	3.35 (±2.50)	5.02 (±3.02)	2.56 (±1.47)	5.02 (±2.47)
Min–max	0.002–11.99	0.002–12.0	0.03–7.11	0.02–8.97

*Percentage for each category was based on subjects with non-missing values in each exposure group. Percentage for missing was based on total subjects in each exposure group.
†Follow-up was started from 1 year after the OHA index date.

Table 2. Incidence rates of cancer and death without cancer.

Exposure	Events (N)	Person-years	Crude incidence rate/ 1000 person-years (95% CI)	Age standardized incidence rate/ 1000 person-years (95% CI)
Overall malignancies				
Metformin	1389	131 186	10.59 (10.05–11.16)	7.49 (6.40–9.04)
Sulphonylurea	1165	85 075	13.69 (12.93–14.50)	8.49 (7.09–10.36)
Malignant solid tumour				
Metformin	1290	130 903	9.85 (9.33–10.41)	6.97 (5.92–8.48)
Sulphonylurea	1082	84 812	12.76 (12.02–13.54)	7.88 (6.54–9.70)
Haematological malignancy				
Metformin	110	127547	0.86 (0.76–0.98)	0.61 (0.37–1.13)
Sulphonylurea	88	81 149	1.08 (0.94–1,26)	0.70 (0.39–1.33)
Death without cancer				
Metformin	2097	131 186	15.99 (15.32–16.69)	11.81 (10.34–13.69)
Sulphonylurea	2605	85 075	30.62 (29.47–31.82)	17.96 (15.62–21.22)

and haematological malignancies. The incidence rate of death without cancer is also shown in this table.

Incidences of total cancers were a little higher in the sulphonylurea group (14/1000 person-years) compared to the metformin group (11/1000 person-years). After age standardization, the two exposure groups had similar incidences (7–8/1000 person-years). For malignant solid tumours, the incidence rate was also higher in the sulphonylurea group (13/1000 person-years) and lower in the metformin group (10/1000 person-years). Age standardized incidences of malignant solid tumours were similar across exposure groups. There also were no significant differences in haematological malignancies among the exposure groups (1/1000 person-years). The age standardized incidence of death without cancer was higher in the sulphonylurea group (18/1000 person-years) and lower in the metformin group (12/1000 person-years).

Table 3 shows unadjusted and adjusted HRs for overall cancer, malignant solid tumour and haematological malignancies and their 95% confidence intervals from Cox proportional hazard models. Exposure to metformin was designated as the reference group. HRs of death without cancer, as well as death or cancer, are also presented in this table.

Potential confounders were tested one by one in models containing the single covariate and the exposure variable. On the basis of the 'change in estimate' criterion, age-adjustment changed the estimates of HRs for all endpoints. Adjusting for BMI changed the estimate of risk for haematological malignancy only. No other potential confounders changed the unadjusted HR by more than 10%. In the final adjusted models, age and gender were included as covariates for the outcomes of overall cancer, malignant solid tumour, death without cancer and death or cancer. Age, gender and BMI were included in the model for haematological malignancy.

In unadjusted models, sulphonylurea was associated with a 25% increased risk of overall cancer, malignant solid tumour and haematological malignancy. After adjusting for potential confounders, the sulphonylurea group showed no increased risk of overall cancer, malignant solid tumour or haematological malignancy as compared to use of metformin. Sulphonylurea was associated with significantly increased risk of death without cancer (adjusted HR = 1.39, 95% CI: 1.31, 1.48), compared to metformin. It was also significantly associated with the outcome of 'death or cancer' as single, composite endpoint (adjusted HR = 1.27, 95% CI: 1.21, 1.33).

Sensitivity Analyses for OHAs and Cancer Risk

The first sensitivity analysis investigating the influence of missing covariates on estimating the HR of cancers showed that eliminating subjects with missing values for HbA1c or diabetes duration changed the HR estimates of haematological malignancies from 1.24 (0.93–1.65) to 1.46 (0.96–2.22) and to

Table 3. Hazard ratios for cancer and death without cancer comparing sulphonylurea to metformin.

Exposure	Unadjusted HR (95% CI)	Age adjusted HR (95% CI)	Final adjusted HR (95% CI)*
Overall malignancies			
Full cohort follow-up	1.25 (1.16–1.35)	1.08 (0.99–1.17)	1.07 (0.98–1.15)
Primary exposure follow-up	1.25 (1.12–1.39)	1.05 (0.94–1.17)	1.03 (0.93–1.15)
Malignant solid tumour			
Full cohort follow-up	1.25 (1.15–1.36)	1.07 (0.99–1.17)	1.06 (0.98–1.16)
Primary exposure follow-up	1.24 (1.11–1.39)	1.05 (0.93–1.17)	1.03 (0.92–1.15)
Haematological malignancies			
Full cohort follow-up	1.24 (0.93–1.65)	1.06 (0.80–1.42)	1.00 (0.68–1.46)
Primary exposure follow-up	1.34 (0.91–1.96)	1.10 (0.75–1.61)	0.97 (0.59–1.60)
Death without cancer			
Full cohort follow-up	1.77 (1.67–1.88)	1.40 (1.32–1.49)	1.39 (1.31–1.48)
Primary exposure follow-up	2.17 (2.00–2.35)	1.67 (1.54–1.82)	1.65 (1.52–1.79)
Cancer or death			
Full cohort follow-up	1.57 (1.49–1.64)	1.28 (1.22–1.34)	1.27 (1.21–1.33)
Primary exposure follow-up	1.77 (1.66–1.88)	1.41 (1.32–1.50)	1.39 (1.30–1.48)

