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European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by David Margel on pp. 1021–1022 of this issue

Metformin Use and Prostate Cancer Risk

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Article info

Article history:
Accepted April 29, 2014

Keywords:
Chemoprevention
Danish registry
Epidemiology
Incidence
Metformin
Prostate cancer

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Abstract

Background: Metformin may decrease prostate cancer (PCa) risk by reducing hyperinsulinemia-associated carcinogenesis or through direct effects on cancer cells.
Objective: To evaluate the association between metformin use and PCa diagnosis.
Design, setting, and participants: We used the Danish Cancer Registry and the Aarhus University Prescription Database to conduct a nested case–control study among men residing in northern Denmark from 1989 to 2011. We identified 12 226 cases of PCa and used risk-set sampling to select 10 population controls per case (n = 122 260) from among men alive on the index date and born in the same year. A sensitivity analysis was conducted using subjects who had prostate-specific antigen (PSA) testing prior to 1 yr before the index date.
Intervention: Metformin exposure was assessed using prescriptions redeemed before the index date.
Outcome measurements and statistical analysis: Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression. The association between metformin use and PCa diagnosis was determined, controlling for diabetes severity and other potential confounders.
Results and limitations: Metformin users were at decreased risk of PCa diagnosis compared with never-users (adjusted OR [aOR]: 0.84; 95% CI, 0.74–0.96). Diabetics on no medication (aOR: 0.98; 95% CI, 0.89–1.09) or on other oral hypoglycemics (aOR: 0.98; 95% CI, 0.86–1.10) did not have a reduced risk of PCa, while users of insulin did have a reduced risk (aOR: 0.77; 95% CI, 0.64–0.93). In the PSA-tested group, metformin use was associated with decreased risk of PCa compared with nonuse (aOR: 0.66; 95% CI, 0.51–0.86). Diabetics on no medication (aOR: 1.03; 95% CI, 0.86–1.24), diabetics on other oral hypoglycemics (aOR: 0.92; 95% CI, 0.70–1.20), and insulin users (aOR: 0.83; 95% CI, 0.56–1.24) did not have a statistically significant reduced risk of cancer.
Conclusions: Metformin use was associated with decreased risk of PCa diagnosis, whereas diabetics using other oral hypoglycemics had no decreased risk.
Patient summary: We studied the relationship between metformin (a diabetic medication) and prostate cancer in Denmark. We found that metformin reduced the risk of prostate cancer diagnosis, whereas other oral antidiabetic medications did not.

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http://dx.doi.org/10.1016/j.eururo.2014.04.027
0302-2838/

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1. Introduction

Prostate cancer (PCa) is the second leading cause of cancer mortality in men and the most commonly diagnosed noncutaneous malignancy [1,2]. Because of the high incidence, substantial personal distress [3–5], and societal costs [6] associated with the diagnosis and treatment of PCa, prevention would have a powerful impact.

Hyperinsulinemia, associated with type 2 diabetes, may play a role in carcinogenesis and be negatively associated with cancer prognosis [7,8]. Increased levels of insulin in obese men may lead to worse PCa prognosis [7,9,10]. This theory is supported by laboratory evidence showing that hyperinsulinemia upregulates insulin receptors in PCa cells and increases tumor growth [11]. However, diabetes has also been associated with decreased diagnosis of PCa, potentially mediated by lower levels of testosterone in these patients [12,13].

Metformin, a biguanide, is the most widely prescribed antidiabetic drug in the world because of its clinical effectiveness and tolerability [14]. Its primary mechanism is to activate 5′ AMP-activated protein kinase in the liver, inhibit gluconeogenesis, and reduce circulating insulin levels [15]. Metformin may reduce insulin-stimulated cancer growth [16] through this mechanism, in addition to possessing other antineoplastic properties such as reduction of the c-Myc oncogene [17]. However, no randomized trial has evaluated the effect of metformin on PCa risk, while observational studies have yielded conflicting results [18–24].

We performed a large population-based study of metformin use and PCa. We hypothesized that metformin use would be associated with decreased risk of PCa diagnosis.

2. Material and methods

2.1. Source population and study design

We conducted a nested case–control study within a well-defined cohort of Danish males identified between January 1989 and December 2011. Individuals eligible for case and control sampling resided in the former counties of North Jutland (1989–2011), Aarhus (1996–2011), Ringkoebing (1998–2011), and Viborg (1998–2011). In 2007, the Danish regions replaced counties as the main administrative units. Because the four counties started contributing data to the Arhus University Prescription Database (AUPD) at different times, they differ with respect to the earliest availability of prescription data (the earliest being 1989) [25]. The Central and North Denmark Regions encompass the four former counties, and the periods of required residence correspond to the period of availability of data on prescription medication use. Together, the two regions represent approximately one-third of the Danish population (approximately 1.8 million inhabitants). Health-related services are recorded using the unique civil personal registration (CPR) number assigned to all Danish citizens since 1968 by the Danish Civil Registration System (CRS). The CPR number encodes gender and date of birth [26] and permits accurate individual-level linkage among all Danish registries.

