

The use of metformin in patients with prostate cancer and the risk of death

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Abstract

Background: Given the conflicting results from observational studies, we assessed whether the use of metformin after a prostate cancer diagnosis is associated with a decreased risk of cancer-specific and all-cause mortality.

Methods: This study was conducted linking four databases from the United Kingdom. A cohort of men newly-diagnosed with non-metastatic prostate cancer with a history of treated type 2 diabetes, between April 1, 1998 and December 31, 2009, was followed until October 1, 2012. Nested case-control analyses were performed for cancer-specific mortality and all-cause mortality, where exposure was defined as use of metformin during the time to risk-set. Conditional logistic regression was used to estimate adjusted rate ratios (RRs) of each outcome with 95% confidence intervals (CIs).

Results: The cohort consisted of 935 men with prostate cancer and a history of type 2 diabetes. After a mean follow-up of 3.7 years, 258 deaths occurred, including 112 from prostate cancer. Overall, the post-diagnostic use of metformin was not associated with a decreased risk of cancer-specific mortality (RR: 1.09, 95% CI: 0.51-2.33). In a secondary analysis, a cumulative duration ≥ 938 days was associated with an increased risk (RR: 3.20, 95% CI: 1.00-10.24). The post-diagnostic use of metformin was not associated with all-cause mortality (RR: 0.79, 95% CI: 0.50-1.23).

Conclusion: The use of metformin after a prostate cancer diagnosis was not associated with an overall decreased risk of cancer-specific and all-cause mortality.

Impact: The results of this study do not support a role for metformin in the prevention of prostate cancer outcomes.

Introduction

Metformin is a safe and effective treatment that improves elevated insulin and glucose levels in patients with type 2 diabetes (1, 2). In recent years, there has been interest in the antineoplastic activity of this compound demonstrated in several *in vitro* models (3, 4). Proposed mechanisms of action begin with metformin inhibiting ATP production in the mitochondria, resulting in energetic stress (2). Energetic stress results in the activation of AMPK which inhibits mTOR, and minimizes cellular energy consumption, thus inhibiting tumor growth (2). Apart from this 'direct' mode of action, metformin may also act by lowering circulating levels of mitogens such as insulin or other cytokines that can stimulate tumor growth (2).

With respect to prostate cancer, observational studies investigating the association between metformin and a decreased incidence of this cancer have produced mixed findings (5, 6). However, there has been renewed interest in the effect of this drug on cancer outcomes in patients with prostate cancer. To date, six observational studies have investigated the effects of metformin on cancer-related mortality, distant metastasis, and all-cause mortality in men diagnosed with prostate cancer (7-12). In three studies, the use of metformin was associated with strong decreased risks (ranging between 24% to 80% risk reductions) of several prostate cancer outcomes (8, 10, 11), while the other three studies reported non-significant findings (7, 9, 12). However, these studies had important methodological shortcomings. In particular, three of these studies had immortal time bias (8-10). This bias has been previously described in this literature (13), and likely exaggerated the potential benefits of metformin on prostate cancer outcomes in the two studies reporting strong decreased risks (8, 10). Furthermore, none of the six observational studies accounted for latency and reverse causality (7-12), a necessary consideration for studies investigating cancer outcomes. Finally, three studies did not assess the

effects of metformin duration and dose to determine whether there was a dose-response relationship between the use of this drug and incidence of the different prostate cancer outcomes (7-9).

Given the methodological limitations of the observational studies conducted to date, the primary objective of this population-based study was to determine whether the use of metformin after a prostate cancer diagnosis is associated with a decreased risk of cancer-related mortality. A secondary objective was to determine whether the use of this drug is associated with a decreased risk of all-cause mortality.

Material and methods

Data sources

This study was conducted by linking four large electronic databases from the United Kingdom (UK), the UK National Cancer Data Repository (NCDR), the Clinical Practice Research Datalink (CPRD), the Hospital Episode Statistics (HES) database, and the Office for National Statistics (ONS) database.