*For overall cancer, malignant solid tumour, death without cancer, and cancer or death, age and gender were adjusted in the final models. For haematological malignancy, age, gender and BMI were adjusted in the final model.

1.06 (0.77–1.46), respectively. No other HRs shown in Table 3 was changed by more than 10% by eliminating subjects with missing variables.

The second sensitivity analysis used the primary exposure period as the duration of follow-up. The metformin and sulphonylurea groups had similar mean durations as the primary exposure (35 ± 23 and 38 ± 26 months, respectively). Medians of the durations of primary exposure were 29 and 31 months for metformin and sulphonylurea groups, respectively. Approximately, half of the metformin (56%) group remained on the primary exposure throughout the total cohort follow-up. This percentage was lower for the sulphonylurea (35%) group. In the metformin group, 22% of patients changed to another monotherapy and another 22% added one medication (OHA or insulin). These percentages were 36 and 29% for the sulphonylurea group, respectively. HRs from this sensitivity analysis showed no substantial changes compared to those shown for the total follow-up period (Table 3).

The third sensitivity analysis excluded 3477 patients who had the earliest diagnosis of diabetes earlier than the CPRD registration date or <1 year after the CPRD registration date. The HRs did not change appreciably from those shown in Table 3 (overall malignancies, adjusted HR = 1.07, 95% CI = 0.95, 1.20; malignant solid tumour: adjusted HR = 1.06, 95% CI = 0.95, 1.20; haematological malignancies: adjusted HR = 1.17, 95% CI = 0.69, 1.98).

Analyses on individual cancers are listed in Table 4. For CRC, age-standardized incidences were 0.98 and 1.26 per 1000 person-years for the metformin and sulphonylurea exposure groups, respectively. These rates were 2.47 and 2.95 per 1000 person-years for breast cancer, and 1.72 and 1.53 per 1000 person-years for prostate cancer. Compared to metformin exposure, exposure to sulphonylurea was not associated with an increased risk of CRC (adjusted HR = 1.17, 95% CI: 0.95, 1.44), breast cancer (adjusted HR = 1.04, 95% CI: 0.83, 1.31) or prostate cancer (adjusted HR = 0.88, 0.71, 1.11).

Discussion

Our study identified a cohort of type 2 diabetes patients who were newly exposed to antidiabetic treatment. Age-standardized incidences of cancers and subtypes of cancer were estimated for metformin and sulphonylurea exposure groups. Relationships between initial monotherapy of metformin or sulphonylurea and cancer occurrence (malignant solid tumour, CRC, breast cancer, prostate cancer and haematological malignancy) were investigated in the analyses.

Among type 2 diabetes patients who initiated metformin or sulphonylurea monotherapy, age-standardized incidence of overall malignancies were 7.49 and 8.49 per 1000 person-years, respectively. These rates for malignant solid tumours were 6.97 and 7.88 per 1000 person-years, respectively. There was no difference in risk of cancer, or cancer sub-types, when comparing sulphonylurea to metformin as initial monotherapy.

Table 4. Age standardized incidence rates of CRC, breast cancer, and prostate cancer.

		Colorectal cancer	Breast cancer	Prostate cancer
Incidence rate/1000 person-years (95% CI)*	Metformin	0.98 (0.66–1.55)	2.47 (1.62–3.87)	1.72 (1.22–2.54)
	Sulphonylurea	1.26 (0.84–1.97)	2.95 (1.70–5.78)	1.53 (1.06–2.33)
HR (95% CI)†		1.17 (0.95–1.44)	1.04 (0.83–1.31)	0.88 (0.71–1.11)

*Age standardized.
†Comparing sulphonylurea to metformin.

Metformin reduces blood glucose by inhibiting hepatic glucose production and increasing the sensitivity of peripheral tissue to insulin [20]. In addition to the insulin sensitizer effects, metformin has direct antiproliferative effects on cell growth. Metformin may suppress protein synthesis and cell proliferation directly via activation of the AMP-activated protein kinase (AMPK) through liver kinase B1 LKB1 [21,22]. Multiple studies have found reduced cancer occurrences and a dose–response relationship among metformin exposed populations compared to other treatments [7,14,23].