The Danish National Health Service provides tax-supported universal health care to all residents of the country and refunds part of patients' expenditures for most physician-prescribed drugs, including drugs used to treat diabetes [25]. The Danish regions are served by pharmacies equipped with computerized accounting systems, through which data on prescriptions for refundable drugs are sent to the AUPD [25]. The database includes information on each patient's CPR number, the type of drug prescribed (coded according to the Anatomical Therapeutic Chemical classification system), the amount of drug dispensed, and the date of sale [25,27].

2.2. Cases

Cases were men with an incident diagnosis of PCa and no previous cancer diagnosis (except nonmelanoma skin cancer) who were identified using the Danish Cancer Registry (see Appendix A for International Classification of Diseases codes), which has recorded all incident cancers diagnosed in Denmark through December 31, 2011 [28]. To be included in the study, men had to be residents of the Central or North Danish Regions, with $\geq$2 yr of prescription history before their index date (date of PCa diagnosis).

2.3. Population controls

Controls were identified using the CRS [26,29]. For each man in the case series, 10 controls were randomly selected from among male residents of the two regions who had the same birth year, were alive, and were free of PCa diagnosis on the index date. Men who resided in the study area for $<$2 yr before the index date and men with a diagnosis of cancer (except nonmelanoma skin cancer) before the index date were excluded.

2.4. Exposure

We used the AUPD [25] to identify all prescriptions for antidiabetic medications before the index date, disregarding 365 d prior to that date. Diabetic treatment categories were defined as metformin use with no prior insulin prescription, metformin and insulin use, any metformin use, other oral antidiabetic medication use, and no medication. The primary analysis included only metformin users with no exposure to insulin. We identified hospital diagnoses of diabetes in the Danish National Registry of Patients (DNRP), which contains records on all nonpsychiatric hospital admissions since 1977 and records on outpatient and emergency department visits since 1995 [30].

2.5. Covariates

From the available sources, we obtained data on the use of selected medications (proton pump inhibitors [PPIs], statins, and 5α-reductase inhibitors [5-ARIs]) from the AUPD and data on selected hospital diagnoses (diabetes complications and comorbidities) from the DNRP before the index date (see Appendix A). We assessed diabetic severity using the presence of diabetic complications and hemoglobin A1c (HbA1c) levels measured in the year prior to the index date. We disregarded prescriptions and diagnoses recorded within the year prior to the index date.

2.6. Statistical analysis

We tabulated distributions of the demographic variables and other covariates among cases and controls. We used conditional logistic regression analysis to compute crude ORs and adjusted ORs (aORs) and their associated 95% confidence intervals (CIs), with simultaneous adjustment for comorbidities (Charlson Comorbidity Index scores 0, 1–2, $\geq$3), diabetic complications, marital status (married, never married, divorced, or widowed), and ever use of PPIs, statins, and 5-ARIs.

An analysis was conducted stratified by localized and advanced-stage (regional or distant metastases) PCa. To assess potential confounding through prostate-specific antigen (PSA) testing, we repeated the analysis restricted to subjects who had PSA testing during the 5-yr period ending 1 yr prior to the index date. Laboratory data on PSA levels were recorded from 1997 on, covering all hospitals in the regions as of 2007 [31]. We also studied the association between metformin use and PCa restricted to diabetic men by rematching controls to cases among diabetic men with the

same birth year and with similar duration of diabetes. Under the risk-set sampling of controls used in this study, the ORs are unbiased estimates of the underlying incidence rate ratios [32]. Unconditional logistic regression was used with multivariable adjustment, including age for the PSA and HbA1c subanalyses. We used SAS 9.2 (SAS Institute Inc., Cary, NC, USA) for the analyses. The Danish Data Protection Agency approved the study (2004–41–4693).

3. Results

We identified 12 226 cases of PCa and 122 660 individually matched controls. The median age was 71.7 yr (range: 35–99) for cases and controls (range 34–100). The prevalence of diabetes, comorbidities, marital status, statin use, PPI use, 5-ARI use, and diabetic complications was similar for cases and controls (Table 1).

