Metformin and the risk of renal cell carcinoma: a case–control analysis

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Metformin use has been associated previously with a decreased risk of cancer, but its association with renal cell carcinoma has not yet been investigated in observational studies. We aimed to explore the association between the use of metformin and other antidiabetic drugs and the risk of renal cell carcinoma (RCC). We carried out a case–control analysis in the UK-based Clinical Practice Research Datalink. We included individuals with an incident RCC between January 1995 and December 2013 younger than the age of 90 years. Six controls per case were matched on age, sex, calendar time, general practice, and number of years of active history in the Clinical Practice Research Datalink before the index date. We included BMI, smoking, alcohol consumption, hypertension, and diabetes mellitus as potential confounders in a multivariate model using conditional logistic regression to calculate odds ratios with 95% confidence intervals, and we carried out a sensitivity analysis restricted only to diabetic cases and controls. Long-term use of metformin was not associated with an altered relative risk of RCC (≥30 prescriptions, adjusted odds ratio 1.18, 95% confidence interval 0.88–1.58), nor was use of other antidiabetic drugs. Results in the sensitivity analysis including only diabetic cases and controls were largely the same. Use of metformin or other antidiabetic drugs was not associated with a materially altered risk of RCC. Further studies are warranted. ***European Journal of Cancer Prevention*** **26:257–262**

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Introduction

More than 300 000 new cases of kidney cancer were diagnosed in 2012 worldwide (Ferlay *et al.*, 2015). The age-standardized incidence rates in 2012/100 000 person-years were 12.6 in men and 6.2 in women in more developed areas and 3.4 in men and 1.8 in women in less developed areas of the world (Torre *et al.*, 2015). Renal cell carcinoma (RCC) is more common in men than in women (Ferlay *et al.*, 2015). Furthermore, the incidence of RCC has almost doubled (from 7.6 in 1988 to 11.7/100 000 person-years in 2006) in North America (Sun *et al.*, 2011). The 5-year survival rate for RCC is 5–80% depending on the stage at cancer diagnosis (Cancer Research UK, 2015). RCC, the most frequent renal malignancy, includes several histological cell types; the most common subtype (70%) is clear cell RCC (Ljungberg *et al.*, 2011).

Known risk factors for RCC are cigarette smoking (Hunt *et al.*, 2005), obesity (Pischon *et al.*, 2006; Adams *et al.*, 2008; Renehan *et al.*, 2008), and hypertension (Chow *et al.*, 2000; Vatten *et al.*, 2007). Alcohol consumption has repeatedly been associated with a decreased risk of RCC (Bellocco *et al.*, 2012; Song *et al.*, 2012).

Patients with urinary tract infections (Parker *et al.*, 2004), end-stage renal disease (Farivar-Mohseni *et al.*, 2006), cystic kidney disease (Denton *et al.*, 2002), or kidney transplantation (Kasiske *et al.*, 2004) have been shown to have an increased risk for RCC. NSAIDs including acetylsalicylic acid (ASA) have been associated with an increased risk of cancer in one study (Cho *et al.*, 2011), whereas other studies have not reported such an association (Tavani *et al.*, 2010; Liu *et al.*, 2013b). Oral contraceptives (OC) have previously been found to protect against RCC in women (Kabat *et al.*, 2007), whereas the effect of exposure to hormone replacement therapy (HRT) is not clear (Molokwu *et al.*, 2007; Lee *et al.*, 2009). There is no agreement on whether type 2 diabetes mellitus is causally associated with the risk of RCC or whether the association is confounded by obesity (Lindblad *et al.*, 1999; Larsson and Wolk, 2011).

In recent years, considerable research has been devoted to studying the association between metformin and various cancer entities (Decensi *et al.*, 2010; Noto *et al.*, 2012; Franciosi *et al.*, 2013). Metformin is believed to have anticancer properties on the basis of two different mechanisms. First, metformin decreases insulin resistance [insulin resistance has been associated with an increased risk of several cancer types, such as breast, colon, and pancreatic cancer (Lipscombe *et al.*, 2006; Frasca *et al.*, 2008; Hernandez-Diaz and Adami, 2010)] and it also lowers circulating insulin levels [insulin has

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mitogenic properties (Frasca *et al.*, 2008)]. Second, metformin acts as a growth inhibitor. It has been shown that this growth inhibition, at least in part, is mediated by upregulation of AMP-activated protein kinase activity and downstream suppression of signaling through the mammalian target of rapamycin (mTOR).

