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Type 2 diabetes and the risk of mortality among patients with prostate cancer

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Abstract
Purpose The aim of this study was to determine whether type 2 diabetes is associated with the incidence of prostate cancer mortality and all-cause mortality.
Methods This study was conducted by linking four databases from the United Kingdom: the National Cancer Data Repository, the Clinical Practice Research Datalink, the Hospital Episodes Statistics database, and the Office for National Statistics database. The cohort consisted of men newly diagnosed with non-metastatic prostate cancer between 1 April 1998 and 31 December 2009, followed until 1 October 2012. Cox proportional hazard models were used to estimate adjusted hazard ratios with 95 % confidence intervals (CIs) of prostate cancer mortality and all-cause mortality comparing patients with to without type 2 diabetes. All models were adjusted for a number of potential confounders, which included excessive alcohol use, smoking, comorbidities, and prostate cancer-related variables.
Results The cohort consisted of 11,920 patients, which included 1,132 (9.5 %) with preexisting type 2 diabetes. During a mean follow-up of 4.7 (SD 3.0) years, there were 3,605 deaths (incidence rate: 6.4 %/year) including 1,792 from prostate cancer (incidence rate: 3.3 %/year). Type 2 diabetes was associated with a 23 % increased risk of prostate cancer mortality (HR 1.23, 95 % CI 1.04–1.46) and a 25 % increased risk in all-cause mortality (HR 1.25, 95 % CI 1.11–1.40).
Conclusions The results of this large population-based study indicate that type 2 diabetes is associated with an increased risk of prostate cancer mortality and all-cause mortality, which may signal an association between hyperinsulinemia or other diabetes-associated metabolic derangements and cancer aggressivity.

Keywords Type 2 diabetes · Prostate cancer · Mortality · Hazard ratios

Abbreviations

CPRD	Clinical Practice Research Datalink
HES	Hospital Episodes Statistics
ICD-10	International Classification Of Diseases, 10th revision
NSAIDs	Nonsteroidal anti-inflammatory drugs
ONS	Office of National Statistics
OPCS-4	Office of Population Censuses and Surveys classification of interventions and procedures, 4th version
PSA	Prostate-specific antigen
UK	United Kingdom

Introduction

Over the years, a number of observational studies have associated type 2 diabetes with an increased risk of several

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cancers [1], with the exception of prostate cancer where an inverse relationship has been reported [2]. This may be related to the fact that type 2 diabetes is associated with reduced circulating prostatic levels of androgens [3]. However, these studies contrast with those that have assessed the association between type 2 diabetes and prostate cancer outcomes [4–11], where type 2 diabetes was associated with increased risks of prostate cancer recurrence [4, 6], cancer-related mortality [7, 8], and all-cause mortality [9–11].

While the results of these observational studies have been relatively consistent [4–11], residual confounding is a concern given that patients with type 2 diabetes may have risk factors, such as obesity, smoking, and other comorbidities that may potentially confound the association with mortality. Furthermore, only one of the previous studies assessed the association between diabetes duration on mortality [7].

Thus, the primary objective of this population-based study was to determine whether type 2 diabetes is associated with the incidence of prostate cancer mortality in men newly diagnosed with prostate cancer. A secondary objective was to determine whether this condition is also associated with the incidence of all-cause mortality and to assess whether the risk varies with duration of type 2 diabetes.

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) (previously known as the General Practice Research Database), the Hospital Episode Statistics (HES) database, and the Office for National Statistics (ONS) database. These four databases were linked via patients' National Health Services number.

The NCDR includes information on the tumor site of primary growth [coded using the International Classification of Diseases, 10th revision (ICD-10)], as well as information on tumor characteristics (such as grade, stage, and primary treatments received). The CPRD is a general practice database comprising the medical records 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 [12]. General practitioners are trained to record medical information including demographic data, medical diagnoses, procedures, and deaths using a standardized form. The database records information on body mass index (BMI), smoking, and excessive alcohol use, and prescriptions issued by general practitioners are automatically transcribed into the computer record. Read codes are used to enter medical diagnoses and procedures, which is the standard clinical terminology system used in general practice in the UK [13], and a coded drug dictionary based on the UK Prescription Pricing Authority Dictionary is used for recording prescriptions. Data in the CPRD are regularly audited, and diagnoses and drug exposures recorded in the CPRD have been validated and shown to be of high quality [14–18].

The HES database contains details of all inpatient encounters in National Health Services hospitals in England since 1997. This database contains dates of hospital admissions, outpatient visits, 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 contains the electronic death certificates of all citizens living in England and Wales and 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 population

Using the NCDR, we identified all men diagnosed for the first time with prostate cancer (ICD-10: C61) between 1 April 1998 and 31 December 2009, with follow-up until 1 October 2012. We excluded patients with less than 1 year of 'up-to-standard' medical history in the CPRD prior to diagnosis, those with metastases at the time of diagnosis, patients previously diagnosed with type 1 diabetes, as well as those with less than 6 months of follow-up after the prostate cancer diagnosis. The latter was necessary to exclude those who died from prostate cancer soon after their cancer diagnosis, suggesting that they were already metastatic at the time of diagnosis.