3.1. Metformin use

A total of 264 cases (2.2%) and 3111 controls (2.5%) used metformin for ≥1 yr before the index date (Table 1). The median duration of metformin use was 3.2 yr (interquartile range [IQR]: 1.5–5.7). An additional 90 cases used insulin in addition to metformin, for a total of 354 cases (2.9%) with any use of metformin during the study period. Metformin use was associated with a decreased risk of PCa compared with never-use in crude analysis (odds ratio [OR]: 0.84; 95% CI, 0.74–0.95), with little change after adjustment for potential confounders (adjusted OR [aOR]: 0.84; 95% CI, 0.74–0.96). A reduced risk of PCa was associated with insulin use (aOR: 0.77; 95% CI, 0.64–0.93), but not with use of other antidiabetic medications (aOR: 0.98; 95% CI, 0.86–1.10) or with diabetes managed without antidiabetic medication use (aOR: 0.98; 95% CI, 0.89–1.09) (Table 2).

Table 1 – Characteristics of case and control subjects (*n* = 134 486)

Characteristic	Prostate cancer cases, *n* = 12 226	Controls, *n* = 122 260
Age, yr, median (range)	71.7 (34.9–99.2)	71.7 (34.2–99.9)
Diabetes, no. (%)	1213 (10)	13 516 (11)
Metformin use only	264 (2)	3111 (2)
Metformin and insulin use	90 (0.7)	1254 (1)
Any metformin use	354 (3)	4365 (4)
Insulin use	118 (1)	1564 (1)
Other antidiabetic medication use	294 (2)	3048 (2)
No antidiabetic medication use	447 (4)	4539 (4)
Stage, no. (%)		
Localized	5202 (43)	
Regional	498 (4)	
Metastatic	2199 (18)	
Unknown	4327 (35)	
Prostate biopsy >1 yr prior to index date, no. (%)		
No	11 882 (97)	12 0101 (98)
Yes	344 (3)	2159 (2)
Charlson Comorbidity Index score, no. (%)		
0	8547 (70)	81 653 (66.8)
1–2	3257 (27)	35 087 (28.7)
≥3	422 (3)	5520 (4)
Diabetic complications, no. (%)	1275 (10)	14 987 (12)
Marital status, no. (%)		
Married	8879 (73)	85 057 (70)
Never married	733 (6)	9602 (8)
Divorced or widowed	2614 (21)	27 601 (23)
Statin ever used, no. (%)	2276 (19)	22 952 (19)
PPI ever used, no. (%)	2472 (20)	23 407 (19)
5-ARI ever used, no. (%)	562 (5)	4733 (4)

5-ARI = 5α-reductase inhibitor; PPI = proton pump inhibitor.

3.1.1. Duration of metformin use

Increasing duration of metformin use was associated with decreasing incidence of PCa. Metformin use of <1.5 yr was not associated with a risk reduction (aOR: 0.94; 95% CI, 0.74–1.18), but durations of 3 to <5 yr (aOR: 0.76; 95% CI, 0.58–1.01) and ≥5 yr (aOR: 0.75; 95% CI, 0.57–0.98) were associated with a risk reduction compared with nonuse (Table 2).

3.1.2. Intensity and cumulative dose of metformin use

Increasing intensity of metformin use (calculated as number of pills per day, in quartiles) was also associated with decreased incidence of PCa. Compared with nonuse, metformin intensity in the first quartile was not associated with risk of PCa (aOR: 0.93; 95% CI, 0.73–1.19), but intensity in the fourth quartile was (aOR: 0.57; 95% CI, 0.42–0.79) (Table 2). A similar pattern was seen for quartiles of cumulative dose (Table 2).

3.2. Sensitivity analyses

3.2.1. Prostate-specific antigen testing

To evaluate possible confounding by PSA screening, we conducted an analysis limited to subjects with a PSA test during the 5-yr period ending 1 yr prior to the index date. During this timeframe, the median PSA level was 11.0 ng/ml (IQR: 6.5–27.9) for cases and 1.8 ng/ml (IQR: 1.0–4.0) for controls. Among patients who had PSA testing, metformin use was associated with decreased risk of PCa compared with nonuse (aOR: 0.66; 95% CI, 0.51–0.86). We observed no significant reduction in PCa risk among users of insulin (aOR: 0.83; 95% CI, 0.56–1.24), users of other diabetic medications (aOR: 0.92; 95% CI, 0.70–1.20), and diabetics with no medication use (aOR: 1.03; 95% CI, 0.86–1.24) (Table 3).