In RCC pathogenesis, mTOR inhibition has been shown to play a central role in the suppression of tumor growth (Hager *et al.*, 2009; Keefe *et al.*, 2013). Thus, temsirolimus, an mTOR-inhibitor, has been approved for the treatment of metastatic RCC (Hudes *et al.*, 2007). Metformin has also been shown to inhibit mTOR signaling in RCC cells *in vitro*, as well as to inhibit RCC tumor growth in a xenograft model (Liu *et al.*, 2013a).

To the best of our knowledge, no observational study has as yet evaluated the effect of antidiabetic drug use on the risk of renal carcinoma. We therefore carried out a case–control analysis using the UK-based Clinical Practice Research Datalink (CPRD) to explore whether the use of metformin or other antidiabetic drugs alters the risk of developing RCC.

Methods

Data source

We carried out a retrospective case–control analysis using data from the CPRD (Williams *et al.*, 2012). The CPRD provides health care information on some eight million patients in the UK and has been previously described in detail (Walley and Mantgani, 1997; Williams *et al.*, 2012). General practitioners record information on demographics, diagnoses, and drug prescriptions as well as on patient referrals and hospital admissions using standardized coding systems. The general practitioners generate prescriptions directly with the computer and this information is automatically transcribed into the individual computerized patient records. In addition, the CPRD records information on BMI and the lifestyle variables alcohol consumption and smoking. Recorded information on drug exposure and diagnoses has been validated repeatedly and proven to be of high quality (Jick *et al.*, 2003; Herrett *et al.*, 2010). The CPRD currently covers about 7% of the UK population and enrolled patients are representative of the UK with respect to age, sex, and geographic distribution (Lawrenson *et al.*, 1999). The CPRD is managed by the Medicines and Healthcare products Regulatory Agency in the UK. The study protocol was reviewed and approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research (reference number 14_175) and made available to the journal reviewers. The investigators had access to anonymous information only.

Study population

We defined as cases all individuals in the base population younger than the age of 90 years between January 1995 and December 2013 who had an incident diagnosis of RCC in their record. We excluded all patients with a recorded diagnosis of HIV, alcoholism, or any malignancy, as well as those with less than 3 years of medical history in the CPRD computer record before the diagnosis date. We shifted the diagnosis date backwards in time by 2 years to account for cancer latency and to ensure that potential exposure to antidiabetic drugs occurred before cancer onset. The subsequently used term 'index date' will refer to the shifted diagnosis date. To minimize case misclassification, we identified codes (subsequently referred to as supporting codes) that provided reassurance that the cancer diagnosis was valid, such as codes for cancer-related surgery, radiotherapy, chemotherapy, antiangiogenic therapy, immunotherapy, targeted therapy, or other oncology-specific codes recorded within 1 year before or after the first recorded RCC diagnosis.

Up to six controls (individuals with no evidence for RCC) were matched to each case on calendar time (same index date), age, sex, general practice, and number of years of active history in the CPRD before the diagnosis date. We applied the same exclusion criteria to controls as to cases.

Exposure to metformin or other antidiabetic agents

We identified prescriptions for insulin and/or for oral antidiabetic drugs (metformin, sulfonylureas, thiazolidinediones, megltinides, dipeptidyl peptidase-4 inhibitors, incretin-mimetics, and glucosidase inhibitors) documented in the computer records before the index date. We classified patients by type of antidiabetic treatment and defined the extent of exposure according to the recorded number of prescriptions before the index date (short-term 1–29, or long-term use ≥ 30 prescriptions). Exposure to meglitinides, dipeptidyl peptidase-4 inhibitors, incretin-mimetics, and glucosidase inhibitors was low and we therefore could not include these drugs in the final multivariate model. We compared the use of each antidiabetic drug with nonuse of that drug and adjusted for sequential or concurrent use of other antidiabetic drugs in the multivariate models.