Thus, cohort entry was set to the 6 months after the prostate cancer diagnosis, and patients were followed until one of the study outcomes [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 (1 October 2012), whichever came first.

Assessment of type 2 diabetes

For all patients included in the cohort, we determined whether they had preexisting type 2 diabetes. This was assessed by searching for either diagnoses of type 2 diabetes or prescriptions of anti-diabetic drugs (metformin, sulfonylureas, thiazolidinediones, insulins, and others) at any time prior to the prostate cancer diagnosis. Patients deemed to have type 2 diabetes were then categorized into tertiles, according to their duration of their disease prior to the prostate cancer diagnosis. This was calculated as the time between the earliest indication of type 2 diabetes (first-ever recorded diagnosis of type 2 diabetes or a prescription of an anti-diabetic drug) and the prostate cancer diagnosis.

Statistical analysis

Descriptive statistics were used to describe the baseline characteristics of patients with and without preexisting type 2 diabetes. Kaplan–Meier curves were constructed comparing the cumulative incidence of prostate cancer mortality between patients with and without preexisting type 2 diabetes. Cox proportional hazard models were used to estimate hazard ratios (HRs) with 95 % confidence intervals (CIs) of the mortality outcomes (prostate cancer mortality and all-cause mortality), comparing patients with to without preexisting type 2 diabetes. In a first model, we assessed whether type 2 diabetes was associated with the incidence of prostate cancer mortality, which was considered the primary outcome. Patients who died from other causes were censored in this analysis. In a secondary model, we determined whether type 2 diabetes was associated with the incidence of all-cause mortality. For both outcomes, we also assessed whether the risk varied with duration of type 2 diabetes, which was entered in tertile categories in the models.

All the models were adjusted for the following potential confounders measured prior to the prostate cancer diagnosis: age, year of cohort entry, ethnicity (white, black, other, and unknown), excessive alcohol use (based on alcohol-related disorders such as alcoholism, alcoholic cirrhosis of the liver, and alcoholic hepatitis and failure), smoking status (ever, never), BMI ($\leq$25, 25–30, $\geq$30 kg/m^2), comorbidities (chronic kidney disease, myocardial infarction, ischemic stroke, transient ischemic attack, and peripheral artery disease), previous cancer (other than non-melanoma skin cancer), and ever use of antihypertensive drugs (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers, diuretics, and other antihypertensive drugs), aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), statins, 5-alpha reductase inhibitors, and prostate cancer-related variables [prostate-specific antigen (PSA) levels last measurement prior to the prostate cancer diagnosis, Gleason score, radical prostatectomy, radiation therapy, chemotherapy, and androgen-deprivation therapy, all measured in the 6 months between the prostate cancer diagnosis and cohort entry]. Tumor stage was not included as a covariate since it was missing for over 90 % of the patients. For variables with missing data (such as smoking, BMI, and PSA), an 'unknown' category was created and analyzed as such in the models. For all models, we verified the proportional hazards assumption for each variable using Schoenfeld residuals [19] and found no violations.

Sensitivity and secondary analyses

To account for the possibility that some patients in the non-diabetes group may have developed type 2 diabetes during follow-up, which would have the effect of diluting the HRs, we conducted a sensitivity analysis censoring such patients at the time of a first diagnosis of type 2 diabetes or prescription of an anti-diabetic agent occurring during follow-up.

We conducted four additional secondary analyses. In the first, we assessed the association between type 2 diabetes and non-prostate cancer mortality. In the second and third analyses, we assessed whether obesity (BMI $\geq$ 30 kg/m^2) and age (<60, 60–75, $\geq$75 years) were effect modifiers of the association between type 2 diabetes and the primary outcome of prostate cancer mortality. Finally, in the fourth analysis, we determined whether tumor grade was an effect modifier of the association between type 2 diabetes and the mortality outcomes. For this analysis, tumor grade was categorized as low grade (Gleason scores 2–6) versus high grade (Gleason scores 7–10) and was restricted to patients with available Gleason score information. Effect modification for obesity, age, and tumor grade was assessed by including interaction terms between these variables and the type 2 diabetes indicator variable in the models. All analyses were conducted with SAS version 9.3 (SAS Institute, Cary, NC).

Results

A total of 11,920 men newly diagnosed with non-metastatic prostate cancer were included in the study (Fig. 1), which included 1,132 (9.5 %) with preexisting type 2 diabetes. During a mean follow-up of 4.7 [standard deviation (SD): 3.0] years, there were 3,605 deaths (incidence rate: 6.4 % per year) including 1,792 from prostate cancer (incidence rate: 3.3 % per year).

