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Research Article

Diabetes Mellitus and Prostate Cancer Risk; A Nationwide Case–Control Study within PCBaSe Sweden

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Abstract

Background: Diabetes mellitus (DM) increases the risk for cancer at almost all sites, but data on the association with prostate cancer are inconsistent.

Methods: We assessed the risk of a prostate cancer diagnosis among men with type 2 (T2)DM in a nationwide population-based case-control study including 44,352 men with prostate cancer identified through the Prostate Cancer data Base Sweden (PCBaSe) between 2002 and 2006 and 221,495 age-matched men from the general population.

Results: Overall, the risk of prostate cancer among men with T2DM was lower than among men without T2DM [OR, 0.80; 95% confidence interval (CI), 0.76–0.85]. The risk decreased with longer disease duration and was observed across all tumor risk categories, although most clearly among men with low risk tumors (OR, 0.71; 95% CI, 0.64–0.80). The risk for prostate cancer was reduced among diabetic men on dietary treatment only (OR, 0.89; 95% CI, 0.80–0.99) but more markedly among men on oral hypoglycemic agents (OR, 0.80; 95% CI, 0.74–0.87) and insulin (OR, 0.72; 95% CI, 0.69–0.81). Obese diabetic men (BMI > 30 kg/m$^{2)}$ showed a reduced risk (OR, 0.72; 95% CI, 0.65–0.80) compared with men without diabetes. There was a trend of decreasing risk with increasing levels of HbA1c ($P < 0.05$).

Conclusions: This nationwide study confirmed a reduced risk of being diagnosed with prostate cancer among men with T2DM, especially for low-risk tumors. An altered hormonal milieu is a plausible explanation, although the possibility of decreased prostate cancer detection among diabetic men cannot be ruled out.

Impact: This is the largest study to examine the association between T2DM and prostate cancer accounting for tumor risk group and diabetes treatment. *Cancer Epidemiol Biomarkers Prev; 22(6); 1102–9. ©2013 AACR.*

Introduction

Insulin resistance and hyperinsulinemia have been associated with an increased risk of malignancies (1, 2) including prostate cancer in some (3, 4) but not all studies (5). In line with these findings, type 2 diabetes mellitus (T2DM) increases the risk of a range of malignancies (6–8). In contrast, a growing body of evidence supports a reduced risk for a diagnosis of prostate cancer among men with T2DM; 2 meta-analyses totally including 22,000 prostate cancer cases (9, 10), as well as a number of smaller studies have reported a modest risk reduction among men with diabetes mellitus (11–15). Still, no large-scale population-based study has comprehensively evaluated the potential link between T2DM, related treatments, and prostate cancer occurrence.

This study examines the risk of prostate cancer, overall, and for prostate cancer risk categories among men with T2DM carefully characterized regarding glucose-lowering therapy, duration of disease, body mass index (BMI), and circulating levels of glycated hemoglobine (HbA1c). We have used detailed data from the Prostate Cancer data Base Sweden (PCBaSe) including more than 40,000 cases from the Swedish National Prostate Cancer Register (NPCR) in combination with prospectively collected exposure information from the Swedish National Diabetes Register (NDR).

Material and Methods

Study participants

We identified 44,352 men diagnosed with prostate cancer between 2002 and 2006 in the PCBaSe which is based on the NPCR, a population-based register that is nationwide since 1998 (16). Reporting to the NPCR exceeds the 96% coverage of the Swedish Cancer Register, to which registration is mandatory by law. Individual data on tumor characteristics and prostate-specific antigen (PSA; at diagnosis) were obtained from NPCR. For each

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prostate cancer case in PCBaSe, 5 population-based prostate cancer–free male controls were randomly selected from the continuously updated population register, matched on calendar time, age, and county of residence ($N = 221,495$). All Swedish citizens are assigned a personal identity number (PIN), a unique identifier that allows record linkage across the Swedish Health Care Registers (17). By use of the PIN, we obtained data on vital status, comorbiditiy, and socioeconomic factors for men in NPCR and their matched controls from The Inpatient Register, the Population Register, and the National Longitudinal Integrated Database from Statistics Sweden, as previously described (18).