The UK NCDR contains tumour information, including site of primary growth (coded using the International Classification of Diseases, 10th revision [ICD-10]), grade, stage, and primary treatment received. The CPRD contains the complete medical record for more than 12 million people enrolled in more than 650 general practices. The geographic distribution of the practices participating in the CPRD has been shown to be representative of the UK population, and age and sex distributions of patients in the CPRD are similar to those reported by the National Population Census (14-16). Participating general practitioners have been trained to record medical information including demographic data, medical diagnoses, procedures, and deaths. Prescriptions written by CPRD physicians are automatically transcribed into the

computer record. In addition, unlike administrative databases, the CPRD collects information regarding lifestyle variables such as body mass index (BMI), and quantitative and qualitative data pertaining to smoking and alcohol use. Read codes are used to enter medical diagnoses and procedures, which is the standard clinical terminology system used in general practice in the UK (14, 17), and a coded drug dictionary based on the UK Prescription Pricing Authority Dictionary is used for recording prescriptions (17). The data collected are audited regularly and the participating general practices are subjected to a number of quality checks. Data recorded in the CPRD have been previously validated and proven to be of high quality (15, 17-19).

The HES database is a data warehouse containing details of all inpatient encounters in National Health Services hospitals in England since 1997. This database contains dates of hospital admissions, primary and secondary diagnoses (coded using the ICD-10 classification), and related procedures (coded using the ICD-10 classification and Office of Population Censuses and Surveys classification of interventions and procedures, 4th version [OPCS-4]). Finally, the ONS is the UK's largest independent producer of official statistics, which contains the electronic death certificates of all citizens living in the UK. This database was used to identify the underlying cause of death (coded using the ICD-10 classification) for all patients who died during follow-up.

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD and the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

Study cohort

Using the UK NCDR, we identified all patients newly-diagnosed with prostate cancer (ICD-10 code: C61) between April 1, 1998 and December 31, 2009. Cohort entry corresponded to the date of the prostate cancer diagnosis. We excluded patients with less than one year of ‘up-to-standard’ medical history in the CPRD prior to cohort entry, as well as patients diagnosed with metastatic disease (as identified in the UK NCDR, CPRD, or HES database). Furthermore, the cohort was restricted to patients who had used anti-diabetic agents (metformin, sulfonylureas, thiazolidinediones, insulins, and other agents) in the year prior to cohort entry. This latter restriction was necessary to ensure that all patients had type 2 diabetes, which was necessary to minimize confounding by indication since this condition has been associated with an increased risk of prostate cancer mortality (20). Patients meeting the study inclusion criteria were followed until one of the outcomes of interest: prostate cancer mortality (primary outcome) and all-cause mortality (secondary outcome), end of registration with the general practice, or the end of the study period (October 1, 2012), whichever came first.

Case-control selection

Two nested case-control analyses were conducted to assess the association between post-diagnostic use (i.e. after the prostate cancer diagnosis) of metformin with each of the study outcomes (prostate cancer mortality and all-cause mortality). This approach was used due to the time-varying nature of metformin exposure and is computationally more efficient than a time-dependent survival analysis (21). This approach produces odds ratios that are unbiased estimators of rate ratios (RRs) (21-23).

From the cohort defined above, we identified all cases of prostate cancer mortality (ICD-10: C61) and all-cause mortality occurring during follow-up. The date of each case’s outcome

(prostate cancer mortality and all-cause mortality) defined the index date. Up to 10 controls were randomly selected from the case's risk set (i.e. among patients from the cohort still at risk of the event at the time of a case's event date), after matching on year of birth, year of cohort entry, and duration of follow-up. By definition, all controls were alive, and registered with their general practice when 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 matched controls, necessary for latency considerations.

Exposure to metformin

For cases and controls, we obtained prescriptions for all anti-diabetic agents prescribed between cohort entry and index date. We excluded exposures initiated in the year immediately prior to index date in order to take into account a biologically meaningful latency time window, and to minimize reverse causality, where signs or symptoms of cancer progression may influence the initiation or termination of a particular treatment.