Statistical analysis

We carried out conditional logistic regression analyses using SAS Statistical Software, version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) to calculate relative risk estimates as odds ratios (OR) with 95% confidence intervals (CIs). We controlled for the previously mentioned matching variables as well as for smoking status (never, exsmoker, current, or unknown), BMI (< 25, 25–29.9, $\geq 30\,kg/m^2$, or unknown), alcohol consumption (never, current, past, or unknown), and the comorbidities hypertension and diabetes mellitus in the multivariate model. We included these confounders on the basis of previous clinical knowledge. In addition, we explored the association between various potential confounders and the risk of RCC in univariate analyses including recorded

urinary tract infections, renal failure, renal transplantation, polycystic kidney disease, and other comorbidities such as congestive heart failure, ischemic heart disease, stroke, dyslipidemia, previous A1c levels, as well as drug therapy with ASA, NSAIDs, OCs, or HRT. However, as these variables did not alter the risk estimate by more than 10%, we decided not to include them in the final multivariate model.

We then carried out a sensitivity analysis restricted to cases with at least one supporting code and their matched controls.

Diabetes mellitus has been shown to be associated with an increased risk of cancer in some previous studies. We therefore carried out an additional analysis restricted to cases with diabetes and newly matched controls who also had diabetes. In this sensitivity analysis, we additionally adjusted for diabetes duration. Diabetes duration was defined as the time from the date of a first recorded diagnosis of diabetes to the index date. In addition, we explored whether cases with long-term metformin use (≥30 prescriptions) had a longer duration of diabetes mellitus than controls and therefore had more opportunity to receive prescriptions. This was done to address potential exposure opportunity bias.

Results

We identified a total of 3506 cases with incident RCC and 21 038 matched controls between January 1995 and December 2013. Almost 60% of the cases were men. The mean (±SD) age of the cases and controls at the index date was 65.0 (±12.8) years. The mean duration of medical history recorded in the CPRD before the cancer diagnosis was 11.2 (±4.8) years. Eighty percent of the cases had either radiotherapy, chemotherapy, an oncology code, RCC-related surgery or antiangiogenic, immunotherapy, or targeted therapy documented in their record within 1 year of the index date.

The main characteristics of the cases and controls are shown in Table 1. Having a history of cystic kidney disease or of renal transplant was each associated with a strong risk of RCC: ORs 2.53 (95% CI 1.2–5.33) and 3.30 (95% CI 1.5–7.24), respectively. Current smokers compared with nonsmokers, and obese compared with normal weight patients were at a slightly increased risk of developing RCC. Alcohol use was not materially associated with the risk of RCC, nor was use of ASA, NSAIDs, OCs, and HRT (Table 1). Hypertension was associated with a slightly increased risk of RCC. Diabetes mellitus was also associated with a slightly increased OR for RCC; however, we did not observe a trend toward an increased risk with longer diabetes duration (test for trend: $P=0.25$) and increased A1c levels were not associated with RCC.

