



# Metformin Does Not Affect Cancer Risk: A Cohort Study in the U.K. Clinical Practice Research Datalink Analyzed Like an Intention-to-Treat Trial

DOI: 10.2337/dc14-0584

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## OBJECTIVE

Meta-analyses of epidemiologic studies have suggested that metformin may reduce cancer incidence, but randomized controlled trials did not support this hypothesis.

## RESEARCH DESIGN AND METHODS

A retrospective cohort study, Clinical Practice Research Datalink, was designed to investigate the association between use of metformin compared with other anti-diabetes medications and cancer risk by emulating an intention-to-treat analysis as in a trial. A total of 95,820 participants with type 2 diabetes who started taking metformin and other oral antidiabetes medications within 12 months of their diagnosis (initiators) were followed up for first-incident cancer diagnosis without regard to any subsequent changes in pharmacotherapy. Cox proportional hazards models were used to estimate multivariable-adjusted hazard ratios (HR) and 95% CI.

## RESULTS

A total of 51,484 individuals (54%) were metformin initiators and 18,264 (19%) were sulfonylurea initiators, and 3,805 first-incident cancers were diagnosed during a median follow-up time of 5.1 years. Compared with initiators of sulfonylurea, initiators of metformin had a similar incidence of total cancer (HR 0.96; 95% CI 0.89–1.04) and colorectal (HR 0.92; 95% CI 0.76–1.13), prostate (HR 1.02; 95% CI 0.83–1.25), lung (HR 0.85; 95% CI 0.68–1.07), or postmenopausal breast (HR 1.03; 95% CI 0.82–1.31) cancer, or any other cancer.

## CONCLUSIONS

In this large study, individuals with diabetes who used metformin had a similar risk of developing cancer compared with those who used sulfonylureas.

The effects of antidiabetes medications on cancer risk have recently attracted significant public interest. In particular, meta-analyses of observational studies have found that the biguanide metformin, which is an insulin sensitizer and the most commonly used first-line therapy for type 2 diabetes, may reduce cancer incidence (1,2). However, a meta-analysis of randomized controlled trials did not support this hypothesis (3).

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Received 6 March 2014 and accepted 24 April 2014.

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-0584/-/DC1>.

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Many of the published pharmacoepidemiologic studies are difficult to interpret, however, because they may be subject to several biases (4). The progressive nature of type 2 diabetes requires changes in pharmacotherapy over time and makes very difficult the assessment of the independent association of a specific medication and cancer risk. The lack of randomization makes observational effect estimates vulnerable to confounding by indication due to the different prognoses of individuals between treatment groups. Moreover, most randomized clinical trials are not designed or sufficiently powered to examine cancer outcomes due to short follow-up periods and very few cancer events.

To overcome these limitations, we emulated the design and analysis of a trial in a large retrospective cohort study within the U.K. Clinical Practice Research Datalink (CPRD), one of the world's largest electronic medical record databases, to investigate associations of cancer risk among users of metformin compared with users of sulfonylurea or other first-line oral hypoglycemic agents (OHAs) among individuals with newly diagnosed diabetes. This "incident diabetes drug" cohort design and intention-to-treat (ITT) analysis can be regarded as the equivalent of a nonrandomized "trial" that avoids many of the biases of traditional observational studies (5).

## RESEARCH DESIGN AND METHODS

### Data Source

This study was conducted using the U.K. CPRD, previously known as General Practice Research Database (6) and was approved by the Medicines and Healthcare Products Regulatory Agency Independent Scientific Advisory Committee. The CPRD was established in 1987 and currently encompasses more than 5 million people enrolled from over 600 general practitioners nationwide. The people enrolled in the CPRD are representative of the U.K. population with regard to age, sex, and geographical distribution (7). Prior studies have found complete agreement between prescription information received from general practitioners and that recorded in the database (7,8). The diagnostic codes contained in the CPRD have shown excellent agreement with those from

medical records, with 95% of neoplasms and 88% of endocrine and metabolic disorders identified in the CPRD confirmed with alternate data sources (8,9).

### Study Population

We extracted data on all participants with type 2 diabetes aged 35 to 90 years who were prescribed at least one antidiabetes agent between 1 January 1987 and 31 December 2010, provided that the first prescription was dated at least 6 months after the CPRD registration date of the participant. This was to ensure that most of the included participants with diabetes would be new users of antidiabetes drugs and to exclude prevalent users with unknown type and duration of treatment. In addition, eligible participants had never a history of cancer. We also excluded the initial 12 months of follow-up after the first antidiabetes prescription, because any cancer diagnoses occurring within that time are unlikely to be attributable to the medications. Of the initial 113,301 participants with type 2 diabetes identified, 95,820 were available for statistical analysis (Fig. 1).

### Exposure Assessment

Exposure to antidiabetes medications was assessed by the presence of antidiabetes prescription records in the CPRD using British National Formulary codes. Treatment-naïve participants with diabetes at CPRD enrollment who first started using metformin (metformin initiators) were compared with initiators of other OHAs. Exposure to certain antidiabetes drugs was classified based on the initial 12-month treatment period, and an individual's treatment pattern was categorized into one of the following mutually exclusive groups:

1. monotherapy with metformin, if they were only exposed to metformin during their initial 12-month treatment period;
2. monotherapy with sulfonylureas, either first generation (tolbutamide, chlorpropamide, tolazamide, acetohexamide) or second generation (gliclazide, glibenclamide, glipizide, glimepiride, gliquidone, glibornuride, glymidine sodium);
3. monotherapy with thiazolidinediones (rosiglitazone, pioglitazone);
4. monotherapy with other OHAs, including  $\alpha$ -glucosidase inhibitors

(acarbose), meglitinide analogs (nateglinide, repaglinide), GLP-1 receptor antagonists (exenatide), dipeptidyl peptidase 4 inhibitors (sitagliptin, vildagliptin);

5. monotherapy with insulin;
6. combination therapies with metformin if the participants were simultaneously exposed to two or more OHAs including metformin during the initial 12-month treatment period;
7. combination therapies with insulin; and
8. other combination therapies.