Exposure to metformin was defined in three ways. In the first approach, patients were considered exposed to metformin after their prostate cancer diagnosis if they received at least one prescription between cohort entry and the year prior to index date. For the second and third approach, we determined whether there were duration- and dose-response relationships between metformin and the two outcomes. Therefore, for patients deemed to be post-diagnostic users of metformin, we calculated their cumulative duration of use by summing the durations of each metformin prescription between cohort entry and the index date. In one analysis, cumulative duration was entered as a continuous variable with regression coefficients transformed to express the association of each additional 6 months of metformin use for prostate cancer mortality. This

analysis was performed to directly compare our results with those of a recent study reporting a 24% (hazard ratio: 0.76, 95% CI: 0.64-0.89) decreased risk in prostate cancer mortality with each additional 6 months of metformin use (11). In another analysis, cumulative duration was categorized in tertiles based on the distribution in the controls. Finally in the third approach, cumulative dose was computed by multiplying the daily dose of each metformin prescription by its specified duration of use. Thus, cumulative dose was calculated by summing the total quantities received between cohort entry and index date, and was categorized in tertiles based on the distribution in the controls.

Statistical analysis

Conditional logistic regression was used to estimate RRs with 95% confidence intervals (CIs) of the two prostate cancer outcomes in relation to the post-diagnostic use metformin. For the primary analysis, we evaluated whether post-diagnostic use of metformin was associated with a decreased risk of prostate cancer mortality. In a secondary analysis, we determined whether post-diagnostic use of metformin was associated with a decreased risk of all-cause mortality. We also evaluated whether there was a dose-response relationship in terms of cumulative duration of use and cumulative dose for each outcome.

In addition to year of birth, year of cohort entry, and duration of follow-up on which the logistic regression was conditioned, the models were adjusted for the following potential confounders measured prior to cohort entry: excessive alcohol use (based on alcohol-related disorders such as alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and failure), smoking status (never, ever, unknown), obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$), hemoglobin A1c (HbA1c) (last measure prior to cohort entry), pre-diagnostic use of anti-diabetic agents (metformin,

sulfonylureas, thiazolidinediones, insulins, and other agents entered individually in the models), Charlson comorbidity index, prostate-specific antigen (PSA) levels (last measure prior to cohort entry), Gleason score, and anti-diabetic drugs (measured between cohort entry and the year prior to index date). Tumor stage was not included as a covariate since it was missing for over 90% of the patients. In a secondary model, additional adjustments included prostate cancer-related interventions measured between cohort entry and the year prior to index date: PSA testing activity (defined as the total number of tests performed), prostatectomy, radiation therapy, chemotherapy, and androgen deprivation therapy (ADT).

Sensitivity and secondary analyses

For all of the analyses described above, we applied a one year lag period prior to index date to account for a latency time window as well as to minimize reverse causality. Since the length of the true latency window is unknown, we performed a sensitivity analysis by varying that lag period to two years.

We also conducted secondary analyses to determine whether pre-diagnostic use of metformin, obesity ($BMI \geq 30 \text{ kg/m}^2$), $age \geq 75$ years, Gleason score (low-grade [scores: 2-6], high-grade [7-10], unknown), and use of ADT were effect modifiers of the association between post-diagnostic use of metformin and prostate cancer mortality. This was assessed by including interaction terms between post-diagnostic metformin use and these variables in the models. All analyses were conducted with SAS version 9.2 (SAS Institute, Cary, NC).

Results

A total of 935 men newly-diagnosed with non-metastatic prostate cancer with a history of treated diabetes were included in the study (Figure 1). The mean follow-up time was 3.7 (standard deviation [SD]: 2.8) years, during which there were 258 deaths (overall incidence rate: 7.5% (95% CI: 6.6-8.4) per year), including 112 from prostate cancer (overall incidence rate: 3.2% (95% CI: 2.7-3.9) per year).

Table 1 presents the characteristics of the cases and matched controls for the primary outcome of prostate cancer mortality. Compared to controls, cases were more likely to have used alcohol excessively, to have been smokers, and obese. As expected, cases had higher PSA levels at cohort entry, Gleason scores, higher PSA testing activity, and more likely to have used ADT compared to controls.