Exposure information

Exposure information was obtained from the NDR, a register initiated in 1996 that currently covers 86% of all incident cases of diabetes mellitus. We retrieved data on type of diabetes mellitus, date of diagnosis, duration of diabetes, pharmacologic treatment, BMI, HbA1c, and microalbuminuria (19). The definition of T2DM was treatment with diet only, oral hypoglycemic agents only, or onset age of diabetes ≥40 years and insulin only or combined with oral agents. We disregarded exposure information from later than 1 year before the date of prostate cancer diagnosis to minimize potential influence of impending prostate cancer. HbA1c analyses were quality assured nationwide by regular calibration with the HPLC Mono-S method. In this study, all HbA1c values were converted to the DCCT standard values using the formula: HbA1c (DCCT) = 0.923 × HbA_{1c} (Mono-S) + 1.345; $R^2 = 0.998$ (20). Microalbuminuria was defined as urine albumin excretion 20 to 200 μg/min in 2 of 3 consecutive tests.

Statistical analysis

Logistic regression, conditioned on age, year, and county of residency at date of diagnosis, was used to estimate ORs and 95% confidence intervals (CI) for prostate cancer risk. Models were adjusted for socioeconomic status (SES; high, low, and not gainfully employed), civil status (married, widower, divorced, not married), comorbidity (CCI; 0, 1, 2, 3+), age at prostate cancer diagnosis (<65, 65–69, 70–74, 75–79, 80–84, 85+ years), and recorded diabetes prevalence in the county of residence (levels, <0.1%, 0.1%–1%, 1%–2%, 2%+). To explore the potential influence of factors related to T2DM, we conducted stratified analyses where the diabetic men were grouped according to type and duration of T2DM, pharmacologic treatment, BMI, HbA1c, creatinine, and microalbuminuria.

In NPCR, men with prostate cancer are categorized into 5 risk categories according to a modified version of the National Comprehensive Cancer Network (NCCN) guidelines. Risk categories are defined as: low-risk = clinical local stage T1,T2 tumor, PSA < 10 ng/mL and Gleason score < 6; intermediate-risk = T1, T2, and PSA 10–<20 ng/mL or Gleason score 7; high-risk = T3 tumor or PSA 20–<50 ng/mL or Gleason score > 8; regional metastases = T4 or N1 or PSA 50–100 ng/mL; and distant metastases = M1 or PSA > 100 ng/mL. In the present analysis, the groups of high risk, regionally metastatic, and distant metastatic disease were merged into one group.

The study protocol was approved by the Central Research Ethics Board (DNR: Ö 14-2007).

Results

The mean age at diabetes mellitus onset among cases was 60.3 (SD = 13.2) and among controls 62.2 (SD = 12.4; Table 1). A slightly higher proportion of men with prostate cancer were married and belonged to a higher socioeconomic category than among the controls. The groups did not differ with regard to comorbidity score.

Among the total of 44,410 men with prostate cancer, 1,539 had a previous diagnosis of diabetes mellitus (3.5%; Table 2). Mean age at prostate cancer diagnosis was 72.4 years among men with T2DM and 70.2 years in men without T2DM (Table 2). Prostate cancer cases with T2DM tended to have a more adverse risk profile at the date of diagnosis than cases without T2DM; there was a higher proportion of cases with advanced local disease T3,4 tumors (27.6% vs. 25%), a higher proportion of poorly differentiated tumors, Gleason score 8–10 (25.7% vs. 19.3%), and metastatic disease (24.3% vs. 21%).

Diabetes mellitus duration and treatment

Overall, there was a 20% reduced risk of being diagnosed with prostate cancer among men with T2DM

Table 1. Characteristics of men diagnosed with prostate cancer between 2002 and 2006 in the NPCR in Sweden, ($n = 44,352$) and their matched controls ($n = 221,495$)

	Prostate cancer cases	Controls
Age, median (Q1–Q3)	71 (64–78)	71 (64–78)
	n (%)	*n* (%)
SES		
High	22,102 (49.8)	100,483 (45.4)
Low	21,666 (48.9)	115,009 (51.9)
Not gainfully employed/ unclassified/missing	584 (1.3)	6,003 (2.7)
Civil status		
Married	30,369 (68.5)	143,269 (64.7)
Widower	4,509 (10.2)	22,258 (10.0)
Divorced	5,686 (12.8)	30,958 (14.0)
Not married	3,788 (8.5)	25,010 (11.3)
Charlson comorbidity index		
0	30,874 (69.6)	153,395 (69.1)
1	6,743 (15.2)	36,370 (16.4)
2	3,994 (9.0)	19,519 (8.8)
3	2,741 (6.2)	12,211 (5.6)

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Table 2. Characteristics of men diagnosed with prostate cancer between 2002 and 2006 NPCR in Sweden, by T2DM status

