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Research Article

Metformin and the Incidence of Prostate Cancer in Patients with Type 2 Diabetes

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Abstract

Background: Several *in vitro* studies have indicated that metformin may reduce the risk of prostate cancer; however, epidemiologic studies have been inconclusive. The objective of this study was to determine whether metformin decreases the risk of prostate cancer in patients with type 2 diabetes.

Methods: A nested case–control analysis was conducted within a population-based cohort from the UK General Practice Research Database. The cohort included patients over the age of 40 who were prescribed a first oral hypoglycemic agent (OHA) between 1988 and 2009. Cases of prostate cancer were matched up to ten controls on year of birth, date of cohort entry, and duration of follow-up. Adjusted rate ratios (RR) were estimated using conditional logistic regression.

Results: The cohort included 63,049 incident users of OHAs, in which 739 cases of prostate cancer were matched to 7,359 controls. Metformin use did not decrease the risk of prostate cancer (RR: 1.23, 95% CI: 0.99–1.52). In secondary analyses, prostate cancer risk was found to increase as a function of the number of metformin prescriptions received (one to seven prescriptions: RR: 1.05, 95% CI: 0.80–1.37; seven to eighteen prescriptions: RR: 1.29, 95% CI: 0.99–1.69; eighteen to thirty-six prescriptions: RR: 1.37, 95% CI: 1.04–1.81; more than thirty-six prescriptions: RR: 1.40, 95% CI: 1.03–1.89).

Conclusion: The results of this study indicate that metformin does not reduce the risk of prostate cancer in patients with type 2 diabetes.

Impact: The secondary analyses need to be interpreted with caution given the inverse association between type 2 diabetes and prostate cancer. *Cancer Epidemiol Biomarkers Prev; 20(2); 337–44. ©2010 AACR.*

Introduction

Prostate cancer remains the most frequently diagnosed malignant tumor among men in developed countries (1). As a result, much research has focused on identifying pharmacologic agents that may prevent or delay its occurrence (2–4). These include randomized controlled trials on the 5-α reductase inhibitors, finasteride and dutasteride, which have shown promise (3, 4). Recently, the potential antitumor effect of metformin has become the subject of a number of observational studies (5–14).

Metformin is the most widely used oral hypoglycemic agent in type 2 diabetes, because of its favorable toxicity profile and clinical effectiveness (15). The drug lowers glucose levels mainly by decreasing hepatic gluconeogenesis, which leads to a secondary decline in insulin levels, and also promotes glucose uptake in muscle (16, 17). Several *in vitro* and *in vivo* studies have suggested that metformin acts to decrease growth of certain tumors indirectly by reducing circulating insulin levels and/or by direct activation of AMP kinase in transformed cells (18–21). However, there is a paucity of experimental data concerning actions of metformin relative to prostate carcinogenesis, as distinct from proliferation of established tumors.

Several observational studies have investigated the effects of metformin on the incidence and mortality of different cancers (5–12), but only three have focused on prostate cancer (10, 13, 14). Two case–control studies conducted in the general population (which included diabetic and nondiabetic individuals), found that metformin decreased the risk of prostate cancer by 20% (13) and 44% (14). However, type 2 diabetes is associated with a reduced risk of prostate cancer (22). Thus, these studies were likely subject to confounding by indication and were not designed to differentiate between the effects of the drug from that of the underlying disease. Finally, a recent cohort study from the United Kingdom did not find any association between metformin and prostate cancer (10). Although this study was conducted within a cohort of patients with type 2 diabetes,

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it may have been limited by its short duration of follow-up (mean of 2 years) and few prostate cancer cases identified.

Thus, in view of the methodologic shortcomings of the previous studies (10, 13, 14), large-scale epidemiologic studies are needed to assess the long-term effects of metformin use on the incidence of prostate cancer in patients with type 2 diabetes. Therefore, the objective of this large population-based study was to determine whether metformin decreases the risk of prostate cancer in patients with type 2 diabetes.