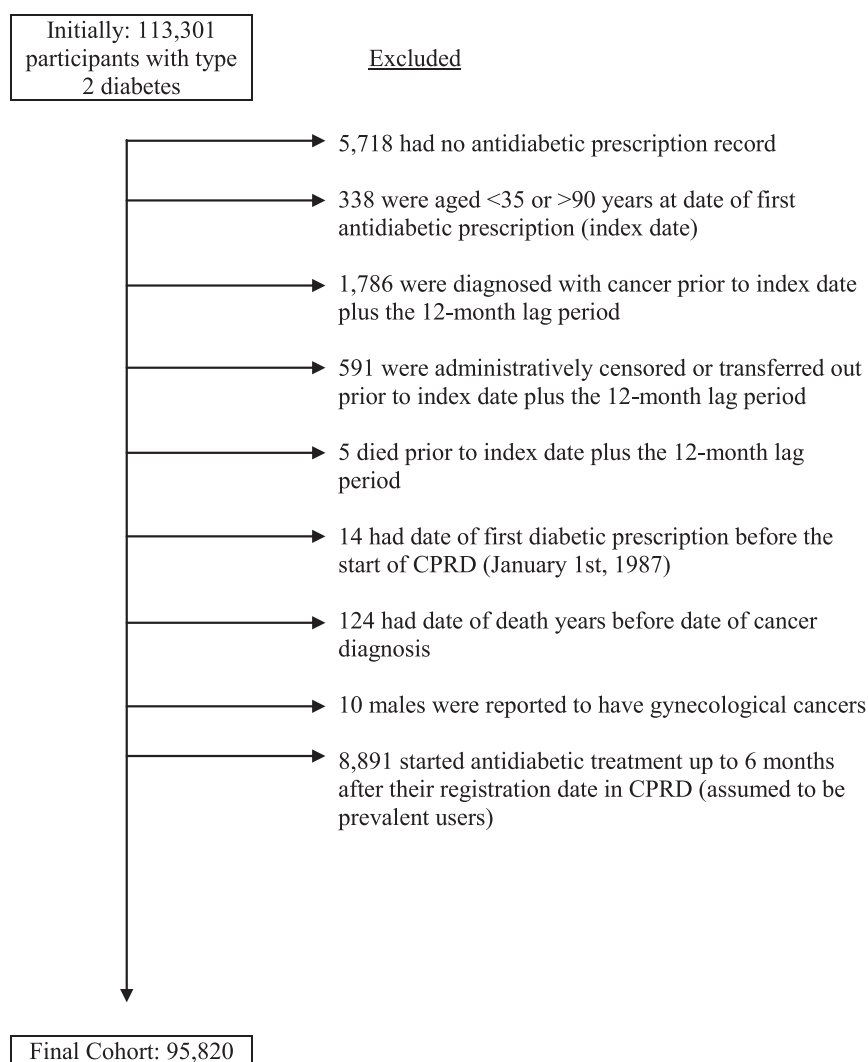
The main analysis was based on a comparison of those who started using metformin compared with those who used sulfonylureas because these two medications were the most common and because sulfonylureas had similar clinical indications to metformin.

### Outcome Assessment

First-incident cancer cases were defined by the presence of National Health Service Read codes in the CPRD. The Read code dictionary was first searched to identify malignant neoplasms, excluding nonmelanoma skin cancers, using several sensitive and specific algorithms and code lists. Two researchers (K.K.T. and D.C.) manually reviewed and confirmed the codes identified by the initial searches and excluded codes for borderline, in situ, or suspected malignancies. A similar process was followed to define type 2 diabetes.

### Covariate Assessment

Information on sociodemographic data, lifestyle characteristics, anthropometric variables, medical conditions, and treatments was extracted from the CPRD at approximately the time of the first antidiabetes prescription (index date). Age and sex were recorded at the time of the first prescription. BMI measurements and smoking status (never, former, current) were retrieved for the 1 year before the index date. Alcohol consumption (never, former, current) was defined from information derived from up to 5 years before the index date to diminish the proportion of missing values for this variable. Treatment with aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs), statins, and exogenous hormones in women was retrieved from the number of prescriptions



**Figure 1**—Selection criteria for the study population in the CPRD.

for the year before the index date. Participants who had a mammogram, a colonoscopy, or a prostate-specific antigen measurement during the 10 years before the index date were considered as having ever received a cancer-screening test.

Duration of diabetes was calculated from the date of diabetes diagnosis to the index date. Diabetic complications or hospitalizations any time before the index date were also considered. Glycemic control was defined as a time-weighted average of glycosylated hemoglobin (HbA<sub>1c</sub>) concentrations for the year before the index date. Because menopausal status is not directly recorded in the CPRD, we used the age of 49 years, previously reported as the median age of menopause among British women (10), to define menopausal status for the breast cancer analysis. A

sensitivity analysis was conducted using 55 years as the cutoff value to increase the specificity of the definition.

#### Statistical Analysis

Within this retrospective cohort, cancer risk was compared among those who first started using metformin and those who started using other OHAs, and then participants were followed up without regard to any subsequent changes in pharmacotherapy (i.e., akin to an ITT analysis). Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% CI for cancer risk using the date since start of follow-up as the underlying time scale. Follow-up time began at the end of the 12-month period after the first prescription and ended at the diagnosis of the first cancer, death, loss to follow-up, or censoring at the end of the follow-up (31

December 2011), whichever came first. Proportionality of hazards was verified based on the slope of the Schoenfeld residuals over time. All models were stratified by age (in 5-year groups from 35 to 90 years) at the index date and sex. Models were adjusted for known or suspected risk factors for cancer, including smoking status (never, former, current), BMI (<18.5, 18.5–25.0, 25.0–30.0, ≥30.0 kg/m<sup>2</sup>), alcohol consumption status (never, former, current), use of aspirin or NSAIDs (based on percentile distribution of the number of prescriptions: no, sparse [1–5 prescriptions], medium [6–16 prescriptions], or frequent use [>16 prescriptions]), use of statins (no, sparse [1–6 prescriptions], medium [7–15 prescriptions], or frequent use [>15 prescriptions]), use of exogenous hormones in women (no,

sparse [1–2 prescriptions], medium [3–7 prescriptions], or frequent use [ $>7$  prescriptions]), for colorectal, breast and endometrial cancer, diabetes duration (in days), and year of the first antidiabetes prescription. Missing values were assigned to separate categories for smoking status (12.5% missing data), BMI (7.5%), alcohol consumption (28.4%), and duration of diabetes (9.1%). Analyses that excluded participants with missing values for any of these covariates and analyses that included further adjustments for family history of cancer, cancer screening history, diabetes complications, and HbA<sub>1c</sub> produced very similar results and are not presented here.