3.2.2. Severity of diabetes

We investigated the impact of diabetic duration by stratifying patients using diabetic medication into two groups: a <6-yr or a ≥6-yr duration of diabetes. The median duration of diabetes among the study population was 6.6 yr (IQR: 3.6–11.0). Metformin use in diabetics with a <6-yr history of diabetes was not associated with decreased risk of PCa (aOR: 0.90; 95% CI, 0.73–1.09), while metformin use in diabetics with a ≥6-year history was (aOR: 0.81; 95% CI, 0.69–0.96). Insulin use was associated with a decreased risk of PCa (aOR: 0.77; 95% CI, 0.63–0.95) in men with a ≥6-yr history of diabetes, while other antidiabetic medication use and no antidiabetic medication use were not associated with risk in these patients (Table 4). Metformin use also was not associated with decreased PCa incidence among

Table 2 – The association between metformin use and incident prostate cancer using conditional logistic regression (*n* = 134 486)

	Cases, *n* = 12 226, no. (%)	Controls, *n* = 122 260, no. (%)	Adjusted OR	95% CI
No diabetes	11 013 (90)	108 744 (89)	ref	
Diabetes treatment*				
Metformin use only	264 (2)	3111 (3)	0.84	0.74–0.96
Metformin and insulin use	90 (1)	1254 (1)	0.73	0.58–0.90
Insulin use	118 (1)	1564 (1)	0.77	0.64–0.93
Other antidiabetic medication use	294 (2)	3048 (2)	0.98	0.86–1.10
No antidiabetic medication use	447 (4)	4539 (4)	0.98	0.89–1.09
Metformin ever use^	354 (3)	4365 (4)	0.81	0.72–0.91
Metformin use^				
Recent (1–2 yr ago)	241 (2)	2882 (2)	0.83	0.72–0.95
Former (>2 yr ago)	23 (0.2)	229 (0.2)	1.04	0.68–1.60
Metformin duration of use^				
<1.5 yr	78 (0.6)	834 (0.7)	0.94	0.74–1.18
1.5 to <3 yr	74 (0.6)	812 (0.7)	0.91	0.71–1.15
3 to <5 yr	54 (0.4)	702 (0.6)	0.76	0.58–1.01
≥5 yr	58 (0.5)	763 (0.6)	0.75	0.57–0.98
Metformin intensity of use^				
First quartile	74 (0.6)	785 (0.6)	0.93	0.73–1.19
Second quartile	80 (0.7)	847 (0.7)	0.94	0.74–1.18
Third quartile	70 (0.6)	776 (0.6)	0.89	0.69–1.14
Fourth quartile	40 (0.3)	703 (0.6)	0.57	0.42–0.79
Metformin cumulative dose^				
First quartile	84 (0.7)	837 (0.7)	1.00	0.80–1.25
Second quartile	71 (0.6)	868 0.7)	0.81	0.63–1.03
Third quartile	61 (0.5)	775 (0.6)	0.79	0.60–1.02
Fourth quartile	48 (0.4)	631 (0.5)	0.75	0.56–1.01

CI = confidence interval; 5-ARI = 5α-reductase inhibitor; OR = odds ratio; PPI = proton pump inhibitor; ref = reference.
* Model adjusted for comorbidities; diabetic complications; marital status; and use of statins, PPIs, and 5-ARIs.
^ Model adjusted for comorbidities; diabetic complications; marital status; use of statins, PPIs, and 5-ARIs; and diabetics taking insulin, other medications, or no medication.

diabetic patients with HbA1c levels of 7% to <8% (aOR: 0.78; 95% CI, 0.59–1.03) or among patients with HbA1c levels ≥8% (aOR: 0.93; 95% CI, 0.67–1.29) (Table 4). Use of insulin or use of both metformin and insulin was associated with a reduction in PCa risk among patients with HbA1c ≥8%. Users of other diabetic medications or no antidiabetic medications had no reduction in PCa incidence, regardless of HbA1c level.

3.2.3. Stage

In the stage-stratified analysis, metformin use was associated with a reduced risk of localized cancer (aOR: 0.70; 95% CI, 0.57–0.87) but was not associated with a significantly altered risk of regional or distant metastatic PCa (aOR: 1.13; 95% CI, 0.85–1.49) (Table 5).

4. Discussion

We used a large, unselected population drawn from national registries to investigate the association between metformin use and PCa risk. Metformin users were approximately 16% less likely to be diagnosed with PCa than nonusers, even after adjustment for diabetic severity and other confounders. We also observed an inverse relationship between PCa risk and duration, intensity of use, and cumulative dose of metformin.

In the stage-stratified analysis, metformin was associated with a reduced risk of localized cancer but was not associated with a significantly altered risk of regional/distant metastatic disease. This finding may stem from inadequate sample size or decreased detection, or it may indicate that metformin has less effect on advanced disease. Fall et al. showed that oral hypoglycemic agents were associated with a greater reduction in low-risk PCa (OR: 0.75; 95% CI, 0.63–0.89) than high-risk/metastatic cancer (OR: 0.86; 95% CI, 0.77–0.97) in a Swedish population [24]. That study, however, does not provide an ideal comparison with ours, as high-risk cancers were grouped with metastatic and metformin was grouped with other hypoglycemics.