The results of the primary analysis are presented in Table 2. Compared to non-use, post-diagnostic use of metformin was not associated with a decreased risk of prostate cancer mortality (adjusted RR: 1.09, 95% CI: 0.51-2.33). Similar null findings were obtained with all-cause mortality (Table 3). In the sensitivity analysis, varying the lag period prior to index date to two years resulted in a slightly lower RR for the post-diagnostic use of metformin in relation to the primary outcome of prostate cancer mortality (RR 0.90, 95% CI: 0.32-2.57) (Supplementary Table 1).

In a secondary analysis, each additional 6 months of metformin use was associated with a borderline 9% increased risk of prostate cancer mortality (RR: 1.09, 95% CI: 0.98-1.21). When categorized in tertiles, the highest category of metformin cumulative duration of use was associated with an increased risk of prostate cancer mortality (Table 2). Specifically, after 938 days of use, metformin was associated with approximately a three-fold increased risk (RR: 3.20,

95% CI: 1.00-10.24). For cumulative dose, the RR was elevated for the highest tertile of dose but did not reach statistical significance ($\geq 944,000$ RR: 2.62, 95% CI: 0.91-7.50) (Table 2). No dose-response relationship in terms of cumulative duration and dose were observed for all-cause mortality (Table 3).

Subgroup analyses

In subgroup analyses, pre-diagnostic use of metformin, obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$), and age ≥ 75 years were not found to be effect modifiers of the association between post-diagnostic use of metformin and prostate cancer mortality (Table 4). Similarly, the association between post-diagnostic use of metformin and prostate cancer mortality was not modified by Gleason score (low-grade, RR: 1.26, 95% CI: 0.23-6.89; high-grade, RR: 0.72, 95% CI: 0.27-1.93; unknown, RR: 1.53, 95% CI: 0.52-4.49; p-value for interaction=0.52). Finally, ADT did not modify the association, although the RR was lower among patients not receiving ADT (use of ADT, RR: 1.16, 95% CI: 0.53-2.53 vs no use of ADT: RR: 0.38, 95% CI: 0.06-2.42; p-value for interaction=0.24).

Discussion

The results of this population-based study indicate that the use of metformin after a prostate cancer diagnosis is not associated with a decreased risk of prostate cancer mortality. Similar findings were observed with the secondary outcome of all-cause mortality.

Overall, the results of this study are inconsistent with the favourable effects of metformin on neoplasia observed in previous laboratory models (3, 4), and contrast with some of the results of the observational studies conducted on this topic (7-12). Indeed, of the six observational studies conducted to date (7-12), only three found a statistically significant decreased risk of prostate cancer outcomes (8, 10, 11). However, these studies had several methodological shortcomings. In three studies, immortal time bias was introduced by not considering exposure in a time-dependent fashion (8-10). This bias was introduced by misclassifying the time between cohort entry and first metformin prescription as exposed, which greatly exaggerated the potential effects of metformin in two of these studies (8, 10). In another study, the authors investigated the effect of post-diagnostic use of metformin, thiazolidinediones, sulfonylureas, and low doses of insulin (9). The combination of those drugs was associated with a non-significant decreased risk in prostate cancer mortality (9). Our results also differ from those of a recent study reporting a 24% decreased risk of prostate cancer mortality with each additional 6 months of metformin use (11). In contrast, we observed a borderline 9% increased risk with each additional 6 months of use. Since the previous study used a time-dependent approach and was thus free of immortal time bias (11), it is unclear why the results differ between the studies. However, they do highlight the need of replicating observational studies in different populations and settings. Finally, none of the six observational studies conducted on this topic considered latency (7-12), which is necessary for any study assessing the effect of a drug on cancer outcomes.

