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ORIGINAL REPORT

Metformin Use and All-Cause and Prostate Cancer–Specific Mortality Among Men With Diabetes

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ABSTRACT

Purpose
To evaluate the association between cumulative duration of metformin use after prostate cancer (PC) diagnosis and all-cause and PC-specific mortality among patients with diabetes.

Patients and Methods
We used a population-based retrospective cohort design. Data were obtained from several Ontario health care administrative databases. Within a cohort of men older than age 66 years with incident diabetes who subsequently developed PC, we examined the effect of duration of antidiabetic medication exposure after PC diagnosis on all-cause and PC-specific mortality. Crude and adjusted hazard ratios (HRs) were calculated by using a time-varying Cox proportional hazard model to estimate effects.

Results
The cohort consisted of 3,837 patients. Median age at diagnosis of PC was 75 years (interquartile range [IQR], 72 to 79 years). During a median follow-up of 4.64 years (IQR, 2.7 to 7.1 years), 1,343 (35%) died, and 291 patients (7.6%) died as a result of PC. Cumulative duration of metformin treatment after PC diagnosis was associated with a significant decreased risk of PC-specific and all-cause mortality in a dose-dependent fashion. Adjusted HR for PC-specific mortality was 0.76 (95% CI, 0.64 to 0.89) for each additional 6 months of metformin use. The association with all-cause mortality was also significant but declined over time from an HR of 0.76 in the first 6 months to 0.93 between 24 and 30 months. There was no relationship between cumulative use of other antidiabetic drugs and either outcome.

Conclusion
Increased cumulative duration of metformin exposure after PC diagnosis was associated with decreases in both all-cause and PC-specific mortality among diabetic men.

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INTRODUCTION

Prostate cancer (PC) is the most common male malignancy in the western world and the second leading cause of death.[1] Diabetes is also common and termed "the millennium epidemic."[2] Metformin (1,1-dimethylbiguanide hydrochloride) is an insulin sensitizer that belongs to the biguanide oral hypoglycemic family. There is emerging evidence linking metformin use to decreased cancer risk and improved cancer-related outcomes.[3,4]

Metformin may influence cancer cells indirectly by decreasing insulin levels or directly by influencing cancer cell proliferation and apoptosis.[4] Metformin is a potent adenosine monophosphate–activated protein kinase (AMPK) activator.[4,5] Once activated, AMPK inactivates enzymes involved in adenosine triphosphate consumption such as fatty acid and protein synthesis.[5] Furthermore, AMPK activation inhibits the mammalian target of rapamycin complex 1 pathway and S6K1 phosphorylation implicated in carcinogenesis.[6] Metformin may also be associated with autophagic cell death.[7]

Studies examining the impact of metformin exposure on PC risk had inconsistent results.[8-10] Because metformin is not believed to influence transformation of benign cells to malignant cells but rather to modulate cellular energy, metformin may have a greater impact on cancer survival than incidence. One study reported a beneficial association between metformin and overall survival[11]; however, this was a single-institution study and did not measure PC-specific mortality.

Because PC is a slow-growing disease, medication exposures postdiagnosis may have an impact on disease progression and survival and thus may be ideal for secondary prevention strategies. We tested the hypothesis that increasing duration of exposure to metformin after PC diagnosis is associated with lower PC-specific and all-cause mortality among diabetic men.

PATIENTS AND METHODS

We conducted a population-based, retrospective cohort study approved by the institutional review boards of Sunnybrook and Princess Margaret Hospitals, Toronto, Ontario, Canada.

Data Sources

In Ontario, all residents are covered under a universal health plan. Individuals age 65 years or older are eligible for prescription drug coverage. We used a variety of linkable electronic health data: the Ontario Cancer Registry, a database of cancers estimated to be more than 95% complete[12]; the Ontario Diabetes Database, a validated administrative data-derived registry of diabetics[13]; the Ontario Health Insurance Plan, which tracks claims paid to physicians, laboratories, and out-of-province providers[14]; the Canadian Institute for Health Information (CIHI) Discharge Abstract Database, which contains records for each hospital stay[15]; the CIHI National Ambulatory Care Reporting System, which captures information on ambulatory care; the Registered Persons Data Base, which contains demographics and vital status; and the Ontario Drug Benefit database, which contains information on all outpatient pharmaceuticals.[16] For further information, see the Data Supplement.