Because an association may exist between diabetes—rather than metformin use—and risk of PCa, we controlled for diabetic complications (a proxy for diabetic severity) in multivariable analysis and analyzed diabetic duration and HbA1c levels. These analyses indicated that diabetes does indeed appear to reduce PCa incidence. However, metformin users had a more pronounced reduction in risk compared with users of other diabetic medications or no diabetic medications. In a sensitivity analysis limited to patients with diabetes (Table 6), metformin was associated with significantly reduced risk of cancer compared with no medication use (aOR: 0.83; 95% CI, 0.70–0.99).

Insulin use also appears to be associated with decreased incidence of PCa. Fall et al. reported a similar reduction in PCa incidence with insulin use [24]. Men requiring insulin for diabetic control usually have more severe diabetes and might be less likely to undergo PSA testing or potentially

Table 3 – Characteristics of subjects with prostate-specific antigen testing in a 5-yr period prior to 1 yr before diagnosis and association between metformin use and incidence of prostate cancer, using unconditional logistic regression with multivariable adjustment, including age

	Cases, *n* = 2511	Controls, *n* = 22 273	Adjusted OR	95% CI
Prior PSA tests, ǂ no., mean (SD)	2.9 (3.0)	2.8 (3.4)		
PSA, ng/ml, median (IQR)	11.0 (6.5–27.9)	1.8 (1.0–4.0)		
No diabetes	10.6 (6.4–26.1)	1.8 (1.0–4.1)		
Metformin use only	11.8 (7.4–29.8)	1.4 (0.7–3.1)		
Metformin and insulin use	11.0 (7.5–35.1)	1.2 (0.7–2.9)		
Insulin use	18.0 (5.5–51.7)	1.4 (0.8–3.5)		
Other antidiabetic medication use	18.0 (7.8–41.8)	1.7 (1.0–4.0)		
No antidiabetic medication use	13.1 (6.9–35.4)	1.7 (0.9–3.8)		
No diabetes, no. (%)	2200 (88)	18 836 (85)	ref	
Diabetes treatment,* no. (%)				
Metformin use	62 (2)	877 (4)	0.66	0.51–0.86
Metformin and insulin use	28 (1)	353 (2)	0.79	0.53–1.17
Insulin use	27 (1)	323 (1)	0.83	0.56–1.24
Other antidiabetic medication use	59 (2)	634 (3)	0.92	0.70–1.20
No antidiabetic medication use	135 (5)	1250 (6)	1.03	0.86–1.24
Metformin use,^ no. (%)				
Recent (1–2 yr ago)	56 (2)	800 (4)	0.65	0.49–0.86
Former (≥2 yr ago)	6 (0.2)	77 (0.4)	0.79	0.34–1.83
Metformin duration of use,^ no. (%)				
<1.5 yr	19 (0.8)	238 (1.1)	0.75	0.47–1.21
1.5 to <3 yr	20 (0.8)	227 1.0)	0.8	0.50–1.27
3 to <5 yr	10 (0.4)	185 (0.8)	0.51	0.27–0.97
≥5 yr	13 (0.5)	227 (1.0)	0.54	0.31–0.95
Metformin intensity of use,^ no. (%)				
First quartile	21 (0.8)	215 (1.0)	0.9	0.57–1.42
Second quartile	16 (0.6)	252 (1.1)	0.6	0.36–0.99
Third quartile	16 (0.6)	216 (1.0)	0.7	0.42–1.17
Fourth quartile	9 (0.4)	194 (0.9)	0.43	0.22–0.85
Metformin cumulative dose,^ no. (%)				
First quartile	21 (0.8)	253 (1.1)	0.78	0.50–1.22
Second quartile	19 (0.8)	233 (1.1)	0.74	0.46–1.19
Third quartile	12 (0.5)	211 (1.0)	0.54	0.30–0.97
Fourth quartile	10 (0.4)	180 (0.8)	0.53	0.28–1.00

CI = confidence interval; 5-ARI = 5α-reductase inhibitor; IQR = interquartile range; OR = odds ratio; PPI = proton pump inhibitor; PSA = prostate-specific antigen; ref = reference; SD = standard deviation.

ǂ Number of PSA tests ending 1 yr prior to index date.

* Model adjusted for age; comorbidities; diabetic complications; marital status; and use of statins, PPIs, and 5-ARIs.