An unexpected finding of this study was the three-fold increased risk of prostate cancer mortality (RR: 3.20, 95% CI: 1.00-10.24) associated with the highest tertile metformin cumulative duration of use. This elevated risk was not observed for all-cause mortality. It is plausible that patients treated with long-term metformin may have had metabolic or clinical characteristics associated with an adverse prostate cancer outcome. For example, some clinicians may prefer to avoid insulin and maintain oral agent diabetes treatment in their patients who are seen clinically to have aggressive cancer. Thus, it is possible that patients were maintained on metformin or switched to this therapy as part of the palliative approach, resulting in what appears to be worse outcomes associated with longer durations of use. On the other hand, as previously reviewed (2), there are some models where metformin leads to increased vascular endothelial growth factor production by tumor cells, which could theoretically worsen prognosis. Thus, the apparent long-term adverse effect of metformin observed in this study requires further investigation.

This nested case-control study has several strengths. First, by linking four electronic databases from the UK, we were able to obtain complete patient medical histories (including medication use, diagnoses, and treatments), lifestyle measurements (smoking, excessive alcohol use, and BMI), and cancer-related variables (Gleason scores, PSA levels, and prostate cancer treatments). Therefore, we were able to adjust for a number of important potential confounders. Second, information in the CPRD database is prospectively collected, eliminating the likelihood of recall bias. Second, controls were matched to cases using risk set sampling, and thus post-diagnostic use of metformin and other covariates measured during follow-up were assessed in a time-dependent fashion, eliminating the possibility of immortal time bias which affected some of the previous studies (8-10). Finally, exposures were lagged to consider a minimum latency time

window and minimize biases related to reverse causality.

This study has some limitations. First, drug information in the CPRD 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. Furthermore, tumor stage was not included as a covariate since it was incomplete in the UK NCDR, and there was missing information of Gleason scores. However, we adjusted for prostate cancer-related treatments (such as prostatectomy, radiation therapy, ADT, and chemotherapy), which are likely closely correlated with tumor characteristics. Thus, we believe that this lack of information did not affect the validity of the study. Furthermore, despite adjusting the models for several potential confounders, residual confounding may still be present. Moreover, some variables such as smoking and BMI had missing information. However, we believe that the distribution of this missing information was not differential between users of metformin and users of other anti-diabetic agents in this cohort of patients with type 2 diabetes. Lastly, misclassification of the primary outcome of prostate cancer mortality is a possibility, although prostate cancer mortality was previously shown to be generally well recorded in death certificates (24).

The combination of two chronic diseases, prostate cancer and type 2 diabetes, is a major public health concern (25). Contrary to previous studies that have found associations suggestive of a decreased risk (8, 10, 11), this study did not find an association between use of metformin and prostate cancer outcomes. A phase III randomized controlled trial (RCT) comparing metformin to placebo for men with early prostate cancer who meet specific criteria for active surveillance rather than immediate treatment has been initiated, and other RCTs for prostate cancer prevention or treatment of advanced metastatic disease have also been proposed. While

these RCTS may provide more definitive evidence on the effects of metformin on prostate cancer outcomes, our results do indicate that caution must be used in basing the rationale for conducting such RCTS solely on prior observational studies.

While certain RCTS can be justified by provocative laboratory data, the absence of a beneficial effect of metformin in the present study indicates that such RCTS should be carefully designed to address specific patient subgroups likely to benefit on the basis of pre-clinical evidence, and perhaps should incorporate early stopping rules in their design.

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Table 1. Characteristics of prostate cancer mortality cases and matched controls