Study Population and Cohort Definition

We used the Ontario Diabetes Database to identify patients age 66 years or older with newly diagnosed diabetes between March 1, 1997, and March 31, 2008. We restricted our cohort to those older than age 66 years in order to have a 1-year look-back and verify that all patients were not exposed to antidiabetic medication before study entry. We then cross-referenced with the Ontario Cancer Registry to identify patients with newly diagnosed PC after the diagnosis of diabetes. We then reviewed pathology reports and excluded patients without pathology. The cohort entry date was defined as date of PC diagnosis. We observed eligible individuals until they experienced an event (PC-specific or all-cause mortality) or, among those who did not die, a last health services contact in Ontario, or March 31, 2009, whichever came first.

Outcome Definitions

We measured two outcomes: (1) PC-specific mortality recorded in the Ontario Cancer Registry (the cause of death in the Ontario Cancer Registry was validated in several studies[17,18]) and (2) all-cause mortality derived from death certificates.

Exposure Measurement

We used the Ontario Drug Benefit database to identify all prescriptions for antidiabetic medications that were filled between the date of diabetes diagnosis and the end of follow-up. Prescription duration was determined from the mandatory days-supply field. By using the date and duration of each prescription, we were able to determine the cumulative daily duration of exposure to antidiabetic medications both before and during follow-up. During periods of nonuse (lapses in use of antidiabetic medication), the cumulative duration of exposure remained unchanged from the value at the time the previous prescription expired. Total cumulative use was divided into prediagnostic duration of use between diabetes and PC diagnosis and cumulative use after PC diagnosis. Duration of use before PC diagnosis remained constant during follow-up, whereas cumulative duration of daily use after PC diagnosis had the potential to vary for every day of follow-up (Data Supplement).

Statistical Analysis

All analyses were conducted by using SAS version 9.2 (SAS Institute, Cary, NC). The effects of cumulative duration of exposure to antidiabetic medication on risk of overall and PC-specific mortality were assessed by using a Cox proportional hazard model. To avoid survival bias (ie, those who take metfomin longer are obviously those who survive longer), all cumulative drug exposures after PC diagnosis were modeled as time-dependent covariates. Therefore, the comparison is not exclusively between users and nonusers but is also between users who have had different durations of exposure. We modeled the exposure as a continuous variable to avoid incorrect inferences, loss of information, and uncertainty of exposure categorization.[19,20]

Because the increment of a single day is clinically negligible, regression coefficients were transformed to estimate the effect of 6 months of use. Before transformation, we used fractional polynomials to test for the distribution that best describes the association between cumulative use of metformin and all-cause and PC-specific mortality.[21,22] The proportional hazard assumption for categorical variables was assessed by using interactions with log-time.

Crude and adjusted hazard ratios (HRs) were estimated, adjusting for all antidiabetic drug exposure. PC-related covariates were tumor grade, tumor volume, primary treatment with radiation or surgery, and cumulative use of androgen-deprivation therapy (ADT). Other covariates were age, Johns Hopkins Adjusted Clinical Groups Case-Mix System weighted sum of adjusted diagnostic groups,[23] year of cohort entry (to adjust for temporal changes in management of diabetes and PC), socioeconomic status, and cumulative use of COX-2 inhibitors and statins. Of note, cancer stage information was unavailable (Fig 1; Data Supplement).