Table 1 Characteristics of renal cell carcinoma cases and controls

	Cases [*n* (%)] (*n* = 3506)	Controls [*n* (%)] (*n* = 21 038)	Crude OR (95% CI)
Age (years)			
<40	126 (3.6)	758 (3.6)	–
40–49	297 (8.5)	1770 (8.4)	–
50–59	651 (18.6)	3944 (18.8)	–
60–69	991 (28.3)	5999 (28.5)	–
70–79	1034 (29.5)	6128 (29.1)	–
≥80	407 (11.6)	2439 (11.6)	–
Sex			
Male	2099 (59.9)	12 594 (59.9)	–
Female	1407 (40.1)	8444 (40.1)	–
Smoking			
Nonsmoker	1459 (41.6)	9742 (46.3)	1.00 (Referent)
Current	711 (20.3)	3361 (16.0)	1.43 (1.30–1.58)
Past	1058 (30.2)	6220 (29.6)	1.14 (1.05–1.25)
Unknown	278 (7.9)	1715 (8.2)	1.08 (0.93–1.26)
BMI			
<25	917 (26.2)	6505 (30.9)	1.00 (Referent)
25–29.9	1174 (33.5)	7221 (34.3)	1.16 (1.06–1.27)
≥30	823 (23.5)	3675 (17.5)	1.61 (1.45–1.79)
Unknown	592 (16.9)	3637 (17.3)	1.15 (1.02–1.29)
Alcohol use			
Never	617 (17.6)	3301 (15.7)	1.00 (Referent)
Current	2442 (69.7)	14 843 (70.6)	0.87 (0.79–0.96)
Past	59 (1.7)	309 (1.5)	1.02 (0.76–1.37)
Unknown	388 (11.1)	2585 (12.3)	0.78 (0.67–0.90)
Comorbidities[a]			
CHF	117 (3.3)	619 (2.9)	1.15 (0.93–1.41)
IHD	494 (14.1)	2742 (13.0)	1.11 (0.99–1.23)
Hypertension	1464 (41.8)	7130 (33.9)	1.43 (1.37–1.60)
Stroke/TIA	231 (6.6)	1223 (5.8)	1.15 (0.99–1.33)
Dyslipidemia	501 (14.3)	2637(12.5)	1.19 (1.06–1.32)
Diabetes mellitus	394 (11.2)	1972 (9.4)	1.23 (1.10–1.39)
DM duration <4 years[b]	117 (33.2)	729 (34.5)	1.00 (Referent)
DM duration 4–9 years[b]	128 (36.4)	780 (36.9)	1.03 (0.78–1.35)
DM duration ≥10 years[b]	107 (30.4)	605 (28.6)	1.11 (0.83–1.47)
A1c <53 mmol/l (7%)[b]	137 (38.9)	781 (36.9)	1.00 (Referent)
A1c ≥53 mmol/l (7%)[b]	156 (44.3)	940 (44.5)	0.94 (0.73–1.21)
Unknown A1c level[b]	59 (16.8)	393 (18.6)	0.82 (0.56–1.19)
UTI	527 (15.0)	2718 (12.9)	1.22 (1.10–1.36)
ESRD	26 (0.7)	101 (0.5)	1.55 (1.01–2.39)
Cystic kidney disease	10 (0.3)	24 (0.1)	2.53 (1.20–5.33)
Renal transplantation	10 (0.3)	19 (0.1)	3.30 (1.50–7.24)
NSAIDs			
No previous use	1300 (37.1)	8157 (38.8)	1.00 (Referent)
1–2 Rx	880 (25.1)	5230 (24.9)	1.06 (0.97–1.17)
3–9 Rx	695 (19.8)	4264 (20.3)	1.04 (0.93–1.15)
≥10 Rx	631 (18.0)	3387 (16.1)	1.19 (1.07–1.33)
ASA			
No prior use	2534 (72.3)	15 598 (74.1)	1.00 (Referent)
1–14 Rx	411 (11.7)	2255 (10.7)	1.14 (1.01–1.28)
≥15 Rx	561 (16.0)	3185 (15.1)	1.11 (0.99–1.23)
Oral contraceptives (women only)			
No previous use	1321 (93.9)	7819 (93.3)	1.00 (Referent)
Any use	86 (6.1)	565 (6.7)	0.82 (0.59–1.15)
HRT (women only)			
No previous use	1074 (76.3)	6341 (75.1)	1.00 (Referent)
1–9 Rx	169 (12.0)	973 (11.5)	1.00 (0.83–1.21)
≥10 Rx	164 (11.7)	1130 (13.4)	0.83 (0.68–1.01)

A1c, glycated hemoglobin (assessed for diabetics only, 'unknown' level includes recordings earlier than 1 year before the cancer diagnosis); ASA, acetylsalicylic acid; CHF, congestive heart failure; CI, confidence interval; DM, diabetes mellitus; ESRD, end-stage renal disease; HRT, hormone replacement therapy; IHD, ischemic heart disease; OR, odds ratio; Rx, prescriptions; TIA, transient ischemic attack; UTI, urinary tract infection

[a]Reference category for comorbidities is 'no recorded diagnosis for the respective disease'.

[b]Analysis restricted to cases and controls with a recorded diagnosis of diabetes mellitus.