Although following the design and the statistical analysis (ITT) of a trial may correct for confounding by indication, it may misclassify exposure over time if participants change medication, thereby biasing the results toward the null. Therefore, adherence curves during follow-up were plotted to evaluate the amount of nonadherence, and adherence-adjusted estimates were calculated using inverse probability weighting. Participants were censored at the discontinuation of their initial treatment, and the uncensored person-years were weighted by the inverse of their estimated probability of remaining uncensored. The probabilities of remaining on treatment for each participant at years 1, 3, and 5 after the start of follow-up were estimated through logistic regression models adjusted for all baseline covariates (outlined above) and the most recent postbaseline values of these covariates in a time-dependent fashion. Separate regression models were used for initiators of metformin and initiators of other OHAs. To improve precision of the models, the inverse probability weights were stabilized by multiplying the weights by the probability of censoring given the baseline values of the covariates, as described elsewhere (5).

Several other sensitivity analyses were performed. First, to better define continuous antidiabetes medication use, participants who had a treatment break of more than 90 days during the initial qualifying 12-month exposure period were excluded. Second, the exposure to an antidiabetes drug class was redefined based on the first 6 months of

each participant's prescription record instead of the 12 months used in the primary analysis. Third, we excluded participants with any treatment breaks of more than 90 days during the latter qualifying 6-month exposure period. Fourth, we excluded the initial 36 months of follow-up after the first antidiabetes prescription (instead of just 12 months) in case cancers diagnosed within 36 months were still not due to the antidiabetes treatment.

Prespecified stratified analyses were conducted according to age at recruitment ( $<62$  vs.  $\geq 62$  years), BMI ( $<30$  vs.  $\geq 30$  kg/m<sup>2</sup> or  $<25$  vs.  $25\text{--}30$  vs.  $\geq 30$  kg/m<sup>2</sup>), smoking status (never vs. ever), NSAID/aspirin use (never vs. ever), and statin use (never vs. ever), because these variables may influence cancer risk and the decision to start or adhere to a certain antidiabetes pharmacotherapy. Tests for interaction were done by using the relevant exposure variables, indicator variables for the potentially modifying factors, and product terms of the two variables. The *P* values for interaction are interpreted in light of the 90 (15 cancers  $\times$  6 modifying variables) comparisons made. All *P* values were two-sided, and all analyses were performed using STATA 12 software (StataCorp LP, College Station, TX).

## RESULTS

### Baseline Characteristics of the Study Population

Included were 95,820 participants with type 2 diabetes and at least one antidiabetes prescription recorded in CPRD (Fig. 1). Of these, 51,484 individuals (54%) started taking metformin monotherapy, 18,264 (19%) started sulfonylurea monotherapy, and a smaller number started taking each of the other therapies (Table 1). The study did not further analyze 4,124 participants (4%) who started antidiabetes therapy with insulin because they likely had type 1 diabetes or long-standing type 2 diabetes that required insulin treatment.

Table 1 also reports the baseline characteristics according to the first antidiabetes treatment prescription. Compared with those who started using sulfonylurea monotherapy, those who started using metformin monotherapy were, on average, younger (mean age: 61.1 vs. 65.3 years), had a higher BMI

(mean: 32.1 vs. 27.7 kg/m<sup>2</sup>), were more likely to be current alcohol drinkers (57% vs. 44%), more likely to frequently use aspirin/NSAIDs (12% vs. 8%) or statins (15% vs. 6%), had a longer median duration of diabetes before the time of their first antidiabetes prescription (99 vs. 54 days), and their median year of the first prescription was more recent (2005 vs. 2000). In early study years, patients were more likely to initiate oral hypoglycemic therapy with a sulfonylurea. More than 75% of the metformin monotherapy group initiated treatment after 2003. The median follow-up time for the metformin and sulfonylurea monotherapy initiators was 5.1 years (interquartile range 2.9–8.1 years; maximum 24 years) and was not different in the two groups. A total of 3,805 first-incident cancers were identified, of which 599 were colorectal cancers, 580 were prostate cancers, 468 were lung cancers, and 460 were postmenopausal breast cancers.

### ITT Estimates for the Effect of Metformin on Cancer

Compared with those who started using sulfonylurea monotherapy, those who started using metformin had a similar incidence of total cancer (HR 0.96; 95% CI 0.89–1.04; Fig. 2) after adjustment for smoking status, BMI, alcohol consumption, use of aspirin or NSAIDs, statins, diabetes duration, and year of first antidiabetes prescription. The HR was 1.06 (95% CI 0.93–1.22) when the analysis was restricted to the first 3 years of follow-up, 1.09 (95% CI 0.98–1.22) for the first 5 years, and 1.02 (95% CI 0.93–1.12) for the first 8 years. Compared with users of sulfonylurea monotherapy, users of metformin also had similar risks for colorectal (HR 0.92; 95% CI 0.76–1.13), prostate (HR 1.02; 95% CI 0.83–1.25), lung (HR 0.85; 95% CI 0.68–1.07), and postmenopausal breast (HR 1.03; 95% CI 0.82–1.31) cancers, and any other cancer types (Fig. 2). When the age of 55 years was used as the cutoff value to define postmenopausal status, the association for postmenopausal breast cancer remained the same (HR 1.01; 95% CI 0.79–1.30) and was also similar for total breast cancer risk (HR 1.04; 95% CI 0.82–1.32).