	No diabetes ($N = 42,871$)	Diabetes ($N = 1,539$)
Age, mean (SD)	70.2 (9.3)	72.4 (8.0)
T-stage,[a] *n* (%)		
T1ab	2,503 (5.8)	125 (8.1)
T1c	15,762 (36.8)	479 (31.1)
T2	13,034 (30.4)	474 (30.8)
T3–T4	10,717 (25.0)	425 (27.6)
M-stage, *n* (%)		
M0	10,551 (24.6)	371 (24.1)
MX, PSA < 100/missing	26,455 (61.7)	926 (60.2)
M1 or PSA ≥ 100	5,865 (13.7)	242 (15.7)
PSA level,[a] *n* (%)		
PSA < 4	2,633 (6.1)	94 (6.1)
4 ≤ PSA < 10	15,134 (35.3)	455 (29.6)
10 ≤ PSA < 20	9,570 (22.3)	332 (21.6)
20 ≤ PSA < 50	7,122 (16.6)	290 (18.8)
500 ≤ PSA < 100	3,070 (7.2)	140 (9.1)
PSA ≥ 100	4,440 (10.4)	185 (12.0)
PSA, median (Q1–Q3)	12 (6.7–31)	15 (7.2–38)
Gleason score,[a] *n* (%)		
2—6	20,286 (47.3)	602 (39.1)
7	13,477 (31.4)	514 (33.4)
8—10	8,284 (19.3)	395 (25.7)
Prostate cancer risk categories,[a] *n* (%)		
Low risk	11,533 (26.9)	318 (20.7)
Intermediate risk	12,850 (30.0)	437 (28.4)
High risk	8,520 (19.9)	365 (23.7)
Regionally metastatic	3,113 (7.3)	133 (8.6)
Distant metastases	5,865 (13.7)	242 (15.7)
SES, *n* (%)		
High	21,478 (50.1)	658 (42.8)
Low	20,826 (48.6)	864 (56.1)
Not gainfully employed/ unclassified/missing	567 (1.3)	17 (1.1)
Civil status, *n* (%)		
Married	29,392 (68.6)	1015 (66.0)
Widower	4,345 (10.1)	169 (11.0)
Divorced	5,499 (12.8)	195 (12.7)
Not married	3,635 (8.5)	160 (10.4)

[a]Number to not add to total because of missing values.

compared with men without (Table 3). We observed a continuous trend of decreasing prostate cancer risk with increasing time since diagnosis of diabetes; among men who were diagnosed 20 years or more before their prostate cancer, the risk was reduced by 35%. On average, this represents a 1% reduced risk per year with diabetes (OR, 0.989; 95% CI, 0.983–0.995). There was a lower risk of prostate cancer both among users of oral hypoglycemic agents (OHA) and insulin than among men without these drugs. However, "diet only" also conferred a modest but statistically significant risk reduction. The overall risk for prostate cancer decreased with increasing BMI among the diabetic men compared with diabetes-free controls, and we observed a trend of lower prostate cancer risks with higher HbA1c levels.

Prostate cancer risk categories

We observed a decreasing prostate cancer risk with longer duration of T2DM across all risk categories but less clearly so among men high-risk/metastatic prostate cancer (Table 4). The use of insulin and OHA therapies was associated with a lower risk of prostate cancer in all risk categories, but the associations were stronger among men with low- and intermediate-risk prostate cancer than among men with high-risk/metastatic prostate cancer. We observed an inverse association between diabetes treated with diet only and low-risk prostate cancer but not with intermediate- or high-risk/metastatic prostate cancer. There was a trend of reduced risk of prostate cancer with higher BMI among diabetic men compared with the average risk among nondiabetic men, but the trend was largely confined to low-risk prostate cancer. Younger age at diabetes onset conferred a reduced prostate cancer risk for low- and intermediate-risk cancer but not for high-risk/metastatic cancer.

BMI and HbA1c

Diabetic men with high HbA1c levels (≥6.2) and high BMI (≥30 kg/m^2) had a 35% decreased risk of prostate cancer (OR, 0.65; 95% CI, 0.55–0.75) compared with controls, whereas diabetic men with a combination of either high HbA1c and low BMI (BMI < 30) or low HbA1c (HbA1c level < 6.2%) and high BMI had 17% (OR, 0.83; 95% CI, 0.76–0.92) and 20% (OR, 0.85; 95% CI, 0.69–0.92) decreased risks, respectively (data not shown).