Table 1 presents the characteristics of patients with and without preexisting type 2 diabetes. Compared to patients without type 2 diabetes, those with the condition were more likely to have used alcohol excessively, to have been

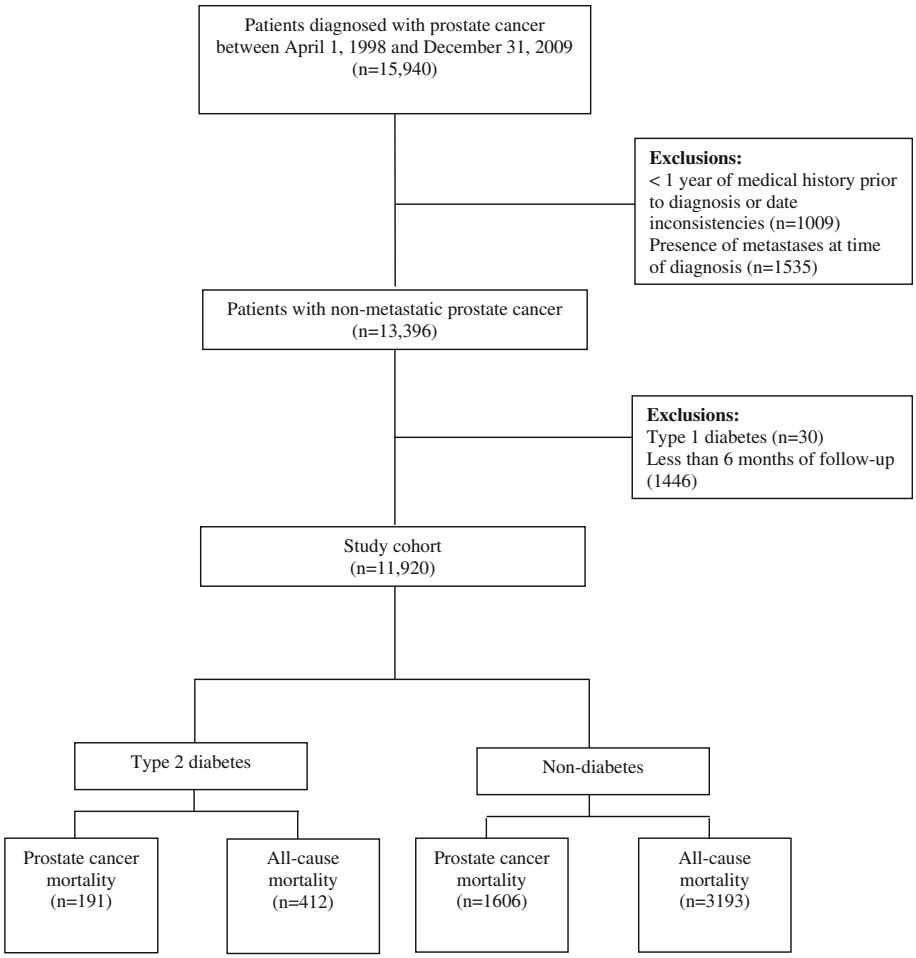

Fig. 1 Study flow chart

smokers, obese, had a higher prevalence of comorbidities, higher Gleason scores, higher baseline PSA levels, and were more likely to have used antihypertensives, aspirin, other NSAIDs, and statins prior to their prostate cancer diagnosis.

Figure 2 presents the Kaplan–Meier curves for prostate cancer mortality of patients with and without preexisting type 2 diabetes. Patients with preexisting type 2 diabetes had a lower 10-year survival than patients without type 2 diabetes (68.2 vs. 73.6 %, respectively).

The results for the primary outcome are presented in Table 2. The prostate cancer mortality incidence rate among patients with type 2 diabetes was 4.2 % (95 % CI 3.7–4.9) per year, compared to 3.1 % (95 % CI 3.0–3.3) per year in patients without the condition. In multivariate analyses, type 2 diabetes was associated with an increased risk of prostate cancer mortality (adjusted HR 1.23, 95 % CI 1.04–1.46). In a secondary model, the risk of prostate cancer mortality increased in the first two tertile duration categories (<2.95 years, HR 1.24, 95 % CI 0.97–1.59; 2.95–7.90 years, HR 1.48, 95 % CI 1.15–1.92) and then declined toward the null at the last tertile category (HR 0.97, 95 % CI 0.72–1.31) (Table 2).

Table 3 presents the results of the secondary outcome. The all-cause mortality incidence rate among patients with type 2 diabetes was higher than in patients without the condition (9.1 %, 95 % CI 8.3–1.01 vs. 6.2 %, 95 % CI 6.4, respectively). In multivariate analyses, type 2 diabetes was associated with an increased risk of all-cause mortality (adjusted HR 1.25, 95 % CI 1.11–1.40). In terms of duration of type 2 diabetes, a similar pattern was observed as with prostate cancer mortality, with the risk increasing in the first two tertile categories, and then decreasing in the third category (Table 3).