We further performed an analysis between metformin and sulfonylurea users who first started taking these

**Table 1—Baseline characteristics by antidiabetes treatment in the CPRD**

	Metformin mono-tx n = 51,484	Metformin combo-tx n = 20,967	Sulfonylurea mono-tx n = 18,264	TZDs mono-tx n = 292	Other OHA mono-tx n = 263	Other OHA combo-tx n = 426	Insulin mono-tx n = 1,723	Insulin combo-tx n = 2,401
<b>Sex</b>								
Male	28,893 (56.1)	11,437 (54.6)	10,578 (57.9)	170 (58.2)	156 (59.3)	246 (57.7)	979 (56.8)	1,330 (55.4)
Female	22,591 (43.9)	9,530 (45.4)	7,686 (42.1)	122 (41.8)	107 (40.7)	180 (42.3)	744 (43.2)	1,071 (44.6)
<b>Age, years</b>								
35–49	9,024 (17.5)	4,329 (20.7)	1,901 (10.4)	38 (13.0)	45 (17.1)	71 (16.7)	547 (31.8)	767 (31.9)
50–64	22,086 (42.9)	9,120 (43.5)	6,327 (34.6)	120 (41.1)	111 (42.2)	162 (38.0)	641 (37.2)	941 (39.2)
65–79	17,616 (34.2)	6,503 (31.0)	7,946 (43.5)	112 (38.4)	91 (34.6)	160 (37.6)	469 (27.2)	609 (25.4)
≥80	2,758 (5.4)	1,015 (4.8)	2,090 (11.5)	22 (7.5)	16 (6.1)	33 (7.7)	66 (3.8)	84 (3.5)
<b>BMI, kg/m<sup>2</sup></b>								
<18.5	46 (0.1)	36 (0.2)	124 (0.7)	2 (0.7)	3 (1.1)	3 (0.7)	11 (0.6)	37 (1.5)
18.5–24.9	4,037 (7.8)	2,112 (10.1)	4,435 (24.3)	49 (16.8)	42 (16.0)	125 (29.3)	306 (17.8)	563 (23.5)
25–29.9	16,321 (31.7)	6,485 (30.9)	6,797 (37.2)	105 (36.0)	103 (39.2)	142 (33.3)	460 (26.7)	638 (26.6)
≥30	29,098 (56.5)	11,024 (52.6)	3,833 (21.0)	128 (43.8)	94 (35.7)	109 (25.6)	468 (27.2)	932 (38.8)
Unknown	1,982 (3.9)	1,310 (6.2)	3,075 (16.8)	8 (2.7)	21 (8.0)	47 (11.1)	478 (27.7)	231 (9.6)
<b>Smoking</b>								
Never	21,214 (41.2)	8,052 (38.4)	6,514 (35.7)	135 (46.2)	93 (35.4)	168 (39.4)	547 (31.8)	811 (33.8)
Former	18,225 (35.4)	7,075 (33.7)	4,194 (23.0)	108 (37.0)	57 (21.7)	118 (27.7)	379 (22.0)	734 (30.6)
Current	8,389 (16.3)	3,545 (16.9)	2,531 (13.8)	42 (14.4)	41 (15.6)	56 (13.2)	283 (16.4)	516 (21.5)
Unknown	3,656 (7.1)	2,295 (11.0)	5,026 (27.5)	7 (2.4)	72 (27.3)	84 (19.7)	514 (29.8)	340 (14.1)
<b>Alcohol</b>								
Never	8,547 (16.6)	3,638 (17.4)	2,868 (15.7)	45 (15.4)	45 (17.1)	71 (16.7)	215 (12.5)	390 (16.2)
Former	1,426 (2.8)	575 (2.7)	283 (1.6)	6 (2.0)	4 (1.5)	10 (2.3)	50 (2.9)	95 (3.9)
Current	29,427 (57.1)	10,641 (50.7)	8,056 (44.1)	169 (57.9)	129 (49.1)	190 (44.6)	595 (34.5)	1,108 (46.2)
Unknown	12,084 (23.5)	6,113 (29.2)	7,057 (38.6)	72 (24.7)	85 (32.3)	155 (36.4)	863 (50.1)	808 (33.7)
<b>Aspirin/NSAID use*</b>								
No	20,414 (39.7)	9,027 (43.0)	9,333 (51.1)	114 (39.0)	136 (51.7)	211 (49.5)	889 (51.6)	1,057 (44.0)
Sparse	13,391 (26.0)	5,829 (27.8)	4,354 (23.8)	65 (22.3)	69 (26.2)	110 (25.8)	419 (24.3)	717 (29.9)
Medium	11,382 (22.1)	4,064 (19.4)	3,124 (17.1)	74 (25.3)	31 (11.8)	75 (17.6)	319 (18.5)	423 (17.6)
Frequent	6,297 (12.2)	2,047 (9.8)	1,453 (8.0)	39 (13.4)	27 (10.3)	30 (7.1)	96 (5.6)	204 (8.5)
<b>Statin use*</b>								
No	19,352 (37.6)	9,709 (46.3)	13,422 (73.5)	81 (27.7)	178 (67.7)	249 (58.5)	1,125 (65.3)	1,238 (51.6)
Sparse	10,783 (20.9)	4,651 (22.2)	1,758 (9.6)	74 (25.3)	28 (10.6)	66 (15.5)	283 (16.4)	585 (24.4)
Medium	13,54 (26.3)	4,334 (20.7)	1,991 (10.9)	79 (27.1)	27 (10.3)	79 (18.5)	233 (13.5)	397 (16.5)
Frequent	7,809 (15.2)	2,273 (10.8)	1,093 (6.0)	58 (19.9)	30 (11.4)	32 (7.5)	82 (4.8)	181 (7.5)
<b>Hormone use**†</b>								
No	19,193 (85.0)	7,830 (82.2)	6,841 (89.0)	106 (86.9)	91 (85.0)	149 (82.8)	624 (83.9)	821 (76.7)
Sparse	1,289 (5.7)	633 (6.6)	316 (4.1)	5 (4.1)	5 (4.7)	10 (5.6)	54 (7.3)	89 (8.3)
Medium	1,389 (6.1)	697 (7.3)	341 (4.4)	6 (4.9)	8 (7.5)	16 (8.9)	52 (6.9)	115 (10.7)
Frequent	720 (3.2)	370 (3.9)	188 (2.5)	5 (4.1)	3 (2.8)	5 (2.7)	14 (1.9)	46 (4.3)