Materials and Methods

Data source

This study was conducted using the General Practice Research Database (GPRD), a primary care database from the United Kingdom (23). The GPRD is the world's largest computerized database of longitudinal records from primary care. It contains the complete primary care medical record for more than 9.4 million people (corresponding to around 7.2% of the UK population) enrolled in more than 520 general practices. The geographic distribution of the practices participating in the GPRD has been shown to be representative of the U.K. population, and age and sex distributions of patients in the GPRD are similar to those reported by the National Population Census (24). Participating general practitioners have been trained to record medical information, including demographic data, medical diagnoses, details of hospital stays, and deaths, using a standardized form. Prescriptions written by GPRD physicians are automatically transcribed into the computer record. In addition, the GPRD collects information regarding lifestyle variables such as body mass index (BMI), and quantitative and qualitative data pertaining to smoking and excessive alcohol use. The Read classification is used to enter medical diagnoses and procedures, and a coded drug dictionary based on the U.K. Prescription Pricing Authority Dictionary is used for recording prescriptions. The recorded information on drug exposures and diagnoses has been validated and proven to be of high quality (25–28). The study protocol was approved by the Scientific and Ethical Advisory Group of the GPRD.

Study population

We identified all male patients who were prescribed at least one antidiabetic agent between January 1, 1988, and December 31, 2009. Cohort entry was defined as the date of the first prescription for an oral antidiabetic agent. To identify incidents users, the cohort was restricted to those who did not receive any antidiabetic agent for at least 1 year prior to cohort entry. The antidiabetic agents considered at cohort entry consisted of sulfonylureas (glyburide, gliclazide, glipizide, glimepiride, glibornuride, gliquidone, tolbutamide, chlorpropamide, tolazamide, or acetohexamide), biguanides (metformin), thiazolidinediones (pioglitazone, rosiglitazone, and troglitazone), meglitinides (repaglinide or nateglinide), DPP-4 inhibitors (sitagliptin, vildagliptin), α-glucosidase inhibitors (acarbose), GLP-1 analogues (exenatide), and guar gum. Patients who initiated their treatment with insulin were not included as these were more likely to be patients with type 1 diabetes or patients with advanced type 2 diabetes. However, patients who eventually required insulin during their follow-up were retained in the cohort. We restricted the cohort to patients aged at least 40 years of age at the time of their first prescription. Patients with less than 1 year of up-to-standard medical history in the GPRD prior to cohort entry were excluded, as well as those previously diagnosed with prostate cancer. The latter criterion was necessary to identify incident cases during follow-up. Patients were followed until a first ever diagnosis of prostate cancer, death from any cause, end of registration with the general practice, or end of the study period (December 31, 2009), whichever came first.

Study design

A nested case–control analysis was conducted within the cohort defined above to investigate the association between metformin and the incidence of prostate cancer. This approach was chosen because of the time-varying nature of exposure, the size of the cohort, and the long duration of follow-up (29). Thus, in comparison to a time-dependent survival analysis, a nested case–control analysis is computationally more efficient (30), whereas producing odds ratios that are unbiased estimators of incidence rate ratios (RR), with little or no loss in precision (29–31).

Case–control selection

From our cohort of patients with type 2 diabetes, we identified all incident cases of prostate cancer using a computerized algorithm that included medical codes for prostate cancer, as well as combinations of medical procedures and treatments related to this outcome. The latter consisted of prostate biopsies, surgeries, radiation therapy, and use of androgen deprivation therapy. Overall, 98% of cases had a diagnosis of prostate cancer. The calendar date of each case's prostate cancer diagnosis was defined as their index date. Up to 10 controls were randomly selected from the case's risk set, after matching on year of birth (±1 year), date of cohort entry (±1 year), to simultaneously control for secular trends in diabetes treatments and detection and diagnosis of prostate cancer during the 22-year study period, and duration of follow-up which was a proxy for diabetes duration (time from first oral antidiabetic prescription to index date). By definition, all controls were alive, not previously diagnosed with prostate cancer, and registered with their general practice when they were matched to a given case. All analyses were restricted to cases and matched controls with at least one year of medical history prior to index date. This was to ensure a minimum exposure history for cases and controls.

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Exposure assessment

For all cases and controls, we obtained prescriptions for all antidiabetic agents prescribed between cohort entry and index date. We excluded exposures in the year immediately prior to index date to take into account the long latency period of prostate cancer (32), and minimize detection bias, where initiation of a new treatment may lead to an increased intensity of diagnostic investigations, possibly leading to an increased probability of detecting a cancer.