Sensitivity and secondary analyses

A total of 54 (0.005 %) patients in the non-diabetes group developed type 2 diabetes during follow-up. Censoring these patients at the time of their diagnosis did not materially affect the HR for prostate cancer mortality (Appendix Table 4). In secondary analyses, type 2 diabetes was associated with an increased risk of non-prostate cancer mortality, which progressively increased with longer durations of type 2 diabetes (Appendix Table 5). Obesity and age were not found to be effect modifiers of the

Table 1 Baseline characteristics of patients with and without type 2 diabetes

Characteristics	Preexisting type 2 diabetes	
	Present (n = 1,132)	Absent (n = 10,788)
Age, *n* (%)	73.4 (7.9)	71.3 (9.0)
Ethnicity, *n* (%)		
White	959 (84.7)	9,528 (88.3)
Black	36 (3.2)	99 (0.9)
Other	31 (2.7)	107 (1.0)
Unknown	106 (9.4)	1,054 (9.8)
Excessive alcohol use, *n* (%)	141 (12.5)	741 (6.9)
Smoking status, *n* (%)		
Never	332 (29.3)	4,403 (40.8)
Ever	773 (68.3)	5,789 (53.7)
Unknown	27 (2.4)	596 (5.5)
Body mass index, *n* (%)		
≤25 kg/m^2	255 (22.5)	3,608 (33.4)
25–30 kg/m^2	544 (48.1)	4,672 (43.3)
≥30 kg/m^2	321 (28.4)	1,669 (15.5)
Unknown	12 (1.1)	839 (7.8)
Comorbidities, *n* (%)		
Chronic kidney disease	173 (15.3)	651 (6.0)
Myocardial infarction	160 (14.1)	865 (8.0)
Ischemic stroke	78 (6.9)	427 (4.0)
Transient ischemic attack	79 (6.8)	531 (4.9)
Peripheral artery disease	742 (65.6)	1,146 (10.6)
Previous cancer, *n* (%)	191 (16.9)	1,690 (15.7)
Angiotensin-converting enzyme inhibitors, *n* (%)	669 (59.1)	2,658 (24.6)
Angiotensin receptor blockers, *n* (%)	200 (17.7)	760 (7.0)
Calcium channel blocker, *n* (%)	509 (45.0)	2,857 (26.5)
Beta-blockers, *n* (%)	492 (43.5)	2,759 (25.6)
Diuretics, *n* (%)	593 (52.4)	3,665 (34.0)
Other antihypertensive, *n* (%)	26 (2.2)	94 (0.9)
Aspirin, *n* (%)	719 (63.5)	3,524 (32.7)
Other nonsteroidal anti-inflammatory drugs, *n* (%)	608 (52.4)	5,291 (49.1)
Statins, *n* (%)	702 (62.0)	2,722 (25.2)
5-alpha reductase inhibitors, *n* (%)	104 (9.2)	706 (6.5)
Prostate cancer-related variables		
Prostate-specific antigen, *n* (%)		
<4 ng/mL	84 (7.4)	609 (5.7)
4–10 ng/mL	228 (20.1)	2,811 (26.1)
>10 ng/mL	505 (44.6)	4,390 (40.7)
Unknown	315 (27.8)	2,978 (27.6)
Gleason score, *n* (%)		
2–6	266 (23.5)	2,688 (24.9)
7	222 (19.6)	2,022 (18.7)
≥8	156 (13.8)	1,214 (11.3)
Unknown	488 (43.1)	4,864 (45.1)
Radical prostatectomy	553 (48.9)	5,458 (50.6)
Radiation therapy	185 (16.3)	1,955 (18.1)
Chemotherapy	43 (3.8)	374 (3.5)
Androgen-deprivation therapy	616 (54.4)	5,518 (51.2)

association between type 2 diabetes and prostate cancer mortality (Appendix Tables 6, 7). Finally, the HRs for prostate cancer mortality and all-cause mortality were the elevated risk in patients with low-grade tumors (Gleason scores 2–6), although the HRs were not statistically different from patients with high-grade tumors (Gleason score 7–10) (Appendix Table 8).

Discussion

The results of this population-based study indicate that type 2 diabetes is associated with an increased risk of cancer-related mortality and all-cause mortality among patients with prostate cancer. Our findings of an association of type 2 diabetes with more aggressive behavior of prostate cancer are of particular interest in the context of the previously reported inverse association between type 2 diabetes and prostate cancer incidence [20]. While the biological basis of the contrasting associations of type 2 diabetes on prostate cancer incidence and prognosis remain unclear, it is possible that the incidence effect is driven dominantly by the relatively low androgen levels in diabetics compared with non-diabetics, while the prognosis effect may be driven by the proposed stimulatory effects of hyperinsulinemia on prostate cancer behavior [21–23]. This would be consistent with the view that hyperinsulinemia and/or other metabolic effects of diabetes are not carcinogenic, but rather encourage progression of preexisting cancers [24]. It is also possible that behavioral factors, such as compliance with prostate cancer treatments, may have played a role, although patients with and without diabetes had similar rates of radical prostatectomy, radiation therapy, and use of androgen-deprivation therapy.