Sensitivity Analyses

We conducted eight separate sensitivity analyses repeating the primary analysis by using eight restrictions. (1) To minimize the healthy-user effect, we compared patients treated with metformin monotherapy with those who were on diet control. We excluded patients who used other antidiabetic medications who may, on average, have more severe diabetes. (2) To create a homogenous group, we used a method described by Wen et al[24] and limited our analysis to those with lower comorbidities. (3) To create a more homogenous cohort in unmeasured characteristics, we used an active comparator approach and included only patients who used statins.[25] These are patients who all used a preventive therapy and thus may represent a cohort that actively seeks preventive medicine. (4) To exclude patients with more severe diabetes, we excluded insulin users. (5) To minimize bias by indication, we limited the analysis to patients who had been prescribed metformin (monotherapy or in combination with other antidiabetic drugs). (6) To identify those with likely localized disease, we analyzed only patients treated primarily with surgery or radiation. (7) To identify men with advanced-stage PC, we analyzed those who received primary treatment with ADT (ie, who received either ADT or bilateral orchiectomy within the first 6 months from diagnosis and who did not have surgery or radiation). (8) We conducted a tracer analysis.[25] We used cataract surgery as a tracer outcome, an outcome that is not expected in association with metformin

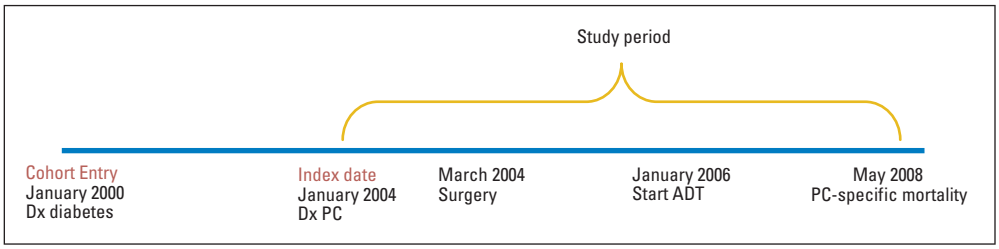

Fig 1. Example of timeline and variable analysis: hypothetical patient diagnosed with diabetes at age 67 in January 2000 who was later diagnosed with prostate cancer (PC) in January 2004. He was treated with surgery in May 2004 and started androgen-deprivation therapy (ADT) in January 2006. He died as a result of PC in May 2008. Dx, diagnosis.

use. Cataract surgery was chosen because it is a common elective surgery, and it was used to control for unmeasured health-seeking characteristics.

RESULTS

During the study period, 105,245 men older than age 66 years were diagnosed with incident diabetes in Ontario. Linkage with the Ontario Cancer Registry yielded 4,736 patients (4.5%) who were later diagnosed with PC. Of these, 3,837 (81%) had pathology reports. The median age at PC diagnosis was 75 years (interquartile range, 72 to 79 years; Table 1). During a median follow-up of 4.64 years (interquartile range, 2.7 to 7.1 years), 1,343 (35%) died, and 291 patients (7.6%) died of PC. At presentation, 976 patients (25.4%) had high-grade tumors (Gleason score $\geq$ 8), and 2,167 (57%) had high-volume tumors ($>$ 30%).

Table 1. Baseline Patient Characteristics (N = 3,837)

Characteristic	No.	%
Age at index date, years		
Median	75	
IQR	72-79	
Time between diabetes and PC diagnosis, years		
Median	2.6	
IQR	1.1-4.8	
Time from PC diagnosis to end of follow-up, years		
Median	4.64	
IQR	2.7-7.1	
Grade at presentation		
Low	1,492	38.9
Intermediate	1,369	35.7
High	976	25.4
Primary treatment		
Surgery	297	7.7
Radiation	937	24.4
Watchful waiting	1,138	29.7
ADT	1,468	38.2
Tumor volume		
High ($>$ 30%)	2,167	57
Low ($\leq$ 30%)	1,670	43
TUR diagnosis	702	18.3
Comorbidity score*		
Low	1,151	29.9
Intermediate	1,918	49.9
High	768	20
SES status†		
1	782	20.5
2	852	22.3
3	756	19.8
4	705	18.4
5	729	19
Urban	3,291	84.9
PC-specific death	291	7.6
Overall mortality	1,343	35

Abbreviations: ADT, androgen-deprivation therapy; IQR, interquartile range; PC, prostate cancer; SD, standard deviation; SES, socioeconomic status; TUR, transurethral resection.
*Comorbidity scores were calculated by using Johns Hopkins Adjusted Clinical Groups Case-Mix System assigning a specific weight to each adjusted diagnostic group (low, weighted adjusted diagnostic group score 5 or lower; intermediate, 6-9; high, 10 or higher).
†Income quintiles from median income in neighborhoods from 1 (low) to 5 (high).