Exposure to metformin was assessed using 2 different approaches. In the first approach, *ever* exposure to metformin was assessed by determining whether cases and controls received at least one prescription for metformin between cohort entry and the year prior to index date. This approach was considered the primary exposure definition. In the second approach, patients deemed to be *ever* exposed to metformin were further categorized according to the number of prescriptions received between cohort entry up to 1 year prior to index date. Prescription categories were based on the quartile distribution of use in the controls. Linear trend was evaluated by entering number of prescriptions as a continuous variable in the model and obtaining the corresponding *P* value.

Statistical analysis

Conditional logistic regression was used to estimate RRs, along with 95% CI. In addition to year of birth, year of cohort entry, and duration of follow-up on which the logistic regression was conditioned, exposure to metformin was adjusted for the following potential confounders measured prior to index date (defined by clinical diagnoses and/or prescriptions): Hemoglobin A_{1c} (HbA_{1c}; last measurement prior to index date), excessive alcohol use, obesity (BMI $\geq$ 30), smoking (ever vs. never), lower urinary tract symptoms (defined as either a diagnosis for benign prostatic hyperplasia or prostatitis and/or prescription for finasteride or dutasteride), previous cancer (other than nonmelanoma skin cancer), and previous use of nonsteroidal anti-inflammatory drugs (NSAID), antihypertensive drugs, and statins. The models were further adjusted for *ever* use of other antidiabetic agents (sulfonylureas, thiazolidinediones, insulins, and other agents). All analyses were conducted with SAS version 9.2 (SAS Institute).

Sensitivity analyses

Four sensitivity analyses were conducted to assess the robustness of the results. In the first sensitivity analysis, the analyses were repeated by excluding the first 2 years prior to index date. The second sensitivity analysis addressed issues related to undiagnosed prostate cancer among selected controls. The impact of this possible misclassification was assessed by excluding controls diagnosed with prostate cancer within one year after being included in a risk set. The third sensitivity assessed the effects of adherence to prostate-specific antigen (PSA) screening on the results. Thus for this analysis, the models were additionally adjusted for PSA screening intensity (defined as the number of tests between cohort entry and one year prior to index date). Finally, the fourth sensitivity analysis was restricted to cases (and matched controls) with at least 5 years of medical follow-up prior to index date.

Results

Of the 113,041 male patients prescribed antidiabetic agents during the study period, 63,049 met the inclusion criteria (Fig. 1). The mean (SD) age at cohort entry was 62.7 (11.4) years, where the median duration of follow-up was 3.7 years. At cohort entry, the median HbA_{1c} was 8.3% and the median PSA was 1.2 ng/mL. Furthermore, the majority of patients received metformin monotherapy (67%), followed by sulfonylurea monotherapy (30%), whereas less than 3% used other agents or combinations at cohort entry. None of the patients received insulin at cohort entry, as per the exclusion criteria.

A total of 975 patients were diagnosed with prostate cancer during 283,720 person-years of follow-up, yielding a mean prostate cancer rate of 343 per 100,000 persons per year (95% CI: 322–365). The analyses were restricted to the 739 cases and 7,359 controls with at least 1 year of available medical history prior to index date. The characteristics of these cases and controls are presented in Table 1. Overall, PSA screening was low, where only 12.4% of controls had at least 1 test between cohort entry and the year prior to index date, reflecting the fact that the United Kingdom has no organized screening program for prostate cancer. As expected, cases had higher median PSA levels than controls at index date (median PSA level 16 vs. 1.7, respectively). However, they were less likely to have used alcohol excessively and being obese, whereas being more likely to have had lower urinary tract symptoms, diagnosed with previous cancer (other than nonmelanoma skin cancer), and have used NSAIDs compared with controls.

The results of the primary analysis are presented in Table 2. *Ever* use of metformin was not associated with a reduced risk of prostate cancer. When *ever* users were further categorized according to the number of metformin prescriptions received, a dose–response relationship was observed, with the risk of prostate cancer increasing as a function of the number of prescriptions received (*P* value for trend: 0.04). Specifically, close to a 40% increased risk was observed in patients prescribed at least 18 prescriptions of metformin (Table 3).