Discussion

This nationwide study adds to the evidence of an inverse association between T2DM and prostate cancer. In these data, there was a trend of decreasing prostate cancer risk with longer T2DM duration and younger age at T2DM onset. The strongest inverse associations were observed for diabetic men treated with insulin, with high levels of HbA1c and high BMI. We observed a reduced risk of being diagnosed with prostate cancer across all tumor risk categories, although risk patterns were less clear for men with high-risk/metastatic cancer.

High- and low-risk tumors

Our finding of an inverse association between T2DM and a diagnosis of prostate cancer is in line with a number of smaller studies (11–14, 21, 22), of which a few have examined the influence of T2DM duration (12–14, 21) and high- versus low-risk tumors (11, 12, 22), separately. Our results largely confirm those of the Prostate Cancer Prevention Trial (PCPT) including 92 prostate cancer cases

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Table 3. Conditional logistic regression–derived ORs and 95% CIs for the association between T2DM and prostate cancer, stratified by selected diabetes-related variables

	Control subjects ($N = 221,495$)	Prostate cancer cases ($N = 44,352$)	OR[a] (95% CI)
Diabetes			
No diabetes	212,255	42,871	Ref
Diabetes	9,240	1,481	0.80 (0.76–0.85)
Duration			
No diabetes	212,255	42,871	Ref
1–4 y	2,513	434	0.87 (0.79–0.96)
5–9 y	2,537	428	0.85 (0.77–0.93)
10–19 y	2,784	434	0.78 (0.71–0.86)
20+ y	1,406	185	0.65 (0.56–0.75)
Treatment			
No diabetes	212,255	42,871	Ref
Diet only	2,055	365	0.89 (0.80–0.99)
Oral hypoglycemic agents	3,713	588	0.80 (0.74–0.87)
Insulin	1,948	285	0.72 (0.64–0.81)
OHA and insulin	1,464	234	0.80 (0.70–0.91)
BMI			
No diabetes	212,255	42,871	Ref
Diabetes, BMI <25	1,836	324	0.87 (0.78–0.97)
Diabetes, BMI 25—30	3,975	668	0.83 (0.77–0.90)
Diabetes, BMI 30+	2,490	350	0.72 (0.65–0.80)
Microalbuminuria			
No diabetes	212,255	42,871	Ref
No microalbuminuria	4,702	684	0.73 (0.68–0.79)
Microalbuminuria	2,428	456	0.92 (0.84–1.02)
Age, years at diabetes diagnosis			
No diabetes	212,255	42,871	Ref
<50	1,224	153	0.63 (0.54–0.74)
50—59	2,546	388	0.77 (0.69–0.85)
60—69	3,185	521	0.82 (0.75–0.89)
70—79	1,918	341	0.88 (0.79–0.98)
80+	367	78	1.04 (0.83–1.30)
Creatinine, μmol/L			
No diabetes	212,255	42,871	Ref
18—76	1,556	254	0.83 (0.73–0.94)
76–86	1,634	268	0.83 (0.74–0.94)
86–96	1,637	262	0.80 (0.71–0.91)
96–112	1,792	276	0.77 (0.68–0.87)
112–891	1,658	267	0.78 (0.69–0.88)
HbA1c (quintile)			
No diabetes	212,255	42,871	Ref
3.5–5.2	1,866	330	0.88 (0.79–0.99)
5.2–5.8	1,584	268	0.84 (0.75–0.95)
5.8,6.4	1,986	313	0.79 (0.71–0.88)
6.4–7.1	1,668	263	0.79 (0.70–0.89)
7.1,14.9	1,936	277	0.72 (0.64–0.81)

NOTE: Numbers do not add to total because of missing data.

[a]Adjusted for SES, marital status, comorbidity, age at prostate cancer diagnosis and diabetes prevalence in county of residence.

with T2DM that reported a risk reduction of 28% for high-grade cancer and a 47% reduction for low-grade cancer (11). The Health Professionals Follow-up study reported an inverse association between T2DM and prostate cancer both among cases of localized and advanced-stage prostate cancer in the pre-PSA era, but no association with

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Table 4. Adjusted ORs and 95% CIs for prostate cancer in relation to diabetes mellitus status, by risk group