Long-term use of metformin (≥30 prescriptions) was not associated with a statistically significantly decreased risk of RCC in either the main analysis (adjusted OR 1.18, 95% CI 0.88–1.58) or in the analysis restricted to diabetic patients (adjusted OR 0.91, 95% CI 0.64–1.29) (Tables 2 and 3). The sensitivity analysis restricted to cases with recorded cancer treatment yielded results very similar to the main analysis (adjusted OR 1.12, 95% CI 0.81–1.57 for RCC in association with the long-term use of metformin). Diabetes duration was similar in cases and controls: among all long-term metformin users, 97% of the cases had diabetes for more than 4 years and 51% for more than 10 years. Similarly, 94% of the controls had more than a 4-year history of diabetes and 50% had more than a 10-year history of diabetes. Use of sulfonylureas, insulin, or thiazolidinediones was not associated with a statistically significant altered risk of RCC in the main analysis or in the various sensitivity analyses (Tables 2 and 3).

Discussion

In this large case–control analysis, metformin exposure was not associated with an altered risk for RCC. To the best of our knowledge, no other observational study has analyzed this association in detail. Results of in-vitro and in-vivo experiments have suggested a possible protective effect of metformin on the development of RCC (Liu *et al.*, 2013b). However, a cohort study from the USA on the risk of cancer after pioglitazone exposure also analyzed ever versus never use of metformin and found an increased risk for cancers of the kidney and the renal pelvis (Ferrara *et al.*, 2011). Furthermore, the results of two US-based retrospective studies did not find protective effects of metformin administered before RCC-related surgery on disease progression or RCC mortality (Hakimi *et al.*, 2013; Psutka *et al.*, 2014). Metformin has been associated with alterations in cancer risk for several, but not for all types of cancer, in numerous observational studies; despite these intriguing findings, only randomized trials can ultimately answer the question of whether metformin is indeed causally linked to a reduced cancer risk for certain cancer types (Gandini *et al.*, 2014).

Our results are consistent with previous studies reporting an increased risk of RCC in smokers (Hunt *et al.*, 2005) and in obese individuals (Pischon *et al.*, 2006; Adams *et al.*, 2008; Renehan *et al.*, 2008), as well as a reduced risk of RCC associated with alcohol consumption (Lee *et al.*, 2007; Bellocco *et al.*, 2012; Song *et al.*, 2012) and OC exposure (Kabat *et al.*, 2007). In addition, we also observed a marginal but statistically significantly increased risk of RCC in association with diabetes. However, the association was independent of diabetes duration, making a causal association questionable.

Our study has several limitations: the date on which the cancer diagnosis was recorded most likely does not correspond to the actual onset of the disease. It is impossible to establish the precise date of cancer onset in any given patient. By shifting the index date 2 years backwards in time, we increased the likelihood that the index date was closer to disease onset and that potential exposure to antidiabetic drugs preceded the development of RCC. In addition, misclassification of RCC cases may be present to some degree in any observational study. We therefore identified documented cancer therapies or oncologic interventions to validate the recorded cancer diagnoses; 80% of the cancer cases had at least one such recording within 1 year of the index date, providing evidence that the degree of misclassification is small. In the CPRD, cancer diagnoses have been shown to be generally of high validity (Boggon *et al.*, 2013). Our sensitivity analysis, which was restricted to cases with a high likelihood of a valid RCC diagnosis, yielded results very similar to the main analysis. We could incorporate many potential confounders into our analysis, such as BMI, smoking, a range of comorbid conditions, and prescriptions for other drugs. However, residual confounding by, for example, physical activity, diet, or socioeconomic status may still exist to some degree as these parameters are not recorded routinely in the CPRD. However, by matching cases and