Table 2. Exposure to Antidiabetic Drugs

Cumulative Exposure	Patients		Median Time (months)	IQR (months)
	No.	%		
Baseline*				
Metformin	1,251	32.6	19	6.3-40
Sulfonylurea	968	25.2	20	2.66-46.8
Thiazolidinedione	64	1.6	10.6	5-17.5
Insulin	107	2.7	6.66	2.6-23.6
After PC diagnosis				
Metformin	1,619	42.2	8.9	3.6-12.3
Sulfonylurea	1,055	27.5	8.2	3.6-12.4
Thiazolidinedione	142	3.7	7.7	3.4-11.3
Insulin	286	7.4	3.66	2-7.8

Abbreviations: IQR, interquartile range; PC, prostate cancer.
*Between diabetes and PC diagnosis.

Overall, 1,251 (32.6%) and 1,619 (42.2%) were exposed to metformin before and after PC diagnosis, respectively (Table 2). Patients were exposed to metformin for a median of 19 months (range, 6.3 to 40 months) before PC diagnosis and 8.9 months (range, 3.6 to 12.3 months) after PC diagnosis. Among metformin users, 53% (n = 858) continued to take metformin once the medication was initiated, whereas 47% (n = 761) of metformin users had periods of nonuse.

PC-Specific Mortality

By using fractional polynomials, we verified that the association between cumulative metformin use after PC diagnosis and PC-specific mortality (Table 3) is linear (Data Supplement). On multivariable analysis, for each additional 6 months of metformin use after PC diagnosis, there was a 24% reduction in PC-specific mortality (adjusted HR [aHR], 0.76; 95% CI, 0.64 to 0.89). Increasing durations of cumulative use of all other antidiabetic medications was not associated with PC-specific mortality.

All-Cause Mortality

By using fractional polynomials, we found that the association between cumulative metformin use after PC diagnosis and all-cause mortality (Table 4) is nonlinear (Data Supplement). We therefore used a square root transformation and are not able to report a uniform HR because it changes over time. On multivariable analysis, the first 6 months of metformin use was associated with a 24% reduction in all-cause mortality (aHR, 0.76; 95% CI, 0.70 to 0.82). This association declines over time, and use of metformin between 24 and 30 months after PC diagnosis is associated with a 7% decrease (aHR, 0.93; 95% CI, 0.91 to 0.96) in all-cause mortality (Table 4).

Sensitivity Analyses

The sensitivity analysis (Table 5), which included only patients who were either receiving metformin monotherapy (n = 850) or were diet controls (n = 1,702), revealed that every additional 6 months of metformin use was associated with a decrease in PC-specific (aHR, 0.56; 95% CI, 0.51 to 0.70) and all-cause mortality (aHR, 0.80; 95% CI, 0.77 to 0.85). Similar point estimates of metformin effect were found for PC-specific and all-cause mortality in other sensitivity analyses that

Table 3. Time-Dependent Multivariable Cox Proportional Hazard Model for PC-Specific Mortality