Characteristics	Cases (n=112)	Controls (n=268)
At index date		
Age (years), mean (SD) ^a	75.5 (8.1)	75.5 (7.6)
Duration of follow-up, mean (SD) ^a	3.4 (2.3)	3.4 (2.3)
At cohort entry		
Excessive alcohol use, n (%)	14 (12.5)	25 (9.3)
Smoking status, n (%)		
Never	29 (25.9)	91 (34.0)
Ever	79 (70.5)	170 (63.4)
Unknown	4 (3.6)	7 (2.6)
Body mass index, n (%)		
<30 kg/m ²	75 (67.0)	195 (72.8)
≥ 30 kg/m ²	36 (32.1)	72 (26.9)
Unknown	1 (0.9)	1 (0.4)
Hemoglobin A1C, n (%)		
≤7% (53 mmol/mol)	53 (47.3)	148 (55.2)
>7% (53 mmol/mol)	30 (26.8)	89 (33.2)
Unknown	29 (25.9)	31 (11.6)
Metformin, n (%)	78 (69.6)	194 (72.4)
Sulfonylureas, n (%)	80 (71.4)	184 (68.7)
Thiazolidinedione, n (%)	13 (11.6)	28 (10.5)
Insulins, n (%)	21 (18.8)	53 (19.8)
Other anti-diabetic drugs, n (%)	8 (7.1)	16 (6.0)
Charlson comorbidity index, mean (SD)	1.92 (0.8)	1.93 (0.8)
Prostate-specific antigen, n (%)		
< 4 ng/mL	1 (0.9)	24 (9.0)
4-10 ng/mL	12 (10.7)	49 (18.3)
>10 ng/mL	57 (50.9)	121 (45.2)
Unknown	42 (37.5)	74 (27.6)
Gleason score, n (%)		
2-4	2 (1.8)	10 (3.7)
5-7	23 (20.54)	102 (38.1)
≥8	29 (25.9)	47 (17.5)
Unknown	58 (51.8)	109 (40.7)
Between cohort entry and index date		
Prostate-specific antigen testing activity, mean (SD)	3.1 (4.3)	2.1 (3.0)
Prostatectomy, n (%)	55 (49.1)	149 (55.6)
Radiation therapy, n (%)	16 (14.3)	50 (18.7)
Chemotherapy, n (%)	4 (3.6)	8 (3.0)
Androgen deprivation therapy, n (%)	105 (93.8)	184 (68.7)

^a Matching factors along with year of cohort entry.

Table 2. Post-diagnostic use of metformin and the risk of prostate cancer mortality

Metformin exposure	Cases (n=112)	Controls (n=268)	Crude RR^a	Model 1 Adjusted RR (95% CI)^b	Model 2 Adjusted RR (95% CI)^c
No use after prostate cancer diagnosis, n (%)	41 (36.6)	97 (36.2)	1.00	1.00 (reference)	1.00 (reference)
Use after prostate cancer diagnosis, n (%)	71 (63.4)	171 (63.8)	1.23	1.12 (0.56-2.25)	1.09 (0.51-2.33)
Cumulative duration^d, n (%)					
1-536 days	18 (16.1)	57 (21.3)	1.09	0.98 (0.38-2.58)	1.03 (0.36-2.96)
537-937 days	15 (13.4)	55 (20.5)	0.73	0.65 (0.26-1.64)	0.54 (0.20-1.44)
≥938 days	38 (33.9)	59 (22.0)	2.37	2.62 (0.91-7.50)	3.20 (1.00-10.24)
Cumulative dose^d, n (%)					
1-514,384 mg	23 (20.5)	57 (21.3)	1.32	1.30 (0.56-3.00)	1.36 (0.54-3.43)
514,385-991,839 mg	14 (12.5)	55 (20.5)	0.99	0.80 (0.33-1.96)	0.66 (0.25-1.78)
≥991,840 mg	34 (30.4)	59 (22.0)	1.34	1.26 (0.52-3.06)	1.28 (0.49-3.33)

Abbreviations: RR, rate ratio; CI, confidence interval.

^a Cases and controls matched on year of birth, year of cohort entry, and duration of follow-up.

^b Model 1 was adjusted for the following variables measured at cohort entry: excessive alcohol use, smoking, obesity, Hemoglobin A1C, pre-diagnostic use of metformin, sulfonylureas, thiazolidinediones, insulins, other anti-diabetic drugs, Charlson comorbidity index, prostate-specific antigen, and Gleason score. The model was also adjusted for the following variables measured during follow-up: post-diagnostic use of sulfonylureas, thiazolidinediones, insulins, other anti-diabetic drugs.

^c Model 2 was additionally adjusted for the following variables measured during follow-up: prostate-specific antigen testing activity, prostatectomy, radiation therapy, chemotherapy, and androgen deprivation therapy.

^d Based on tertile categories.