Although the previous observational studies suggest an increased risk of adverse prostate cancer outcomes among patients with type 2 diabetes [4–11], only three studies assessed the association between type 2 diabetes and prostate cancer mortality [5, 7, 8]. In the first study [5], type 2 diabetes was not associated with an increased risk of prostate cancer mortality (HR 1.28, 95 % CI 0.54–3.03). However, that study was likely underpowered, with only

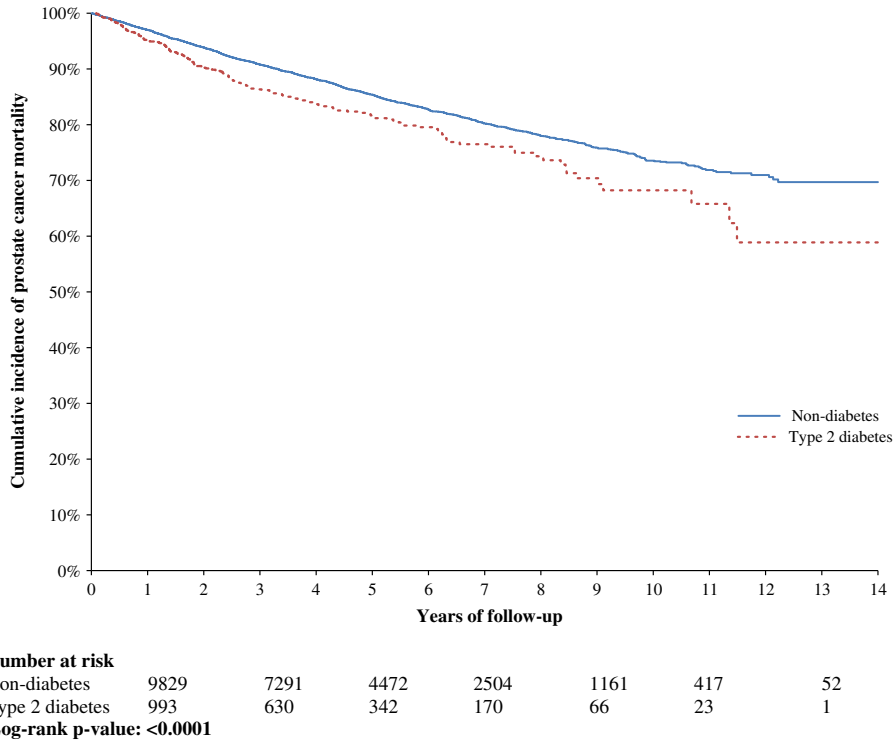

Fig. 2 Kaplan–Meier curves for prostate cancer mortality comparing patients with and without preexisting type 2 diabetes

Table 2 Crude and adjusted hazard ratios for the association between type 2 diabetes and prostate cancer mortality

Preexisting type 2 diabetes	Patients	Cases	Person-years	Rate/100 per year (95 % CI)	Crude HR	Adjusted HR (95 % CI; *p* value)[a]
Absent	10,788	1,606	51,705	3.1 (3.0–3.3)	1.00	1.00 (reference)
Present	1,132	191	4,506	4.2 (3.7–4.9)	1.35	1.23 (1.04–1.46; 0.02)
Duration of type 2 diabetes[b]						
<2.95 years	377	70	1,671	4.2 (3.3–5.3)	1.34	1.24 (0.97–1.59; 0.08)
2.95–7.90 years	379	70	1,492	4.7 (3.7–5.9)	1.50	1.48 (1.15–1.91; 0.003)
≥7.90 years	376	51	1,343	3.8 (2.9–5.0)	1.21	0.97 (0.72–1.31; 0.85)

CI confidence interval, *HR* hazard ratio

[a] Adjusted for age, year of cohort entry, ethnicity, excessive alcohol use, body mass index, smoking status, chronic kidney disease, myocardial infarction, ischemic stroke, transient ischemic attack, peripheral artery disease, previous cancer, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers, diuretics, other antihypertensive drugs, aspirin, other nonsteroidal anti-inflammatory drugs, statins, 5-alpha reductase inhibitors, and the following prostate cancer-related variables: prostate-specific antigen levels, Gleason score, radical prostatectomy, radiation therapy, chemotherapy, and androgen-deprivation therapy

[b] Based on tertile categories

six prostate cancer mortality cases occurring in patients with preexisting type 2 diabetes. We note that the HR is similar in magnitude to the one estimated in this study. In the second study, type 2 diabetes was associated with a statistically significant increased risk of prostate cancer mortality (HR 1.38, 95 % CI 1.35–1.41), though that study was limited to patients hospitalized for type 2 diabetes, thus limiting the generalizability of the results [8]. Finally, in the third study [7], the age-standardized mortality rate ratio was 1.55 (95 % CI 1.29–1.80), 2.60 (95 % CI 2.29–3.13), and 6.84 (95 % CI 5.34–8.70) for ages ≥75, 65–74, and 40–64 years, respectively. However, this analysis did not adjust for potentially important confounders, and thus, the use of mortality rate ratios can lead to biased estimates of the true risk [25].