*Continued on p. 6*



Table 1—Continued

	Metformin mono-tx n = 51,484	Metformin combo-tx n = 20,967	Sulfonylurea mono-tx n = 18,264	TZDs mono-tx n = 292	Other OHA mono-tx n = 263	Other OHA combo-tx n = 426	Insulin mono-tx n = 1,723	Insulin combo-tx n = 2,401
Diabetes duration, days†								
Median (IQR)	99 (1–618)	35 (0–360)	54 (0–414)	259 (5–868)	206 (6–765)	30 (0–347)	18 (0–105)	30 (0–347)
Missing, %	5.6	8.1	17.0	9.2	14.8	15.6	39.0	8.7
First year of therapy								
Median (IQR)	2005 (03–07)	2004 (01–07)	2000 (96–02)	2005 (04–06)	2000 (98–03)	2002 (99–04)	2001 (97–04)	2004 (01–07)

Figures are *n* (%) unless otherwise specified. Combo-tx, combination therapy; IQR, interquartile range; mono-tx, monotherapy; TZDs, thiazolidinediones. \*Based on the percentile distribution of the number of prescriptions as no use, sparse use (1–10% of all prescriptions), medium use (10–50% of all prescriptions), and frequent use (>50% of all prescriptions). The exact distributional cut points were use of aspirin or NSAIDs: no, sparse [1–5 prescriptions], medium [6–16 prescriptions], frequent use [≥16 prescriptions]; use of statins: no, sparse [1–6 prescriptions], medium [7–15 prescriptions], frequent use [≥15 prescriptions]; use of exogenous hormones in women: no, sparse [1–2 prescriptions], medium [3–7 prescriptions], frequent use [≥7 prescriptions]. †Exogenous hormone use (oral contraceptives and hormone replacement therapy) in women. ‡From time of diabetes diagnosis to time of first antidiabetes treatment prescription.

medications between 2000 and 2005 when the transition from sulfonylurea to metformin became evident and individuals with diabetes could equally likely start on either drug; but again, the results remained the same and not statistically significant for any cancer (HR 0.95 for total cancer; 95% CI 0.86–1.06). The strongest confounder in the models for total cancer risk and for most separate cancer sites was the year of the first antidiabetes prescription, although inclusion of this covariate in the models did not change the inference from the risk estimates (Supplementary Table 1).

There was also no difference in cancer risk when initiators of metformin were compared with initiators of any other OHA monotherapy (sulfonylureas, thiazolidinediones, other OHAs) or when combination treatments of metformin or any other OHA were added to the monotherapy regimens (Supplementary Figs. 1 and 2). Very few participants (785 [4.3%]) used a first-generation sulfonylurea, and the results were identical when metformin monotherapy initiators were compared with initiators of second-generation sulfonylureas (data not shown).

#### Adherence-Adjusted Effect Estimates

Approximately half of the participants adhered to their initial therapy 3 years after the start of follow-up, whereas only 20% remained on their initial therapy after 5 years (Fig. 3). The inverse probability weighted HRs for total cancer comparing metformin with sulfonylurea monotherapy were 0.96 (95% CI 0.89–1.03) for the first year of follow-up, 0.95 (95% CI 0.87–1.04) for the first 3 years, and 0.94 (95% CI 0.85–1.04) for the first 5 years. Similar estimates were observed for the associations by cancer site, with few exceptions (Supplementary Table 2). Use of metformin was associated with a higher risk of postmenopausal breast cancer (first year: HR 1.13; 95% CI 0.91–1.41; first 3 years: HR 1.33; 95% CI 1.02–1.74; first 5 years: HR 1.47; 95% CI 1.07–2.02) and endometrial cancer (first year: HR 2.51; 95% CI 1.36–4.65; first 3 years: HR 2.04; 95% CI 1.01–4.11; first 5 years: HR 2.29; 95% CI 0.98–5.38), and with a lower risk of pancreatic cancer (first year: HR 0.66; 95% CI 0.45–0.97; first 3 years: HR 0.70; 95% CI 0.44–1.10; first 5 years:

HR 0.60; 95% CI 0.37–0.98) compared with sulfonylurea monotherapy after adjustment for nonadherence, but these intriguing findings were not statistically significant for all evaluated follow-up time points.

#### Sensitivity Analyses

After we excluded participants with any treatment breaks of more than 90 days during the initial qualifying 12-month exposure period, the results (HR 0.95; 95% CI 0.88–1.03) were almost identical to the main analysis (Fig. 4). Similarly, all other sensitivity analyses, including redefining the exposure groups based on the first 6 months of each participant's prescription record or excluding the initial 36 months of follow-up, led to almost identical results for total cancer (Fig. 4) or by cancer site (Supplementary Figs. 3 and 4).