Sensitivity analyses

The first sensitivity analysis consisted of repeating the primary analysis by excluding exposures in the 2 years immediately prior to index date. This analysis revealed that *ever* use of metformin was associated with an increased risk of prostate cancer (adjusted RR: 1.48, 95% CI: 1.17–1.88). In the second sensitivity analysis,

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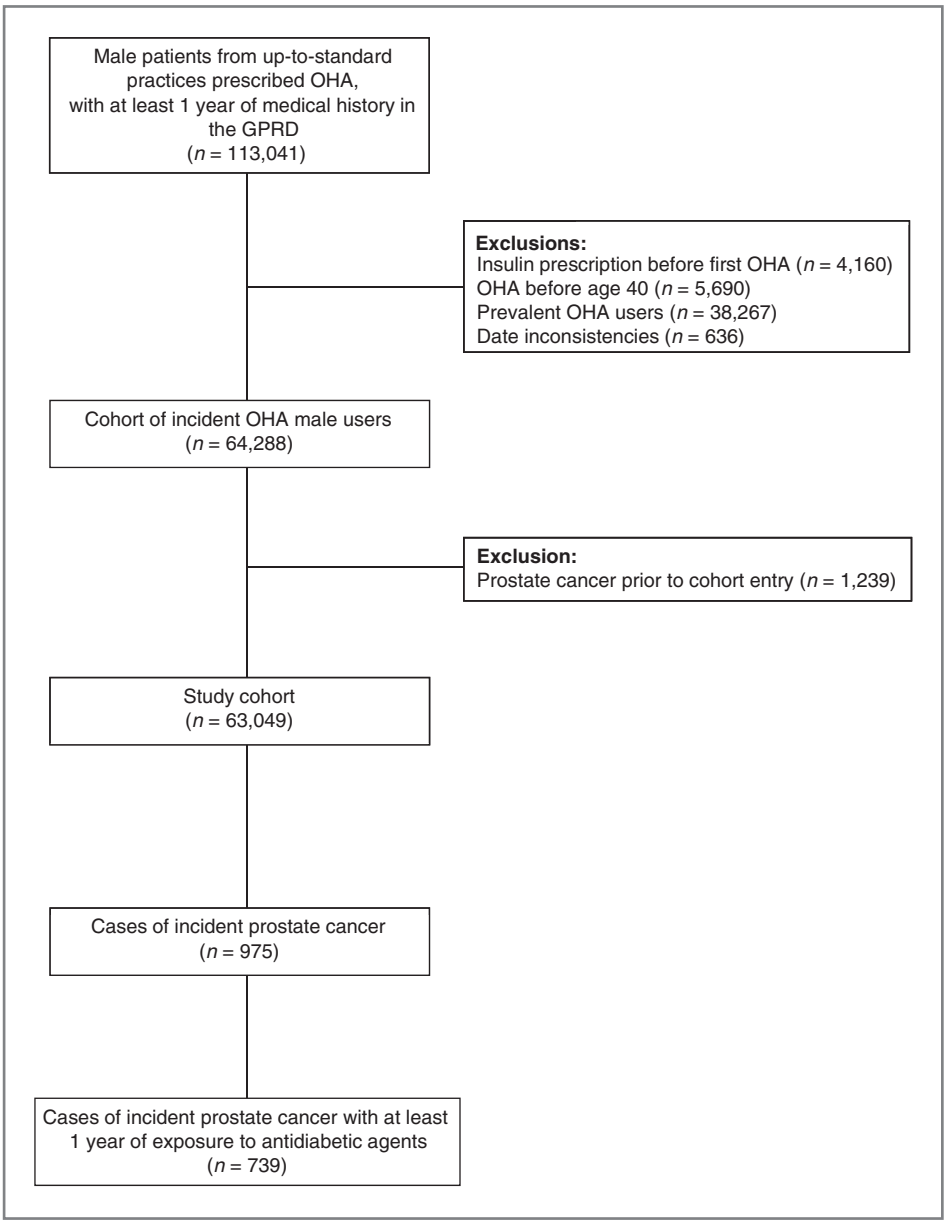

Figure 1. Study flow chart.

excluding controls that became cases within 1 year after being included in a risk set did not materially change the point estimate (adjusted RR: 1.24, 95% CI: 1.00–1.53). In the third sensitivity analysis, additionally adjusting for PSA screening intensity had no effect on the point estimate (RR: 1.23, 95% CI: 0.99–1.53). A similar conclusion was reached in the fourth sensitivity analysis which was restricted to cases with at least 5 years of medical follow-up prior to index date (adjusted RR: 1.35, 95% CI: 0.94–1.92).