With respect to the secondary outcome, previous studies have generally associated type 2 diabetes with an increased risk in all-cause mortality [9–11], although there were differences in the reported magnitude of the effects, ranging from no mortality cases in patients with the type 2 diabetes in one study [9], and modest increased risks in the other two studies [10, 11]. Such discrepancies can be due to certain

Table 3 Crude and adjusted hazard ratios for the association between type 2 diabetes and all-cause mortality

Preexisting type 2 diabetes	Patients	Cases	Person-years	Rate/100 per year (95 % CI)	Crude HR	Adjusted HR (95 % CI; *p* value)[a]
Absent	10,788	3,193	51,705	6.2 (6.0–6.4)	1.00	1.00 (reference)
Present	1,132	412	4,506	9.1 (8.3–10.1)	1.49	1.25 (1.11–1.40; <0.001)
Duration of type 2 diabetes (years)[b]						
<2.95	377	127	1,671	7.6 (6.4–9.0)	1.24	1.10 (0.91–1.32; 0.32)
2.95–7.90	379	147	1,492	9.9 (8.4–11.6)	1.61	1.41 (1.18–1.69; <0.001)
≥7.90	376	138	1,343	10.3 (8.7–12.1)	1.69	1.27 (1.05–1.53; 0.01)

CI confidence interval, *HR* hazard ratio

[a] Adjusted for age, year of cohort entry, ethnicity, excessive alcohol use, body mass index, smoking status, chronic kidney disease, myocardial infarction, ischemic stroke, transient ischemic attack, peripheral artery disease, previous cancer, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers, diuretics, other antihypertensive drugs, aspirin, other nonsteroidal anti-inflammatory drugs, statins, 5-alpha reductase inhibitors and the following prostate cancer-related variables: prostate-specific antigen levels, Gleason score, radical prostatectomy, radiation therapy, chemotherapy, and androgen-deprivation therapy

[b] Based on tertile categories

methodological limitations, such as relying on patient self-report, and no exclusion of patients with type 1 diabetes.

Type 2 diabetes duration is an important variable that was not assessed in the majority of the previous observational studies [4–6, 8–11]. For this reason, we conducted a secondary analysis assessing the association between type 2 diabetes duration on the risk of prostate cancer outcomes. For both prostate cancer mortality and all-cause mortality, the risk was generally higher in the first two tertiles of type 2 diabetes duration, which declined closer to the null in the third category. This surprising finding is likely due to competing risks [26], a situation where patients with longstanding type 2 diabetes may have been more likely to die early from non-cancer causes, mainly cardiovascular in nature. Supporting this hypothesis is a secondary analysis assessing the association between type 2 diabetes and non-prostate cancer death, where the risk gradually increased with longer durations of type 2 diabetes.

This study has several strengths. Selection bias was eliminated by conducting analyses within a large population-based representative cohort of patients with both type 2 diabetes and prostate cancer followed for up to 14 years. We also excluded patients with type 1 diabetes, minimizing possible misclassifications related to the ascertainment of patients with type 2 diabetes. Furthermore, we assessed the relationship between the duration of type 2 diabetes and the mortality outcomes, which could have important clinical implications. Information on exposure and confounders is prospectively collected in the CPRD, eliminating the likelihood of recall bias. Finally, by linking four electronic databases from the UK, we were able to obtain patient medical histories (including diagnoses and treatments), lifestyle measurements (smoking, excessive alcohol use, and BMI), and cancer-related variables (Gleason scores, PSA levels, and prostate cancer-related treatments). As such, we were able to adjust the models for a number of important potential confounders.

This study has some limitations. We were not able to adjust for tumor stage because it was missing for the vast majority of patients. However, the models were adjusted prostate cancer-related treatments, which are likely highly correlated with tumor grade and stage. Furthermore, as with any observational study, residual confounding needs to be considered. The CPRD does not collect information on diet and physical activity, which may have been associated with the mortality outcomes. However, we adjusted the models for several important potential confounders that include smoking, BMI, and excessive alcohol use, which are likely good surrogates of these unmeasured potential confounders. Lastly, misclassification of our primary outcome of prostate cancer is a possibility. However, contrary to other cancers, prostate cancer mortality has been reported to be well recorded in deaths certificates [27].

In summary, type 2 diabetes was associated with an increased risk of prostate cancer mortality and all-cause mortality. Additional well-conducted observational studies are needed to replicate these findings. If confirmed, these findings should raise clinician awareness that patients with prevalent type 2 diabetes may have worse prognosis and may thus require more aggressive prostate cancer and diabetes treatment regimens.

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Conflict of interest The authors declare that they have no conflicts of interest.

Appendix

See Tables 4, 5, 6, 7, and 8.

Table 4 Sensitivity analysis: type 2 diabetes and prostate cancer mortality censoring patients who developed type 2 diabetes in the non-diabetes group during follow-up

Preexisting type 2 diabetes	Patients	Cases	Person-years	Rate/100 per year (95 % CI)	Crude HR	Adjusted HR (95 % CI; *p* value)[a]
Absent	10,734	1,601	49,790	3.2 (3.1–3.4)	1.00	1.00 (reference)
Present	1,132	191	4,343	4.4 (3.8–5.1)	1.35	1.22 (1.03–1.45; 0.02)

CI confidence interval, *HR* hazard ratio

[a] Adjusted for age, year of cohort entry, ethnicity, excessive alcohol use, body mass index, smoking status, chronic kidney disease, myocardial infarction, ischemic stroke, transient ischemic attack, peripheral artery disease, previous cancer, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers, diuretics, other antihypertensive drugs, aspirin, other nonsteroidal anti-inflammatory drugs, statins, 5-alpha reductase inhibitors and the following prostate cancer-related variables: prostate-specific antigen levels, Gleason score, radical prostatectomy, radiation therapy, chemotherapy, and androgen-deprivation therapy