		Low-risk prostate cancer		Intermediate-risk prostate cancer		High-risk/metastatic prostate cancer[a]	
	No prostate cancer		OR[b] (95% CI)		OR[b] (95% CI)		OR[b] (95% CI)
Diabetes							
No	212,255	11,533	Ref.	12,850	Ref.	17,498	Ref.
Yes	9,240	301	0.71 (0.64–0.80)	424	0.76 (0.69–0.84)	713	0.86 (0.80–0.93)
Duration							
No diabetes	212,255	11,533	Ref.	12,850	Ref.	17,498	Ref.
1–4 y	2,513	91	0.74 (0.60–0.91)	145	0.94 (0.8–1.11)	183	0.87 (0.75–1.00)
5–9 y	2,537	88	0.73 (0.59–0.90)	120	0.78 (0.65–0.94)	207	0.93 (0.81–1.07)
10–19 y	2,784	90	0.74 (0.60–0.91)	118	0.70 (0.59–0.84)	216	0.85 (0.74–0.97)
20+ y	1,406	32	0.56 (0.39–0.79)	41	0.49 (0.36–0.67)	107	0.77 (0.64–0.93)
Therapy							
No diabetes	212,255	11,533	Ref.	12,850	Ref.	17,498	Ref.
Diet only	2,055	70	0.78 (0.61–0.98)	116	0.93 (0.77–1.12)	165	0.88 (0.75–1.02)
OHA[c]	3,713	128	0.75 (0.63–0.89)	164	0.73 (0.63–0.86)	283	0.86 (0.77–0.97)
OHA and insulin	1,464	47	0.66 (0.50–0.89)	69	0.78 (0.62–0.99)	111	0.88 (0.73–1.07)
Insulin	1,948	56	0.65 (0.49–0.84)	72	0.60 (0.48–0.76)	148	0.82 (0.69–0.96)
BMI							
No diabetes	212,255	11,533	Ref.	12,850	Ref.	17,498	Ref.
Diabetes, BMI < 25	1,836	63	0.88 (0.68–1.12)	89	0.81 (0.66–1.00)	160	0.88 (0.75–1.03)
Diabetes, BMI 25–30	3,975	139	0.75 (0.64–0.89)	192	0.79 (0.68–0.91)	323	0.90 (0.81–1.01)
Diabetes, 30+	2,490	75	0.59 (0.47–0.74)	106	0.70 (0.58–0.85)	158	0.80 (0.68–0.94)
Age at diabetes mellitus onset							
No diabetes	212,255	11,533	Ref.	12,850	Ref.	17,498	Ref.
<50	1,224	37	0.49 (0.35–0.68)	44	0.59 (0.44–0.8)	69	0.81 (0.64–1.03)
50–59	2,546	120	0.79 (0.66–0.95)	99	0.63 (0.52–0.77)	157	0.85 (0.73–1.00)
60–69	3,185	101	0.71 (0.58–0.86)	158	0.79 (0.68–0.93)	247	0.87 (0.77–0.99)
70–79	1,918	39	0.82 (0.60–1.13)	104	0.94 (0.77–1.14)	185	0.83 (0.72–0.96)
80+	367	4	0.83 (0.31–2.22)	19	1.12 (0.71–1.76)	55	1.05 (0.8–1.37)
HbA1c (quintile)							
No diabetes	212,255	11,533	Ref.	12,850	Ref.	17,498	Ref.
3.5–5.2	1,866	64	0.76 (0.59–0.97)	109	0.96 (0.79–1.16)	145	0.87 (0.74–1.03)
5.2–5.8	1,584	50	0.69 (0.52–0.91)	70	0.72 (0.57–0.91)	142	0.99 (0.84–1.17)
5.8–6.4	1,986	63	0.71 (0.55–0.91)	98	0.81 (0.66–0.99)	139	0.78 (0.66–0.92)
6.4–7.1	1,668	58	0.76 (0.58–0.98)	66	0.66 (0.52–0.84)	133	0.89 (0.75–1.06)
7.1–14.9	1,936	63	0.70 (0.55–0.90)	72	0.63 (0.5–0.79)	139	0.81 (0.69–0.96)

[a]Includes high-risk, regionally, and distant metastatic disease.
[b]Adjusted for SES, civil status, comorbidity, age at prostate cancer diagnosis, and diabetes prevalence in county of residence.
[c]Oral hypoglycemic agents.

advanced-stage tumors in the PSA era (12). The uptake of PSA testing has been slower and less pronounced in Sweden in comparison to the United States. It has been estimated that in 2007, 56% of Swedish men 55–69 years of age had undergone at least one PSA test (23).