Variable	PC-Specific Mortality		
	HR	95% CI	*P*
Cumulative use of medication after PC diagnosis*			
Metformin	0.76	0.64 to 0.89	.001
Sulfonylureas	1.01	0.89 to 1.12	.96
Thiazolidinediones	0.98	0.54 to 1.79	.96
Insulin	0.86	0.69 to 1.5	.93
PC-related			
Age at PC diagnosis (years)	1.06	1.04 to 1.09	< .001
Gleason score at presentation			
≥ 8	5.58	3.7 to 8.2	< .001
7	1.6	1.03 to 2.4	.025
≤ 6	Ref		
Tumor volume (> 30% *v* ≤ 30%)	1.64	1.16 to 2.32	.003
Cumulative ADT use*	0.98	0.96 to 1.25	.052
Radical prostatectomy*	0.5	0.24 to 0.8	.03
Radiation treatment*	0.52	0.3 to 0.85	.009
Demographic			
Comorbidity score			
High	1.53	1.13 to 2.1	.014
Intermediate	1.4	1.08 to 2	.04
Low	Ref		
Rural *v* urban	1.25	0.93 to 1.68	.052
Year of cohort entry	0.81	0.78 to 0.85	< .001
SES status			
1 (low)	Ref		
2	0.8	0.6 to 1.14	.15
3	1.1	0.8 to 1.5	.76
4	0.85	0.59 to 1.22	.4
5 (high)	0.93	0.66 to 1.31	.22
Baseline drug exposure before PC diagnosis			
Metformin	1.02	0.97 to 1.06	.36
Sulfonylurea	1.04	0.99 to 1.06	.1
Thiazolidinedione	0.75	0.49 to 1.4	.61
Insulin	0.99	0.96 to 1.36	.93

NOTE. Multivariable model adjusted for all variables shown in table as well as pre- and postdiagnostic cumulative exposure to statins and cyclooxygenase-2 inhibitors (data not shown). All drug exposure units are per 6 months of use. Comorbidity scores were calculated by using Johns Hopkins Adjusted Clinical Groups Case-Mix System assigning a specific weight to each adjusted diagnostic group (low, score 5 or lower; intermediate, 6-9; high, 10 or higher).
Abbreviations: ADT, androgen-deprivation therapy; HR, hazard ratio; PC, prostate cancer; Ref, reference; SES, socioeconomic status.
*Modeled as time-varying covariates.

Table 4. HR and 95% CI of the Association of Metformin Use and All-Cause Mortality Per 6 Months of Cumulative Use After PC Diagnosis

Postdiagnostic Cumulative Use of Medication (months)	All-Cause Mortality (1,343 events)		
	HR	95% CI	*P*
0-6	0.76	0.70 to 0.82	< .001
6-12	0.88	0.85 to 0.91	< .001
12-18	0.91	0.89 to 0.94	< .001
18-24	0.92	0.90 to 0.94	< .001
24-30	0.93	0.91 to 0.96	< .001

NOTE. For the outcome of all-cause mortality, the relationship is not linear and changes with time (Data Supplement). These hazard ratios (HRs) were calculated from the multivariable model controlling for age, grade, tumor volume, comorbidity score, socioeconomic status, rural housing, and year of cohort entry.
Abbreviation: PC, prostate cancer.

included only statin users (n = 2,405), limiting the cohort to those with a lower comorbidity score (n = 1,940), excluding insulin users (n = 3,551), and limited to only metformin users (n = 1,619). The analysis stratified by localized versus advanced disease also revealed similar trends for PC-specific and all-cause mortality. Finally, the tracer analysis that used cataract surgery did not reveal an association between cumulative exposure to metformin and cataract surgery.

DISCUSSION

Diabetes and PC are common. In the United States, the most commonly diagnosed cancers in men are prostate, lung/bronchus, and colon/rectum.[1] Of the world adult population, an estimated 285 million (6.6%) have diabetes.[2] In 2007, diabetes prevalence in the United States was 10.7%, with an estimated 1.6 million new cases per year.[2] Therefore, an increasingly large number of men will be diagnosed with both diabetes and PC. Our population-based study demonstrated that increased cumulative use of metformin after PC diagnosis is associated with a significant improvement in all-cause and PC-specific survival among older men with diabetes and PC. We have shown that for every additional 6 months of metformin treatment, there is a 24% decrease of PC-specific mortality and a significant decrease in all-cause mortality that declines over time.