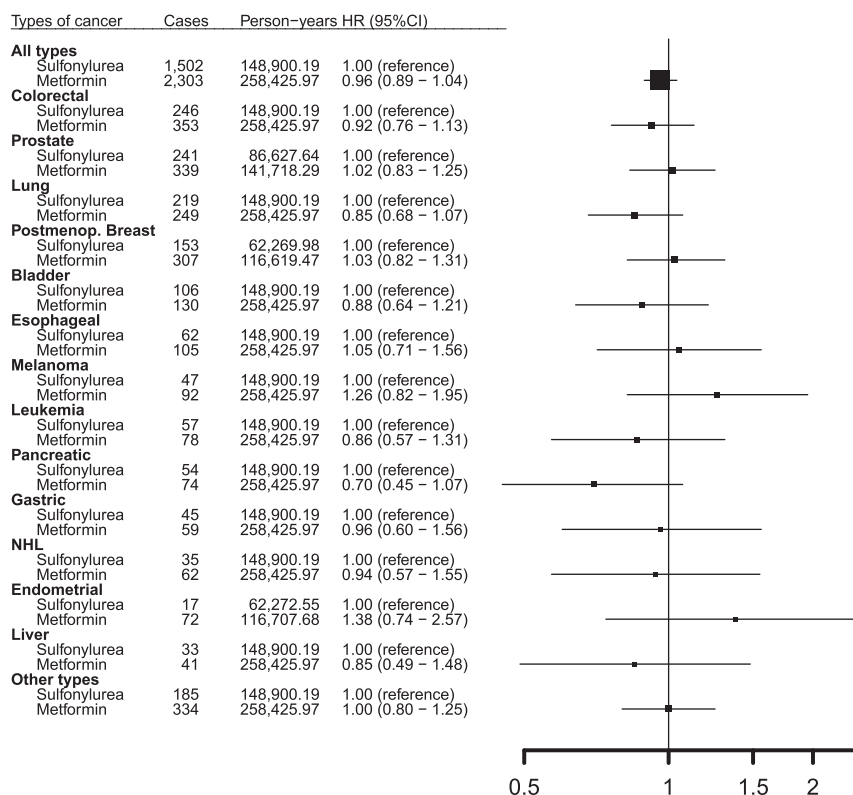
#### Subgroup Analyses

We next examined potential multiplicative interactions, stratifying our ITT estimates by age at recruitment, BMI, smoking status, and NSAID/aspirin and statin use. Eight interactions of 90 were statistically significant at the 0.05 level, but none of these remained significant when we used an adjustment for multiple comparisons with a Bonferroni-corrected *P* value of 0.0006 (Fig. 5 and Supplementary Figs. 5–9). The strongest suggestion of an interaction was by smoking status: the HR of total cancer comparing metformin with sulfonylurea monotherapy was 1.15 (95% CI 0.99–1.33) in never smokers and was 0.88 (95% CI 0.78–0.98; *P* = 0.001 for interaction) in ever smokers (Fig. 5).

## CONCLUSIONS

#### Main Findings

Here, we have reanalyzed the CPRD data using an approach that tried to emulate a clinical trial in all regards other than randomization. Treatment-naïve participants with diabetes who first started using metformin or sulfonylurea monotherapy during their initial 12-month treatment period were compared and followed up without regard to any subsequent changes in their treatment. We found that initiators of metformin had a similar cancer incidence as the initiators of sulfonylurea over a maximum follow-up of 24 years. Similar results were obtained when metformin users were compared with users of other OHAs and after



**Figure 2**—Multivariable-adjusted HRs and 95% CIs for the association between initiators of metformin monotherapy and initiators of sulfonylurea monotherapy and cancer risk using the ITT principle in the CPRD. NHL, non-Hodgkin lymphoma.

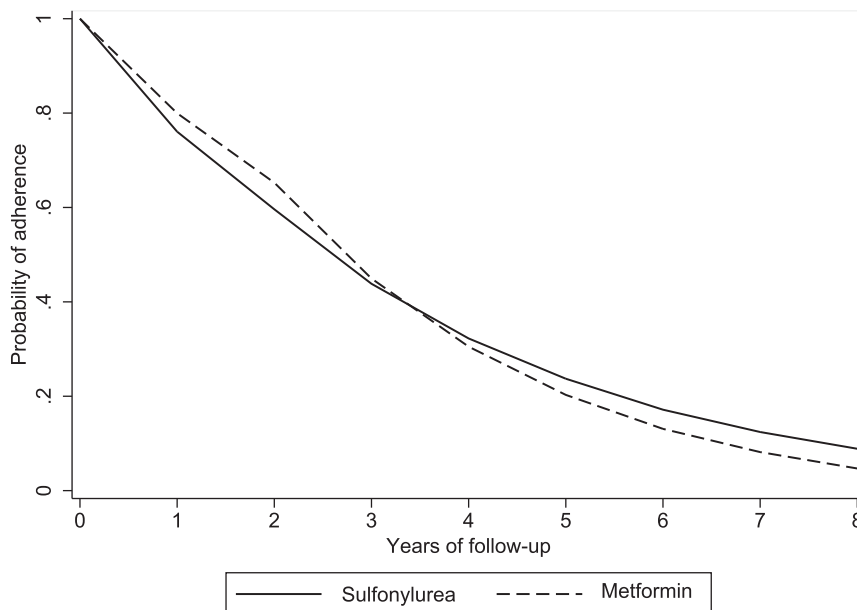
adjustment for nonadherence to the initial treatment.

#### Comparison With Other Studies

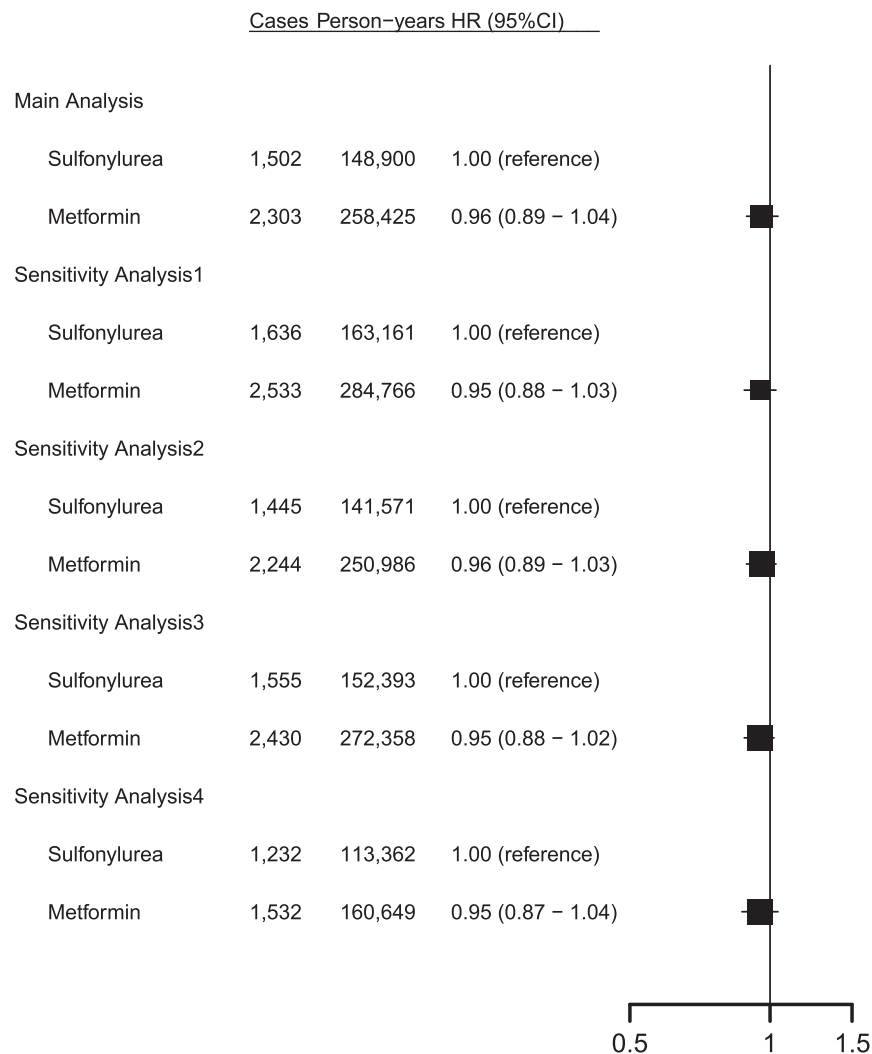
Metformin has been shown to reduce the concentrations of circulating