^ Model adjusted for age; comorbidities; diabetic complications; marital status; use of statins, PPIs, and 5-ARIs; and diabetics taking insulin, other medications, or no medication.

have lower levels of PSA and therefore are less likely to be diagnosed with PCa. In the diabetic-only analysis, insulin no longer resulted in a significant reduction in incidence (aOR: 0.96; 95% CI, 0.75–1.22). This finding may be due to more pronounced confounding by indication with insulin, since the effect dissipated after accounting for increased diabetic severity in the matched analysis.

While our findings support some studies, other studies have reported either no effect or even an increased risk of PCa following metformin use [18–23]. A recent Canadian population-based study found no association between metformin use and risk of PCa (aOR: 1.03; 95% CI, 0.96–1.32) among men >66 yr with diabetes, regardless of cancer grade [22]. The median duration of metformin use, however, was only 18.6 mo (IQR: 6–37). The predominant effect of metformin might be in mitigating cancer progression rather than in prevention, as supported by a study that found that an increasing cumulative dose of metformin after diagnosis was associated with a decrease in PCa–specific mortality among diabetic men [23].

Strengths of our study include its large size, the population-based Danish universal health care system that fully captures the eligible population, and the ability to link high-quality clinical outcomes and prescription data. This setup makes it possible to study a nearly complete and unselected source population with excellent data validity and virtually complete follow-up. Inclusion of PSA testing and assessment of both severity of diabetes using HbA1c levels and presence of diabetic complications are unique strengths not present in previously published reports based on large registries.

Because national registries collect data prospectively, typical concerns associated with retrospective data collection are eliminated. Limitations include lack of information on body mass index and Gleason grade on biopsy or prostatectomy pathology. Misclassification of drug use could have biased the observed associations, and we cannot confirm that men with prescriptions for metformin actually took the medication. Despite all our efforts, incomplete adjustment may remain for confounding by indication, since

Table 4 – Odds ratios for prostate cancer incidence by treatment stratified by hemoglobin A1c level and duration of diabetes using unconditional logistic regression with multivariable adjustment[a]

Antidiabetic medication	HbA1c level					
	<7%		7% to <8%		≥8%	
	No.	OR (95% CI)	No.	OR (95% CI)	No.	OR (95% CI)
Metformin	116	0.88 (0.72–1.06)	53	0.78 (0.59–1.03)	40	0.93 (0.67–1.29)
Metformin and insulin	22	0.86 (0.56–1.33)	26	0.82 (0.55–1.23)	28	0.64 (0.43–0.93)
Insulin	26	0.85 (0.57–1.27)	27	0.86 (0.58–1.27)	23	0.51 (0.33–0.78)
Other antidiabetic medication	110	1.06 (0.87–1.30)	45	1.01 (0.74–1.37)	25	0.71 (0.47–1.06)
No antidiabetic medication	170	1.00 (0.86–1.18)	19	0.92 (0.57–1.47)	6	0.76 (0.33–1.74)

	Duration of diabetes			
	<6 yr		≥6 yr	
	No.	OR (95% CI)	No.	OR (95% CI)
Metformin	109	0.90 (0.73–1.09)	155	0.81 (0.69–0.96)
Metformin and insulin	8	0.69 (0.34–1.41)	82	0.73 (0.58–0.92)
Insulin	21	0.77 (0.50–1.21)	97	0.77 (0.63–0.95)
Other antidiabetic medication	151	0.98 (0.83–1.17)	143	0.97 (0.82–1.15)
No antidiabetic medication	299	1.00 (0.89–1.13)	148	0.96 (0.81–1.13)

CI = confidence interval; HbA1c = hemoglobin A1c; OR = odds ratio.
[a] Models adjusted for age; diabetic complications; comorbidities; marital status; and use of statins, proton pump inhibitors, and 5α-reductase inhibitors.

Table 5 – The association between metformin use and incident prostate cancer stratified by localized and advanced stage using conditional logistic regression (*n* = 134 486)