Patients who were initially stabilized on metformin could have been at lower baseline risk of cancer. Indeed, these patients were younger and had a lower baseline HbA1c, but were less healthy (with more co-morbidity) and heavier (higher baseline BMI). Type 2 diabetes patients treated with metformin had a lower rate of mortality (mostly cardiovascular mortality) than those treated by sulphonylurea [24]. Death without cancer might play a role as a competing risk for the sulphonylurea group. This competing risk might bias the results towards the null, if those who died from other causes were also at higher risk of malignancy (because patients at high risk for cancer would be preferentially removed from the sulphonylurea group by competing causes of death). When considering death or cancer as a composite endpoint, initiation with sulphonylurea monotherapy was associated with a statistically significant 27% increased risk compared to metformin initiation monotherapy, as compared with a 39% increased risk of death without cancer.

The study conducted by Currie et al. [7] utilized a similar UK GP database (THIN), but yielded a rather different conclusion that sulphonylurea was associated with 1.36 (95% CI 1.19–1.54) higher risk of cancer compared with metformin. There are several substantial differences between our cohort and the Currie cohort. Our study was based on the CPRD data which included roughly twice as many practices as the THIN data used by Currie et al. Moreover, we included diabetic subjects initially treated as early as 1995, whereas the Currie cohort was defined later (~2002). A marked secular decline in the use of sulphonylurea took place over the 1995–2008 period such that the Currie cohort was restricted to a smaller, presumably more selected, group of patients taking sulphonylureas than we were (7439 vs. 16 572). Other differences include that the minimum age of our cohort is younger (35 years old) than that in Currie (40 years old), and our cohort excluded those with cancers diagnosed in the first year of follow-up, and they did not.

The UK CPRD is a medical records database, which is collected prospectively in an unbiased manner. It provides objective measures of exposures and outcomes. The database has been widely used as a data source for epidemiologic studies [9–11]. Multiple validation studies have confirmed the reliability of coded diagnoses, especially common outcomes like cancer and diabetes mellitus [9,13,14,25]. Almost all (99.7%) prescriptions are recorded [26]. Although dispensing of and compliance with the prescribed medications are not captured in the database, most medications are likely to be filled as recorded due to the low co-payment or no co-payment for medications in the UK. However, we note that this is an observational study and patients have not been assigned to therapy in a random manner; therefore, potential residual confounding is not avoidable. Although this limitation is inherent in the observational nature of the study, we tested all known potential confounders that were available in the dataset and, except for age, they did not affect the results in a substantive manner. In particular, an uncontrolled cohort effect due to the large difference in cohort entry years within the 14-year time span was a major concern. However, the year of OHA index date was tested as a covariate and it did not change the results to a meaningful degree. On the basis of the above arguments, we do not believe residual confounding is likely to have produced substantial bias.

The CPRD is population based which should mitigate against having a study sample that is non-representative, but there always is the possibility of ascertainment bias, that is, those patients with longer follow-up or followed during different years may have a different level of outcome identification. However, adjusting for index year in the model should mostly account for secular differences in reporting. Another possibility is random error (non-differential misclassification) in outcome ascertainment resulting from lack of adjudication of malignancies. However, as a life threatening condition cancer is more likely than other disease to be recorded accurately in the GP data, and a study on colorectal cancer yielded a 97% confirmation rate through case adjudication [14]. Random under-ascertainment of the outcome measurement will reduce the absolute rates and the precision of the relative rate estimates, rather than introducing bias [27]. Our study has a large sample size which should help to compensate for the lost of precision. Our sensitivity analysis that showed no difference between unadjusted models with and without subjects who had any missing values for covariates gives us some reassurance against systematic bias related to missing values.

In summary, this study provides evidence that there is no substantially different risk of cancer in the first few years after type 2 diabetes patients initiate OHA therapy with metformin or sulphonylurea. Death without cancer (mostly cardiovascular) was not the main subject of this inquiry, but the higher frequency of this endpoint in the patients initially stabilized on sulphonylurea than on metformin is almost certainly a more important consideration in the choice of initial OHA than is cancer risk.

Conflict of Interest

H. Q. conducted the analyses, contributed to the discussion and wrote the manuscript. G. R. contributed to the discussion and reviewed/edited the manuscript. J. A. B. contributed to the discussion and reviewed/edited the manuscript. S. M. contributed to the discussion and reviewed/edited the manuscript. K. D. contributed to the discussion and reviewed/edited the manuscript.

H. Q. and J. A. B. are full-time employees of Janssen Research & Development, which, at the time of this writing, has a new diabetes drug under consideration for approval by regulatory authorities. This drug is in a new class of drugs (SGLT-2 inhibitors) that has a mechanism of action different from those considered in this paper. All other authors have no relevant conflict of interest to disclose.

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