Discussion

Contrary to our hypothesis, in this large population-based study, metformin use was not associated with a reduced risk of prostate cancer in patients with type 2 diabetes. Secondary analyses suggest that its use might be associated with a higher incidence of prostate cancer in a dose-dependent fashion. Several sensitivity analyses were performed, which produced consistent results. However, these results need to be interpreted with caution given the known inverse association between type 2 diabetes and prostate cancer, and the role metformin may have in this association.

These unexpected results contrast with many of the *in vitro* and *in vivo* studies conducted to date (18, 19, 21), which suggested an antitumor effect for metformin. However, our results need to be interpreted with caution and do not necessarily indicate that men taking metformin are at an increased risk of prostate cancer compared

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Table 1. Characteristics of cases and controls

	Cases ($n = 739$)	Controls ($n = 7,359$)
Age at index date, mean (SD)[a]	74.1 (8.1)	74.1 (8.0)
Follow-up time,[a] mean (SD), y	4.7 (3.0)	4.7 (3.0)
HbA_{1c}, median, %	7.0	7.1
Excessive alcohol use, *n* (%)	10 (1.4)	145 (2.0)
BMI		
<30, *n* (%)	501 (67.8)	4,562 (62.0)
≥30, *n* (%)	206 (27.9)	2,426 (33.0)
Unknown, *n* (%)	32 (4.3)	371 (5.0)
Smoking status		
Ever, *n* (%)	469 (63.5)	4,717 (64.1)
Never, *n* (%)	211 (28.6)	1,988 (27.0)
Unknown, *n* (%)	59 (8.0)	654 (8.9)
Lower urinary tract symptoms, *n* (%)	91 (12.3)	483 (6.6)
Previous cancer (other than prostate cancer), *n* (%)	85 (11.5)	494 (6.7)
NSAIDs, *n* (%)	473 (64.0)	4,471 (60.8)
Antihypertensive drugs, *n* (%)	561 (75.9)	5,508 (74.8)
Statins, *n* (%)	422 (57.1)	4,252 (57.8)

[a]Controls matched to cases on these variables.

with the general population. Type 2 diabetes has been shown to be associated with a decreased risk prostate cancer, with longer duration of diabetes associated with greater decrease in prostate cancer risk (22, 33–36). This can be due to the fact that diabetic men have lower PSA levels compared with nondiabetic men, which may affect the detection of this cancer in this population (37–39). Alternatively, this inverse association may indicate that type 2 diabetes, through its metabolic and hormonal changes, alters the baseline risk of prostate cancer. It is therefore possible that by improving the metabolic derangements associated with diabetes (and with decreased prostate cancer risk), metformin may in fact appear to increase prostate cancer risk among diabetics.

A possible explanation for the trend to increased prostate cancer risk associated with increasing use of metformin may relate to effects of the drug on the hormonal profile of patients with type 2 diabetes. There has been speculation that reduced androgen levels represent the specific hormonal alteration associated with diabetes that accounts for reduced prostate cancer risk with this disease (40). In line with this hypothesis, studies have shown that as blood glucose levels increase, androgen levels decrease in diabetic men (41, 42). However, it is unknown whether the relative androgen deficiency associated with diabetes is corrected with metformin use, and whether this also occurs with other antidiabetic treatments. Our results motivate studies of this issue, and of other mechanisms by which metformin exposure might influence prostate cancer risk. Our data do not detract from the rationale for evaluating the possible therapeutic benefit of metformin in men with established prostate cancer, where it may have beneficial effects related to reduction in insulin level (43, 44) and/or to activation of AMP kinase in neoplastic tissue (17), particularly for patients who have already undergone androgen deprivation therapy for advanced disease.

This population-based study has a number of strengths. First, we were able to assemble one of the largest population-based cohorts of male patients with type 2 diabetes, followed for up to 22 years. Second, our exposure definition and covariate information were time dependent as a result of the sampling scheme used to select controls. Third, although residual confounding

Table 2. Ever use of metformin and the risk of prostate cancer

Metformin exposure	Cases ($n = 739$)	Controls ($n = 7,359$)	Crude RR	Adjusted RR (95% CI)[a]
Never, *n* (%)	203 (27.5)	2,123 (28.8)	1.00	1.00 (reference)
Ever, *n* (%)	536 (72.5)	5,236 (71.2)	1.10	1.23 (0.99–1.52)

[a]Adjusted for HbA_{1c}, excessive alcohol use, obesity, smoking, lower urinary tract symptoms, previous cancer, and use of NSAIDs, antihypertensive drugs, statins, and other antidiabetic agents.