	Localized prostate cancer		Advanced prostate cancer	
	Cases/controls, no. (%)	Adjusted OR (95% CI)	Cases/controls, no. (%)	Adjusted OR (95% CI)
No diabetes	4709 (91)/46 392 (89)	ref	2449 (91)/24 204 (90)	ref
Diabetes treatment*				
Metformin use only	101 (2)/1406 (3)	0.70 (0.57–0.87)	59 (2)/539 (2)	1.13 (0.85–1.49)
Metformin and insulin use	37 (1)/579 (1)	0.63 (0.45–0.88)	15 (0.6)/194 (0.7)	0.81 (0.48–1.38)
Insulin use	37 (1)/673 (1)	0.56 (0.40–0.78)	28 (1)/325 (1)	0.89 (0.60–1.32)
Other antidiabetic medication use	116 (2)/1146 (2)	1.02 (0.84–1.24)	67 (2)/757 (3)	0.91 (0.70–1.17)
No antidiabetic medication use	202 (4)/1824 (4)	1.09 (0.94–1.27)	79 (3)/951 (4)	0.85 (0.67–1.08)
Metformin ever use^	138 (3)/1985 (4)	0.68 (0.57–0.82)	74 (3)/733 (3)	1.04 (0.81–1.34)
Metformin use^				
Recent (1–2 yr ago)	94 (2)/1307 (3)	0.70 (0.57–0.87)	54 (2)/505 (2)	1.10 (0.82–1.47)
Former (≥2 yr ago)	7 (0.1)/99 (0.2)	0.72 (0.33–1.55)	5 (0.2)/34 (0.1)	1.55 (0.61–3.97)
Metformin duration of use^				
<1.5 yr	37 (0.7)/386 (0.7)	0.94 (0.67–1.33)	13 (0.5)/136 (0.5)	0.98 (0.56–1.75)
1.5 to <3 yr	28 (0.5)/357 (0.7)	0.77 (0.52–1.14)	19 (0.7)/157 (0.6)	1.25 (0.77–2.02)
3 to <5 yr	17 (0.3)/318 (0.6)	0.52 (0.32–0.85)	13 (0.5)/116 (0.4)	1.15 (0.65–2.05)
≥5 yr	19 (0.4)/345 (0.7)	0.53 (0.34–0.85)	14 (0.5)/130 (0.5)	1.11 (0.63–1.94)
Metformin intensity of use^				
First quartile	27 (0.5)/355 (0.7)	0.74 (0.50–1.09)	18 (0.7)/137 (0.5)	1.36 (0.83–2.23)
Second quartile	34 (0.7)/360 (0.7)	0.92 (0.64–1.31)	16 (0.6)/152 (0.6)	1.07 (0.64–1.80)
Third quartile	25 (0.5)/350 (0.7)	0.70 (0.46–1.05)	16 (0.6)/136 (0.5)	1.20 (0.71–2.02)
Fourth quartile	15 (0.3)/341 (0.7)	0.44 (0.26–0.75)	9 (0.3)/114 (0.4)	0.82 (0.42–1.63)
Metformin cumulative dose^				
First quartile	36 (0.7)/380 (0.7)	0.92 (0.65–1.30)	14 (0.5)/129 (0.5)	1.12 (0.64–1.95)
Second quartile	27 (0.5)/384 (0.7)	0.68 (0.46–1.02)	17 (0.6)/168 (0.6)	1.03 (0.62–1.71)
Third quartile	22 (0.4)/347 (0.7)	0.63 (0.41–0.97)	17 (0.6)/145 (0.5)	1.22 (0.73–2.03)
Fourth quartile	16 (0.3)/295 (0.6)	0.54 (0.32–0.89)	11 (0.4)/97 (0.4)	1.16 (0.62–2.17)

CI = confidence interval; 5-ARI = 5α-reductase inhibitor; OR = odds ratio; PPI = proton pump inhibitor; ref = reference.
* Model adjusted for comorbidities; diabetic complications; marital status; and use of statins, PPIs, and 5-ARIs.
^ Model adjusted for comorbidities; diabetic complications; marital status; use of statins, PPIs, and 5-ARIs; and diabetics taking insulin, other medications, or no medication.

Table 6 – Association between metformin use and incident prostate cancer among only diabetics using matched conditional logistic regression (*n* = 13 331)

	Cases, *n* = 1213, no. (%)	Controls, *n* = 12 118, no. (%)	Adjusted OR	95% CI
Diabetic treatment*				
No antidiabetic medication use	447 (37)	4181 (35)	ref	
Metformin use	264 (22)	2894 (24)	0.83	0.70–0.99
Metformin and insulin use	90 (7)	914 (8)	0.92	0.70–1.19
Insulin use	118 (10)	1163 (10)	0.96	0.75–1.22
Other antidiabetic medication use	294 (24)	2966 (24)	0.99	0.85–1.16
Metformin use^				
Recent (1–2 yr ago)	241 (20)	2677 (22)	0.82	0.69–0.97
Former (≥2 yr ago)	23 (2)	217 (2)	1.02	0.65–1.58
Metformin duration of use^				
<1.5 yr	78 (6)	825 (7)	0.87	0.67–1.14
1.5 to <3 yr	74 (6)	738 (6)	0.92	0.70–1.19
3 to <5 yr	54 (4)	665 (5)	0.74	0.54–1.00
≥5 yr	58 (5)	666 (6)	0.78	0.57–1.05
Metformin intensity of use^				
First quartile	74 (6)	787 (6)	0.86	0.66–1.12
Second quartile	80 (7)	797 (7)	0.91	0.71–1.18
Third quartile	70 (6)	705 (6)	0.89	0.68–1.17
Fourth quartile	40 (3)	605 (5)	0.6	0.43–0.85
Metformin cumulative dose^				
First quartile	84 (7)	836 (7)	0.93	0.72-1.20
Second quartile	71 (6)	787 (6)	0.83	0.63-1.08
Third quartile	61 (5)	721 (6)	0.76	0.57-1.02
Fourth quartile	48 (4)	550 (5)	0.78	0.56-1.08