Most studies of the association of metformin with PC focused on cancer incidence. Wright et al[8] demonstrated that among whites with diabetes, metformin resulted in a 44% reduced risk of PC. Other larger studies did not report similar findings.[9,10] One meta-analysis[26] concluded that current data do not support an association between decreased risk of PC incidence and use of metformin.

Considering the hypothesized biologic mechanisms of the effects of metformin in cancer, it remains plausible that cancer progression may be the most relevant outcome. Furthermore, in the current era, PC incidence is mainly dependent on prostate-specific antigen screening.[1] He et al[11] report a single institutional retrospective cohort of 233 patients with PC in whom both thiazolidinedione and metformin exposure were predictors of improved overall survival. However, this study did not report cancer-specific death and did not consider drug exposure as a time-dependent covariate, which may overestimate its effects.[27]

We used cumulative use of antidiabetic medications as our main exposure. We believe that because metformin may work by preventing progression, simply analyzing whether a patient was exposed to metformin or not may not capture its effect. This method also allows evaluating a dose-response effect, strengthening evidence for a causality.[28] Furthermore, our approach incorporated cumulative metformin as a time-varying covariate, thus circumventing potential survival bias. In addition, we analyzed all drug exposures in the same manner. If our results were attributed to longer duration of survival among patients using medications for a longer time, we should have noticed a significant effect for all medications. However, the only antidiabetic drug associated with improved outcome was metformin.

Healthy-user/adherer biases are a major concern in observational studies.[29,30] Our database offers a unique opportunity to minimize these biases. Most diabetes cohorts are captured by using

Table 5. Sensitivity Analyses of the Association Between Cumulative Use of Metformin and PC-Specific and All-Cause Mortality

Variable	No. of Patients	PC-Specific Mortality			All-Cause Mortality		
		HR	95% CI	*P*	HR	95% CI	*P*
Metformin monotherapy *v* diet control	850 of 1,702	0.56	0.51 to 0.70	.0013	0.8	0.77 to 0.85	.005
Statin users	2,405	0.78	0.62 to 0.99	.004	0.92	0.84 to 1.01	.1
Low comorbidity*	1,940	0.78	0.54 to 1.14	.03	0.91	0.85 to 0.98	.0015
Excluding insulin users	3,551	0.77	0.75 to 0.85	.001	0.88	0.86 to 0.92	< .001
Metformin users	1,619	0.81	0.75 to 0.87	.003	0.95	0.91 to 1.02	.2
Localized PC	955	0.59	0.41 to 1.2	.24	0.95	0.8 to 1.08	.81
Advanced PC	1,109	0.71	0.62 to 0.83	.006	0.92	0.86 to 0.99	.01
Tracer analysis- cataract surgery		0.98	0.96 to 1.1		0.98	0.96 to 1.1	

NOTE. Each unit represents 6 months of follow-up with prostate cancer (PC) –specific and all-cause mortality. The same primary multivariable analysis was repeated separately for each of the eight sensitivity analyses.
Abbreviation: HR, hazard ratio.
*Weighted score of 4 or more by using Johns Hopkins Adjusted Clinical Groups Case-Mix System.

prescriptions.[8-10] Per guidelines for diabetics, metformin is considered first-line therapy.[31] Thus, beneficial effects of metformin in these databases may be partly due to use of metformin among healthier patients. Because our diabetes database uses diagnostic codes rather than medication to capture diabetes, our cohort has a large proportion of patients (n = 1,702) who are not medically treated but are receiving diet control. Although some of these patients may be untreated because of nonadherence or end-stage cancer, many have early-stage diabetes and may be healthier than even metformin users. In the sensitivity analyses, we demonstrated that metformin use was associated with decreased mortality, even when compared with diet control patients.