glucose and insulin by reducing the production of glucose by liver cells and increasing insulin sensitivity, respectively (11). Metformin has also direct antiproliferative effects because it activates the liver enzyme AMPK, which has

been shown to inhibit the growth of cancer cells in several in vitro and in vivo studies (12,13). The upstream regulator of AMPK is the protein kinase LKB1, which is a well-recognized tumor suppressor.



**Figure 3**—Proportion of participants who adhered to their initial antidiabetes treatment in the CPRD.



**Figure 4**—Multivariable-adjusted HRs and 95% CIs for the association between initiators of metformin monotherapy and initiators of sulfonylurea monotherapy and total cancer risk using the ITT principle in the CPRD by type of sensitivity analyses. (Sensitivity analysis 1: after excluding participants with any treatment breaks of more than 90 days during the initial qualifying 12-month exposure period. Sensitivity analysis 2: after redefining the exposure to an antidiabetes drug class based on the first 6 months of each participant's prescription record compared with the 12-month treatment period used in the primary analysis. Sensitivity analysis 3: after excluding participants with any treatment breaks of more than 90 days during the latter qualifying 6-month exposure period. Sensitivity analysis 4: after excluding the initial 36 months of follow-up after the first antidiabetes prescription).

In accordance to the mechanistic evidence, results from some epidemiologic studies conducted in the 2000s suggested that treatment with metformin was associated with a reduced risk of cancer incidence or mortality (14–21). However, these studies were generally limited in their ability to assess an association with specific cancer types, and most of them compared metformin with any other antidiabetes drug regardless of disease severity. Thus, the inverse association observed for metformin and cancer risk might be at least partially due to an increased risk of cancer in long-term patients with diabetes who need to take insulin rather than metformin

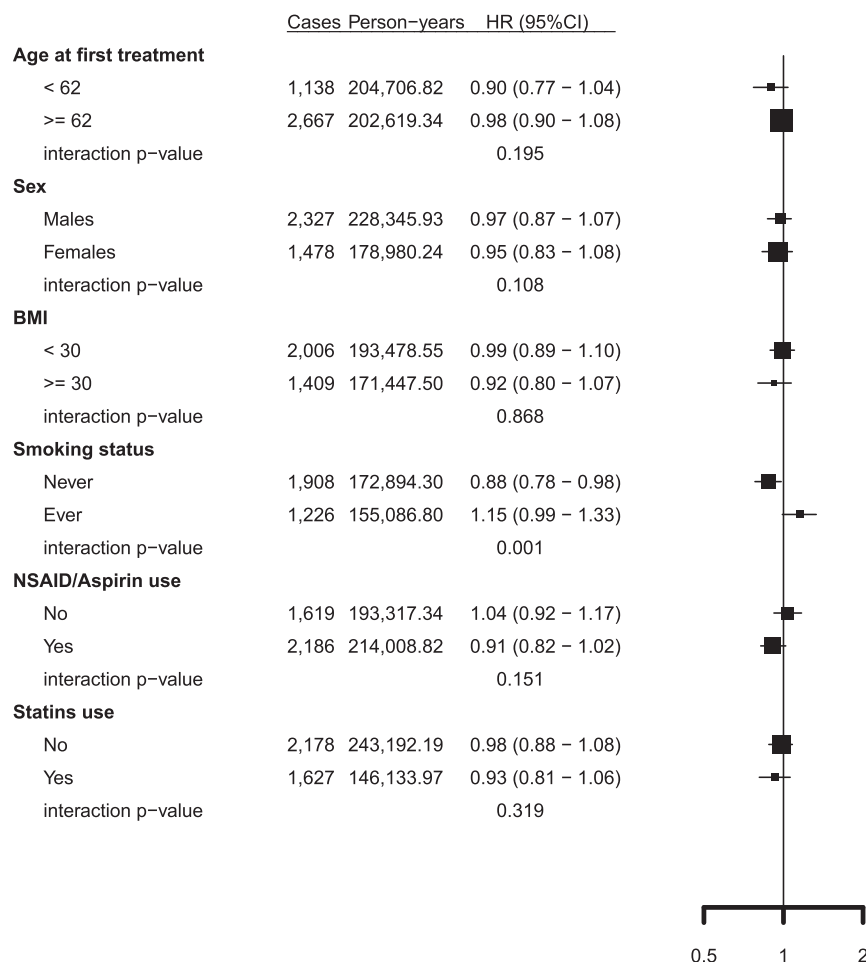
to manage their disease. In addition, some studies have shown that the reduction in risk with the use of metformin starts from the first year of follow-up, which seems biologically implausible (16,21). Several of these studies also suffered from immortal time bias (15,16), whereby misclassification of unexposed time initially in a cohort as metformin exposure during follow-up may create spurious reductions in risk (4).

However, some other more recent studies have found no association between metformin use and cancer risk, which is consistent with our findings. A retrospective cohort in the Kaiser Permanente Northern California Diabetes

Registry found no association with cancer risk between ever users of metformin, defined as two prescriptions in a 6-month period, versus never users, although the maximum duration of follow-up in that study was less than 6 years (22).