Table 5 Type 2 diabetes and the risk of non-prostate cancer mortality

Preexisting type 2 diabetes	Patients	Cases	Person-years	Rate/100 per year (95 % CI)	Crude HR	Adjusted HR (95 % CI; *p* value)[a]
Absent	10,788	1,587	51,705	3.1 (2.9–3.2)	1.00	1.00 (reference)
Present	1,132	221	4,506	4.9 (4.3–5.8)	1.64	1.26 (1.07–1.47; 0.005)
Duration of type 2 diabetes (years)[b]						
<2.95	377	57	1,671	3.4 (2.6–4.4)	1.13	0.96 (0.73–1.25; 0.75)
2.95–7.90	379	77	1,492	5.2 (4.1–6.4)	1.72	1.33 (1.04–1.69; 0.02)
≥7.90	376	87	1,343	6.5 (5.2–8.0)	2.21	1.56 (1.23–1.98; <0.001)

CI confidence interval, *HR* hazard ratio

[a] Adjusted for age, year of cohort entry, ethnicity, excessive alcohol use, body mass index, smoking status, chronic kidney disease, myocardial infarction, ischemic stroke, transient ischemic attack, peripheral artery disease, previous cancer, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers, diuretics, other antihypertensive drugs, aspirin, other nonsteroidal anti-inflammatory drugs, statins, 5-alpha reductase inhibitors and the following prostate cancer-related variables: prostate-specific antigen levels, Gleason score, radical prostatectomy, radiation therapy, chemotherapy, and androgen-deprivation therapy

[b] Based on tertile categories

Table 6 Effect measure modification by body mass index on the association between type 2 diabetes and mortality outcomes

Outcome	BMI < 30 (kg/m^2) Adjusted HR (95 % CI)[a]	BMI ≥ 30 (kg/m^2) Adjusted HR (95 % CI)[a]	*p* value for interaction
Prostate cancer mortality	1.14 (1.38–1.79)	1.26 (1.75–1.86)	0.61
All-cause mortality	1.18 (1.03–1.34)	1.20 (0.96–1.50)	0.86

The analysis was restricted to patients with available body mass index information ($n = 11{,}069$)

CI confidence interval, *HR* hazard ratio

[a] Adjusted for age, year of cohort entry, ethnicity, excessive alcohol use, smoking status, chronic kidney disease, myocardial infarction, ischemic stroke, transient ischemic attack, peripheral artery disease, previous cancer, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers, diuretics, other antihypertensive drugs, aspirin, other nonsteroidal anti-inflammatory drugs, statins, 5-alpha reductase inhibitors and the following prostate cancer-related variables: prostate-specific antigen levels, Gleason score, radical prostatectomy, radiation therapy, chemotherapy, and androgen-deprivation therapy

Table 7 Effect measure modification by age on the association between type 2 diabetes and mortality

Outcome	<60 years Adjusted RR (95 % CI)[a]	60–75 years Adjusted RR (95 % CI)[a]	≥75 years Adjusted RR (95 % CI)[a]	*p* value for interaction
Prostate cancer mortality	1.70 (0.69–4.22)	1.15 (0.88–1.51)	1.27 (1.03–1.56)	0.65
All-cause mortality	1.52 (0.71–3.27)	1.29 (1.08–1.55)	1.23 (1.06–1.41)	0.79

CI confidence interval, *HR* hazard ratio

[a] Adjusted for ethnicity, year of cohort entry, excessive alcohol use, smoking status, body mass index, chronic kidney disease, myocardial infarction, ischemic stroke, transient ischemic attack, peripheral artery disease, previous cancer, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers, diuretics, other antihypertensive drugs, aspirin, other nonsteroidal anti-inflammatory drugs, statins, 5-alpha reductase inhibitors and the following prostate cancer-related variables: prostate-specific antigen levels, Gleason score, radical prostatectomy, radiation therapy, chemotherapy, and androgen-deprivation therapy

Table 8 Effect measure modification by Gleason score on the association between type 2 diabetes and mortality outcomes

Outcome	Gleason scores 2–6 Adjusted HR (95 % CI)[a]	Gleason scores 7–10 Adjusted HR (95 % CI)[a]	*p* value for interaction
Prostate cancer mortality	1.62 (1.00–2.63)	1.18 (0.89–1.58)	0.25
All-cause mortality	1.44 (1.10–1.89)	1.12 (0.91–1.36)	0.11

The analysis was restricted to patients with available Gleason score information ($n = 6{,}568$)

[a] Adjusted for age, year of cohort entry, ethnicity, excessive alcohol use, smoking status, chronic kidney disease, myocardial infarction, ischemic stroke, transient ischemic attack, peripheral artery disease, previous cancer, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers, diuretics, other antihypertensive drugs, aspirin, other nonsteroidal anti-inflammatory drugs, statins, 5-alpha reductase inhibitors and the following prostate cancer-related variables: prostate-specific antigen levels, radical prostatectomy, radiation therapy, chemotherapy, and androgen-deprivation therapy