We used several other methods to minimize healthy-user effects.[25] First, we included patients with incident diabetes who subsequently had PC. Although this restriction limited follow-up time, an incident population compared with a prevalent one is more homogenous, because it is less likely to include patients who tolerate metformin and are adherent to their metformin dosage regimen.[25] This argument is even stronger since diabetes itself is correlated with PC.[8-11] Diabetes is associated with a lower risk of PC but higher risk of high-grade disease and mortality. Including a prevalent cohort would make it hard to disentangle the effect of metformin use from that of diabetes. Furthermore, because our drug exposures are modeled as duration of cumulative exposure after PC diagnosis, the comparison is not exclusively between users and nonusers but rather it is between users who have had different durations of cumulative exposure. This should help mitigate the healthy-user effects and other indication biases.

We observed that cumulative use of statins is also associated with decreased mortality (data not shown). Prior studies of the association of statins and PC demonstrate that statin use is associated with decreased advanced and fatal PC.[32,33] Our study was not designed to test the association of statin use and mortality, but we believe that our data add to the evidence that statin use is associated with a reduced risk of PC-related mortality. Unfortunately, the complexity of analysis with cumulative use time-varying covariates precluded us from testing the effect of an interaction between statin and metformin.

Several limitations merit mention. First, because of its observational nature, treatment was not randomly assigned, and differences between individuals prescribed different drugs for differing durations may be related to the outcomes independent of any metformin-modifying effects. Still, our methodology helped minimize many of the potential biases. Second, we used administrative data and were not able to retrieve information on reason for drug discontinuation, severity of diabetes, laboratory data, body mass index, exercise, smoking status, and PC stage. However, our large sample size enabled us to adjust for many other potential confounders. We also acknowledge that excluding patients without pathology reports may have introduced selection bias, and patients without pathology reports may have, on average, a more advanced cancer that was diagnosed clinically. However, the percentage of patients who had pathology reports is similar to that in other studies that used the Ontario Cancer Registry.[34,35] In addition, pathology abstraction allowed us to adjust for important cancer parameters: Gleason score and tumor volume. Furthermore, we performed several sensitivity analyses to address differences in severity of diabetes and cancer stage, which all revealed similar point estimates. Residual confounding still exists because individual-level data on reason for drug choice, personal habits (smoking, diet, exercise), body size, prostate-specific antigen, and PC stage are lacking. Third, because our population was older, all had diabetes and many were treated initially with ADT; thus, generalizability to a contemporary PC cohort is tempered. However, all eight sensitivity analyses demonstrated similar point estimates. Finally, because our cohort was limited to patients with diabetes, we cannot conclude whether similar effects of metformin would be seen in a nondiabetic population. Thus, our study results do not demonstrate a survival benefit for diabetic men who use metformin compared with men who do not have diabetes.

There are several clinical implications of our findings. First, consistent with current guidelines,[31] metformin should be considered first-line therapy among patients with PC and diabetes, not only for diabetes control but possibly to improve cancer prognosis. Second, we found that metformin was associated with benefit regardless of cancer treatments. These results suggest that metformin may further improve survival as an adjunct therapy, even among those already receiving optimal cancer treatments. Finally, metformin may be ideal for secondary prevention because it is inexpensive, safe, and well tolerated.[31] We believe that these data can serve as proof-of-concept to design interventional studies of metformin to prevent or delay progression in PC. Indeed, large-scale phase III breast cancer studies are underway.[36]

There is some evidence to suggest benefits of metformin among patients without diabetes. Metformin has a demonstrable safety profile among nondiabetics and is used in polycystic ovary syndrome[37] and nonalcoholic fatty liver.[38] In patients who did not have diabetes but who did have breast cancer, metformin decreased tumor proliferation markers.[5] Metformin may also have other benefits for nondiabetic patients who require ADT through its insulin-sensitizing effects. ADT is commonly used as therapy for men with advanced PC. It can be associated with insulin resistance and metabolic syndrome.[39] Recently, a small randomized study demonstrated improvement in metabolic parameters among nondiabetic patients with PC who were randomly assigned to metformin and lifestyle changes.[40]

Our study is among the first to report that cumulative metformin use after PC diagnosis is associated with improved all-cause and PC-specific survival among elderly diabetic men. We believe an interventional study of the use of metformin to delay progression in PC is warranted.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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