Table 2 ORs for RCC for antidiabetic drugs in all cases and controls

Drugs and number of prescriptions	Cases [*n* (%)] (*n* = 3506)	Controls [*n* (%)] (*n* = 21 038)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Metformin				
No previous use	3260 (93.0)	19 879 (94.5)	1.00 (Referent)	1.00 (Referent)
Any use	246 (7.0)	1159 (5.5)	1.31 (1.13–1.51)	1.15 (0.90–1.46)
1–29	128 (3.7)	609 (2.9)	1.29 (1.06–1.57)	1.13 (0.86–1.48)
≥30	118 (3.4)	550 (2.6)	1.32 (1.08–1.62)	1.18 (0.88–1.58)
Sulfonylurea				
No prior use	3320 (94.7)	20 072 (95.4)	1.00 (Referent)	1.00 (Referent)
Any use	186 (5.3)	966 (4.6)	1.17 (0.99–1.37)	0.91 (0.72–1.16)
Insulin				
No previous use	3431 (97.9)	20 658 (98.2)	1.00 (Referent)	1.00 (Referent)
Any use	75 (2.1)	380 (1.8)	1.19 (0.93–1.53)	0.99 (0.75–1.31)
TZD				
No previous use	3458 (98.6)	20 785 (98.8)	1.00 (Referent)	1.00 (Referent)
Any use	48 (1.4)	253 (1.2)	1.14 (0.84–1.56)	0.86 (0.61–1.22)

CI, confidence interval; OR, odds ratio; RCC, renal cell carcinoma; TZD, thiazolidinediones.
[a]Adjusted for all other medications in this table, BMI, smoking, alcohol consumption, hypertension, and diabetes mellitus.

Table 3 ORs for RCC in the subgroup of cases and (newly matched) controls with a recorded diagnosis of diabetes mellitus

Drugs and number of prescriptions	Cases [*n* (%)] (*n* = 352)	Controls [*n* (%)] (*n* = 2114)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Metformin				
No previous use	137 (38.9)	862 (40.8)	1.00 (Referent)	1.00 (Referent)
Any use	215 (61.1)	1252 (59.2)	1.09 (0.86–1.39)	0.99 (0.76–1.31)
1–29	114 (32.4)	641 (30.3)	1.13 (0.86–1.48)	1.04 (0.78–1.39)
≥30	101 (28.7)	611 (28.9)	1.05 (0.78–1.40)	0.91 (0.64–1.29)
Sulfonylurea				
No previous use	183 (52.0)	1118 (52.9)	1.00 (Referent)	1.00 (Referent)
Any use	169 (48.0)	996 (47.1)	1.04 (0.83–1.30)	1.01 (0.78–1.32)
Insulin				
No previous use	287 (80.7)	1705 (80.7)	1.00 (Referent)	1.00 (Referent)
Any use	65 (18.5)	409 (19.3)	0.94 (0.70–1.26)	0.89 (0.64–1.23)
TZD				
No previous use	307 (87.2)	1839 (87.0)	1.00 (Referent)	1.00 (Referent)
Any use	45 (12.8)	275 (13.0)	0.98 (0.69–1.39)	0.91 (0.63–1.32)

CI, confidence interval; OR, odds ratio; RCC, renal cell carcinoma; TZD, thiazolidinediones.
[a]Adjusted for each other, BMI, smoking, alcohol consumption, hypertension, and diabetes duration.

controls on general practice, we were at least in a position to partially control for confounding by socioeconomic status as patients from the same neighborhood are likely to attend the same general practice. Another limitation of our analysis is the number of unknown values for BMI. However, in the sensitivity analysis restricted only to diabetic patients, the percentage of missing values for BMI was low (3.7%).

Our study has several strengths: the data source is a well-established primary care database of high quality and completeness. The information on drug exposure and diagnoses was recorded prospectively and independent of a study hypothesis; thus, recall bias could not have influenced our results. Furthermore, by excluding all patients with less than 3 years of recorded history in the database before the index date, we minimized the risk of including prevalent cancer cases. Also, time window bias did likely not alter our findings as diabetes duration was not meaningfully associated with an altered risk of RCC and, in addition, cases and controls had a comparable duration of diabetes history in each metformin exposure category. Finally, our sensitivity analyses restricted to cases and controls with diagnosed diabetes, or restricted to cases with additional information supporting the validity of the cancer diagnosis, all yielded similar results, which further strengthen our results.

In conclusion, we did not find an altered relative risk of RCC associated with exposure to antidiabetic drugs in this large population-based study.

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Conflicts of interest

There are no conflicts of interest.

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