The association of antidiabetes medication on cancer risk was also previously analyzed within the CPRD data set (23–28). Qiu et al. (23) analyzed the data from 1995 to 2008 using the ITT principle and reported that sulfonylurea use versus metformin monotherapy use, defined as at least six sequential prescriptions of each drug, was not significantly associated with the risk of total cancer (HR 1.07; 95% CI





**Figure 5**—Multivariable-adjusted HRs and 95% CIs for the association between initiators of metformin monotherapy and initiators of sulfonylurea monotherapy and total cancer risk using the ITT principle in the CPRD by subgroups.

0.98–1.15) or colorectal, breast, or prostate cancer, but this analysis included a shorter follow-up time, reported separate results only for a few cancer sites, and did not adjust for nonadherence. In contrast, a nested case-control analysis using data from 1988 to 2009 found a positive association between ever use of metformin, defined as at least one prescription between cohort entry and end of follow-up, versus never use and risk of prostate cancer (HR 1.23; 95% CI 0.99–1.52), but this analysis did not use the ITT principle and had a potentially biased definition (never vs. ever use) of the exposure groups (28). Other reports from the CPRD have generally observed null associations for metformin and cancer risk but reported results for a few cancer sites. Some of these studies used potentially biased exposure definitions as ever use versus never use of metformin without an ITT analysis approach, and other studies conducted

time-varying exposure analyses and/or incorporated dose and duration of anti-diabetes medications in their statistical models but without adjusting for time-varying confounders (25,26,28).

Our findings agree with two large randomized trials. The ADOPT (A Diabetes Outcome Progression Trial) reported no difference in cancer risk between participants randomized to metformin and those randomized to glibenclamide (relative risk 0.78; 95% CI 0.53–1.14) or rosiglitazone (HR 0.92; 95% CI, 0.63–1.35), based on 155 cases during 4 years of follow-up (29). The RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes) also found no difference in cancer risk between individuals receiving metformin and sulfonylurea versus rosiglitazone and sulfonylurea (relative risk 1.22; 95% CI 0.86–1.74), based on 125 cases over a mean of 5.5 years of follow-up (30).

ITT estimates are generally attenuated toward the null due to changes in adherence to medication over time. Our study is the first, to our knowledge, to take account of likely changes in adherence. Although only 20% of the metformin or sulfonylurea monotherapy users were still using these regimens after 5 years, the adherence-adjusted estimates were not appreciably different, with few exceptions. Compared with sulfonylurea users, metformin users seem to have a higher risk for breast and endometrial cancer and a lower risk for pancreatic cancer, although these associations were not always nominally statistically significant when we corrected for nonadherence at several follow-up cut points, and the CIs were often very wide. CPRD did not have consistent time-varying confounder information, and this might have affected the validity of the adherence-adjusted estimates. Future

prospective studies and large consortia should attempt to clarify this issue.

### Strengths and Weaknesses

Our study is one of the largest to date to investigate the association between metformin use and risk of cancer. The comparison of drug initiators ensured that our estimates were not explained by unknown antidiabetes treatment and/or other variables that occurred before entry to the cohort. Sulfonylurea was used as the main comparison group and should have reduced confounding by indication because sulfonylureas had similar indications to metformin and were prescribed as first-line antidiabetes therapy in the 1980s and most of 1990s in the U.K. The follow-up spanned up to 24 years, and 50% of our study population had follow-up time for more than 5 years.

Our study is not without potential limitations. Patients were not assigned to therapy in a random manner, and therefore, potential residual confounding or residual confounding by indication is possible. Several potential confounders were included in our statistical models, most of which did not greatly change the effect estimates. The CPRD lacked information for some other potential confounders, such as diet, physical activity, race/ethnicity, and reproductive factors, but these variables are not considered the strongest confounders for pharmacoepidemiologic cancer outcomes. Moreover, CPRD did not have consistent time-varying confounder information, and this was a reason for not performing a time-varying analysis of actual prescription to complement the ITT analysis, because such an analysis or an analysis that incorporates information on duration and dose of antidiabetes treatments without proper adjustment for time-varying confounders would have aggravated the potential for bias due to confounding by indication. Emulating the design and ITT analysis of a clinical trial has better performance in areas more susceptible to confounding by indication (5).

### Conclusions

In summary, we found no evidence that metformin use was associated with cancer risk compared with sulfonylurea use in a cohort of newly diagnosed diabetic patients designed and analyzed

emulating a clinical trial. Several large trials are currently planned or are in progress testing metformin for the secondary prevention of several cancers (e.g., NCT01864096 plans to enroll 408 men with low-risk localized prostate cancer, and NCT01101438 enrolled 3,649 women with early breast cancer) after the evidence from the mechanistic studies and the results from some early epidemiologic studies suggested an inhibitory effect of metformin on cancer risk or progression. However, several of the latter observational studies were potentially biased, and more rigorous study designs and analyses are needed in future observational studies that could assist in avoiding the future initiation of potentially unnecessary trials.

**Funding Support.** This work was supported by the Seventh Framework Programme of the European Union (PIEF-GA-2010-276017 to K.K.T. and J.P.A.I.).

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

**Author Contributions.** K.K.T. formulated the hypothesis, designed the study, supervised and conducted the statistical analysis, and wrote the manuscript. D.C. carried out the data management and statistical analysis. N.E.A. participated in formulating the hypothesis and reviewed and edited the manuscript. E.C.R. provided valuable ideas for sensitivity and subgroup analyses and reviewed and edited the manuscript. D.S.L., K.v.V., and C.S. reviewed and edited the manuscript. D.A. and P.V. contributed to the discussion of the research hypothesis and reviewed and edited the manuscript. I.T. formulated the hypothesis, designed the study, and reviewed and edited the manuscript. J.P.A.I. wrote the manuscript and supervised the research. All authors approved the final version submitted. K.K.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Prior Presentation.** An abstract of this study was presented as a poster at the 105th Annual Meeting of the American Association for Cancer Research, San Diego, CA, 5–9 April 2014.

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