Table 3. Post-diagnostic use of metformin and the risk of all-cause mortality

Metformin exposure	Cases (n=258)	Controls (n=613)	Crude RR ^a	Model 1 Adjusted RR (95% CI) ^b	Model 2 Adjusted RR (95% CI) ^c
No use after prostate cancer diagnosis, n (%)	103 (39.9)	215 (35.1)	1.00	1.00 (reference)	1.00 (reference)
Use after prostate cancer diagnosis, n (%)	155 (60.1)	398 (64.9)	0.88	0.79 (0.51-1.23)	0.79 (0.50-1.23)
Cumulative duration ^d, n (%)					
1-587 days	41 (15.9)	134 (21.9)	0.82	0.75 (0.42-1.33)	0.74 (0.41-1.34)
588-1115 days	48 (18.6)	128 (20.9)	0.85	0.74 (0.43-1.28)	0.74 (0.42-1.28)
≥1116 days	66 (25.6)	136 (22.2)	1.00	0.96 (0.51-1.81)	0.95 (0.50-1.83)
Cumulative dose ^d, n (%)					
1-562,499 mg	55 (21.3)	132 (21.5)	0.97	0.83 (0.50-1.36)	0.84 (0.51-1.39)
562,500-1,124,999 mg	43 (16.7)	130 (21.2)	0.84	0.78 (0.45-1.36)	0.78 (0.44-1.37)
≥1,125,000 mg	57 (22.1)	136 (22.2)	0.81	0.74 (0.41-1.35)	0.70 (0.38-1.30)

Abbreviations: RR, rate ratio; CI, confidence interval.

^a Cases and controls matched on year of birth, year of cohort entry, and duration of follow-up.

^b Model 1 was adjusted for the following variables measured at cohort entry: excessive alcohol use, smoking, obesity, Hemoglobin A1C, pre-diagnostic use of metformin, sulfonylureas, thiazolidinediones, insulins, other anti-diabetic drugs, Charlson comorbidity index, prostate-specific antigen, and Gleason score. The model was also adjusted for the following variables measured during follow-up: post-diagnostic use of sulfonylureas, thiazolidinediones, insulins, other anti-diabetic drugs.

^c Model 2 was additionally adjusted for the following variables measured during follow-up: prostate-specific antigen testing activity, prostatectomy, radiation therapy, chemotherapy, and androgen deprivation therapy.

^d Based on tertile categories.

Table 4. Potential effect measure modifiers of the association between post-diagnostic use of metformin and prostate cancer mortality

Characteristic	Characteristic absent	Characteristic present	p-value for interaction
	Adjusted RR (95% CI) ^a	Adjusted RR (95% CI) ^a	
Model 1^b			
Pre-diagnostic use of metformin	1.65 (0.49-5.52)	0.91 (0.38-2.18)	0.45
Obesity (body mass index ≥ 30 kg/m ²)	1.16 (0.53-2.51)	1.11 (0.34-3.66)	0.95
Age ≥ 75 years	1.07 (0.40-2.83)	1.16 (0.51-2.64)	0.89
Model 2^c			
Pre-diagnostic use of metformin	1.96 (0.56-6.83)	0.75 (0.28-1.99)	0.25
Obesity (body mass index ≥ 30 kg/m ²)	1.12 (0.48-2.65)	1.07 (0.30-3.82)	0.95
Age ≥ 75 years	1.07 (0.37-3.07)	1.09 (0.45-2.66)	0.98

Abbreviations: RR, rate ratio; CI, confidence interval.

^a Cases and controls matched on year of birth, year of cohort entry, and duration of follow-up.

^b Model 1 was adjusted for the following variables measured at cohort entry: excessive alcohol use, smoking, obesity, Hemoglobin A1C, pre-diagnostic use of metformin, sulfonylureas, thiazolidinediones, insulins, other anti-diabetic drugs, Charlson comorbidity index, prostate-specific antigen, and Gleason score. The model was also adjusted for the following variables measured during follow-up: post-diagnostic use of sulfonylureas, thiazolidinediones, insulins, other anti-diabetic drugs.

^c Model 2 was additionally adjusted for the following variables measured during follow-up: prostate-specific antigen testing activity, prostatectomy, radiation therapy, chemotherapy, and androgen deprivation therapy.