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Table 3. Risk of prostate cancer according to the number of metformin prescriptions

Metformin exposure (number of prescriptions)	Cases ($n = 739$)	Controls ($n = 7,359$)	Crude RR	Adjusted RR (95% CI)[a]
Never, *n* (%)	203 (27.5)	2,123 (28.8)	1.00	1.00 (reference)
1–7, *n* (%)	125 (16.9)	1,379 (18.7)	0.94	1.05 (0.80–1.37)
7–18, *n* (%)	135 (18.3)	1,269 (17.2)	1.15	1.29 (0.99–1.69)
18–36, *n* (%)	141 (19.1)	1,310 (17.8)	1.19	1.37 (1.04–1.81)
≥36, *n* (%)	135 (18.3)	1,278 (17.4)	1.18	1.40 (1.03–1.89)

[a]Adjusted for HbA_{1c}, excessive alcohol use, obesity, smoking, lower urinary tract symptoms, previous cancer, and use of NSAIDs, antihypertensive drugs, statins, and other antidiabetic agents. *P* value for trend = 0.04.

may be present, all efforts were directed at controlling for diabetes severity, to adequately isolate the effects of metformin from that of the underlying disease. This was achieved by selecting individuals newly treated for diabetes, thereby assembling a homogeneous cohort and minimizing a number of biases related to prevalent user designs (45). In addition, cases and controls were matched on duration of follow-up (time from first prescription for an oral hypoglycemic agent to index date), which has been shown to be a good proxy for disease severity (46). Furthermore, we adjusted for HbA_{1c}, a measure recorded in the GPRD. Fourth, we conducted a number of sensitivity analyses, all of which produced consistent results. Fifth, because exposure is prospectively entered in the GPRD, the possibility of recall bias is eliminated. Finally, the GPRD database contains information on a number of important confounders such as BMI, excessive alcohol use, and smoking. Therefore, we were able to adjust for a number of confounders often absent in administrative databases.

However, this study does have limitations. First, drug information in the GPRD represents prescriptions written by general practitioners. As such, it is unknown whether prescriptions were actually filled at the pharmacy and whether patients fully complied with the treatment regimen. Second, the GPRD lacks information on certain prostate cancer risk factors. These include diet (47), physical activity (48), and race/ethnicity (49). With respect to the latter, the vast majority of individuals living in the United Kingdom are white (92%), whereas only a small percentage are black (2%) or other races/ethnic groups (6%; ref. 50). Furthermore, not all are these risk factors are strongly associated with the outcome, and it is reasonable to assume that they are nondifferentially distributed between metformin and nonmetformin users in this type 2 diabetes cohort. Thus, it is unlikely patients with these risk factors were preferentially prescribed metformin versus other antidiabetic treatments. In addition, inclusion of these variables in previous pharmacoepidemiologic studies on prostate cancer risk had little effect on the point estimate (51). Therefore, we believe that this lack of information did not affect the validity of the results. Third, it would have been of interest to stratify cases according to prostate cancer stage and grade to determine whether metformin differentially increases the risk among different subgroups. However, this information is not available in the GPRD, and thus this needs to be investigated in future studies. Finally, confounding by indication always needs to be considered in nonexperimental designs. However, this bias is generally not a problem if a study focuses on unexpected drug effects such as prostate cancer (52). In addition, unlike 2 of the previous studies that have investigated this question (13, 14), cases and controls both had diabetes, and had the same duration of follow-up, thus minimizing the potential effect of this disease on the observed associations.

To our knowledge, this is largest population-based study to have investigated the effects of metformin on prostate cancer risk in patients with type 2 diabetes. Although our primary analysis suggests no association between metformin and prostate cancer incidence, secondary analyses suggest that metformin might increase the risk in a dose-dependent fashion. These results need to be interpreted with caution and need to be confirmed in other carefully designed studies. A recent study using a similar analytic approach and same database (12), provided evidence for a reduction of breast cancer risk associated with metformin use. Other studies have also suggested a protective effect of metformin on other cancer sites (5, 7–11). It is plausible that prostate cancer risk, which is atypical in being negatively rather than positively associated with type 2 diabetes, may also be atypical with respect to its relationship to metformin use. Further studies to examine these issues are in progress.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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