CI = confidence interval; 5-ARI = 5α-reductase inhibitor; OR = odds ratio; PPI = proton pump inhibitor; ref = reference.
* Model adjusted for comorbidities; diabetic complications; marital status; and use of statins, PPIs, and 5-ARIs.
^ Model adjusted for comorbidities; diabetic complications; marital status; use of statins, PPIs, and 5-ARIs; and diabetics taking insulin, other medications, or no medication.

metformin exposure is associated with diabetes, which itself is known to reduce risk of PCa.

5. Conclusions

Metformin use was associated with decreased risk of PCa diagnosis in this population-based study. This finding may be due to decreased diagnostic intensity among asymptomatic men with diabetes. Given clinical and preclinical data suggesting benefit, a randomized trial of metformin for chemoprevention among diabetic patients would be informative.

Author contributions: Mark A. Preston had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data: Riis, Preston, Mucci, Batista.
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Administrative, technical, or material support: Sørensen.
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Other (specify): None.

Financial disclosures: Mark A. Preston certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: This study (management of the data) was supported by a grant from the Danish Cancer Society (R73-A4284–13-S17), the Karen Elise Jensen Foundation, and a grant from Aarhus University Research Foundation. The Department of Clinical Epidemiology is a member of the Danish Center for Strategic Research in Type 2 Diabetes (Danish Research Council, grant nos. 09–075724 and 10–079102).

Appendix A – Anatomical Therapeutic Chemical codes for the primary exposure drugs and potentially confounding drugs, codes for the cancer diagnoses, and International Classification of Diseases hospital diagnosis codes for potentially confounding diseases

Disease	ICD 8 code	ICD 10 code
Prostate cancer		C61
Diabetes	249; 250	E10–E14; H360; O24 except O244
Diabetes complications	377.00; 792.99; 410; 431; 433; 434; 436; 440.20; 440.28; 440.29; 440.99	G62.9; G63.2; H10.2; H33.4; H43.1; H45.0; I61; I63; I64; I70.2; I70.9; N08.3; N18; N19
Charlson Comorbidity Index diseases		
Myocardial infarction	410	I21; I22; I23
Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	430–438	I60–I69; G45; G46
Dementia	290.09–290.19; 293.09	F00–F03; F05.1; G30
Chronic pulmonary disease	490–493; 515–518	J40–J47; J60–J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09; M30; M31; M32; M33; M34; M35; M36; D86
Ulcer disease	530.91; 530.98; 531–534	K22.1; K25–K28
Mild liver disease	571; 573.01; 573.04	B18; K70.0–K70.3; K70.9; K71; K73; K74; K76.0
Diabetes	249.00; 249.06; 249.07; 249.09 250.00; 250.06; 250.07; 250.09	E10.0, E10.1; E10.9 E11.0; E11.1; E11.9
Hemiplegia	344	G81; G82
Moderate to severe renal disease	403; 404; 580–583; 584; 590.09; 593.19; 753.10–753.19; 792	I12; I13; N00–N05; N07; N11; N14; N17–N19; Q61
Diabetes with end organ damage	249.01–249.05; 249.08 250.01–250.05; 250.08	E10.2–E10.8 E11.2–E11.8
Any tumor	140–194	C00–C75
Leukemia	204–207	C91–C95
Lymphoma	200–203; 275.59	C81–C85; C88; C90; C96
Moderate to severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00–456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Metastatic solid tumor	195–198; 199	C76–C80
AIDS	079.83	B21–B24

Procedure	Procedure codes
Prostate biopsy	KKEB, KTKE00

Drug	ATC code
Diabetes overall	A10A; A10B
Insulin	
Fast acting	A10AA01; A10AB01; A10AB04; A10AB05
Intermediate acting	A10AA02; A10AC01
Intermediate, rapid onset	A10AA03; A10AD01; A10AD04; A10AD05
Other analogues, long acting	A10AE; A10AE04; A10AE05
Metformin	A10BA02; A10BD02; A10BD03; A10BD05
Other	Rest of the A10A and A10B codes
Statins	C10AA
Proton pump inhibitors	A02BC

ATC = Anatomical Therapeutic Chemical; ICD = International Classification of Diseases.

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