Figure legend

Figure 1: Study flow chart

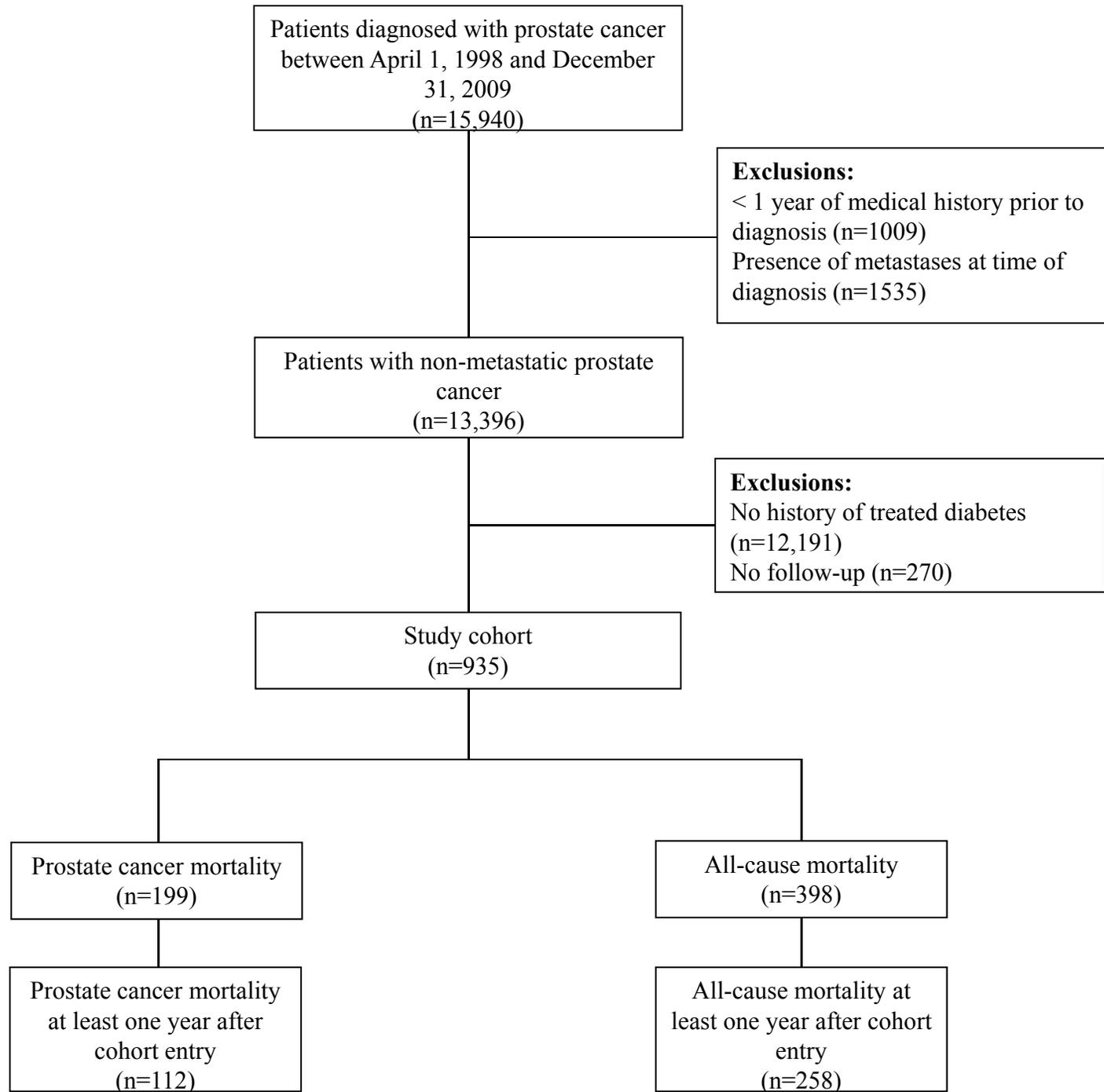


Figure 1