References

1. Chowdhury TA (2010) Diabetes and cancer. QJM 103(12): 905–915
2. Kasper JS, Liu Y, Giovannucci E (2009) Diabetes mellitus and risk of prostate cancer in the health professionals follow-up study. Int J Cancer 124(6):1398–1403
3. Yeap BB, Alfonso H, Chubb SA et al (2012) Reference ranges and determinants of testosterone, dihydrotestosterone, and estradiol levels measured using liquid chromatography-tandem mass spectrometry in a population-based cohort of older men. J Clin Endocrinol Metab 97(11):4030–4039
4. Chan JM, Latini DM, Cowan J, DuChane J, Carroll PR (2005) History of diabetes, clinical features of prostate cancer, and prostate cancer recurrence-data from CaPSURE (United States). Cancer Causes Control 16(7):789–797
5. D'Amico AV, Braccioforte MH, Moran BJ, Chen MH (2010) Causes of death in men with prevalent diabetes and newly diagnosed high- versus favorable-risk prostate cancer. Int J Radiat Oncol Biol Phys 77(5):1329–1337
6. Patel T, Hruby G, Badani K, Abate-Shen C, McKiernan JM (2010) Clinical outcomes after radical prostatectomy in diabetic patients treated with metformin. Urology 76(5):1240–1244
7. Tseng CH (2011) Prostate cancer mortality in Taiwanese men: increasing age-standardized trend in general population and increased risk in diabetic men. Ann Med 43(2):142–150
8. Liu X, Ji J, Sundquist K, Sundquist J, Hemminki K (2012) The impact of type 2 diabetes mellitus on cancer-specific survival: a follow-up study in Sweden. Cancer 118(5):1353–1361
9. Shetti MB, Merrick GS, Butler WM et al (2012) The impact of diabetes mellitus on survival in men with clinically localized prostate cancer treated with permanent interstitial brachytherapy. Am J Clin Oncol 35(6):572–579
10. Yeh HC, Platz EA, Wang NY, Visvanathan K, Helzlsouer KJ, Brancati FL (2012) A prospective study of the associations between treated diabetes and cancer outcomes. Diabetes Care 35(1):113–118
11. Currie CJ, Poole CD, Jenkins-Jones S, Gale EA, Johnson JA, Morgan CL (2012) Mortality after incident cancer in people with and without type 2 diabetes: impact of metformin on survival. Diabetes Care 35(2):299–304
12. Garcia Rodriguez LA, Perez GS (1998) Use of the UK General Practice Research Database for pharmacoepidemiology. Br J Clin Pharmacol 45(5):419–425
13. Read codes. United Kingdom National Health Service. http://www.connectingforhealth.nhs.uk/systemsandservices/data/uktc/readcodes. Accessed 30 Dec 2013
14. Jick H, Jick SS, Derby LE (1991) Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. BMJ 302(6779):766–768
15. Lawrenson R, Williams T, Farmer R (1999) Clinical information for research; the use of general practice databases. J Public Health Med 21(3):299–304
16. Lawrenson R, Todd JC, Leydon GM, Williams TJ, Farmer RD (2000) Validation of the diagnosis of venous thromboembolism in general practice database studies. Br J Clin Pharmacol 49(6): 591–596
17. Jick SS, Kaye JA, Vasilakis-Scaramozza C et al (2003) Validity of the general practice research database. Pharmacotherapy 23(5): 686–689
18. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ (2010) Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol 69(1):4–14
19. Grambsch P, Therneau T (1994) Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 81(3): 515–526
20. Bansal D, Bhansali A, Kapil G, Undela K, Tiwari P (2013) Type 2 diabetes and risk of prostate cancer: a meta-analysis of observational studies. Prostate Cancer Prostatic Dis 16(2):151–158 S1

21. Venkateswaran V, Haddad AQ, Fleshner NE et al (2007) Association of diet-induced hyperinsulinemia with accelerated growth of prostate cancer (LNCaP) xenografts. J Natl Cancer Inst 99(23): 1793–1800
22. Ma J, Li H, Giovannucci E et al (2008) Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. Lancet Oncol 9(11):1039–1047
23. Lubik AA, Gunter JH, Hendy SC et al (2011) Insulin increases de novo steroidogenesis in prostate cancer cells. Cancer Res 71(17): 5754–5764
24. Pollak M (2012) The insulin and insulin-like growth factor receptor family in neoplasia: an update. Nat Rev Cancer 12(3): 159–169
25. Jones ME, Swerdlow AJ (1998) Bias in the standardized mortality ratio when using general population rates to estimate expected number of deaths. Am J Epidemiol 148(10):1012–1017
26. Schatzkin A, Slud E (1989) Competing risks bias arising from an omitted risk factor. Am J Epidemiol 129(4):850–856
27. Albertsen PC, Walters S, Hanley JA (2000) A comparison of cause of death determination in men previously diagnosed with prostate cancer who died in 1985 or 1995. J Urol 163(2):519–523