Detection of prostate cancer among men with T2DM

Speculatively, differences in the mode of detection of prostate cancer could explain the inverse association between T2DM and prostate cancer. Diabetic (24–26) and obese men (27–29) have lower levels of PSA than healthy men. Therefore, men with T2DM and obesity may be less likely to be diagnosed with prostate cancer initiated by an elevated PSA level. Also, less PSA testing has been reported among men with T2DM (21, 30, 31) and overweight (21, 30, 31) than among healthy men. Accordingly, in the REDUCE trial, where all study participants underwent prostate biopsy regardless of serum PSA, no association between T2DM and prostate cancer risk was observed (32). Our findings of higher age and more advanced tumors among men with T2DM and prostate cancer could thus indicate that selection may contribute to the observed inverse association between T2DM and prostate cancer. Differences in

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marital status and social class may point in the same direction.

Hormonal and metabolic factors in relation to prostate cancer risk

The observed risk reduction was not, however, only observed among men with low-risk prostate cancer. Metabolic aberrations including changes in insulin, insulin-like growth factor-1 (IGF-1), and testosterone levels have previously been suggested as a link between T2DM and prostate cancer (12, 33). Elevated C-peptide levels, reflecting serum insulin concentrations, have been associated with high-risk prostate cancer (11, 34) as well as prostate cancer–specific death (35). Moreover, insulin influences prostate cancer cell growth *in vivo* as well as *in vitro* (36–38). In accordance with an earlier finding (5), we found that the risk of low- and intermediate-risk prostate cancer decreased with increasing HbA1c concentrations. In theory, this could be related to higher androgenicity among men with low glucose levels. The influence of metabolic factors may further need a relatively well-differentiated target tissue for their action. T2DM and long-term hyperglycemia frequently results in microvascular complications due to capillary dysfunction and altered shape and size of intraprostatic microvessels have been linked to the risk of lethal prostate cancer (39). Decreased microcirculation might thus alternatively explain the reduced risk among men with T2DM (40).

Diabetic men who did develop prostate cancer showed a higher proportion of high-risk tumors than patients with prostate cancer without diabetes in our study. Low androgen levels among men with diabetes could be involved in driving that difference, as suggested by findings of an increased risk of high-risk tumors among men using 5-α reductase inhibitors (41). In line with results from 2 earlier studies (12, 21), a stronger inverse relation between T2DM and prostate cancer was suggested among diabetic men with a high BMI in our data. Additional influence of an altered hormonal milieu in obese men with low testosterone levels may speculatively explain this observation (42).

Diabetes treatment

Earlier studies have provided evidence in support of a reduced prostate cancer risk among men on glucose-lowering agents (43–45). Our study provides new knowledge with regard to tumor characteristics; we observed that insulin therapy was associated with a clear risk reduction among men with low- and intermediate-risk prostate cancer but less so among men with high-risk tumors. Our data further showed a reduced risk of prostate cancer across all diabetic treatment groups, although most clearly among men on insulin and oral treatment and for low-risk disease. Although clearly difficult to disentangle, this may suggest that diabetes and the severity of the disease affects the risk of prostate cancer rather than the treatment.

Strengths of this study include its size that to our knowledge represents the largest study on this topic, the nested case–control design that preserves the validity of the underlying population-based cohort, the prospective data collection that minimized differential misclassification of the exposure data, as well as the detailed exposure and endpoint information. As prostate cancer incidence is closely linked to diagnostic intensity as shown, for example, by large differences in incidence between regions in Sweden (46), a similar pattern for diabetes diagnosis could have influenced the relation between T2DM and prostate cancer. Controlling for a constructed diagnostic likelihood index in the models left the estimates unchanged, however. Adjustment for other potential confounders did not alter the results materially. However, given the observational design of the study, influence of unknown or unmeasured confounders (such as family history) cannot be entirely ruled out.

In summary, this nationwide register study confirmed earlier findings of an inverse association between T2DM and the diagnosis of prostate cancer. The strongest risk reduction was observed for men with low-risk cancer, long duration of T2DM, and for men who received insulin or oral hypoglycemic agents. We speculate that the association is related to an altered hormonal milieu, most strongly affecting well-differentiated tumors. However, influence of less PSA testing and reduced efficacy of such testing among men with diabetes cannot be excluded. Future studies examining the influence of diabetes on survival among patients with prostate cancer may bring further insights into the underlying mechanism. If confirmed, a link between diabetes—with its associated hormonal milieu—and prostate carcinogenesis could potentially lead to identification of targets for therapeutic intervention.

Disclosure of Potential Conflicts of Interest

B.O.M. Zethelius is employed by the Medical Products Agency (MPA), Uppsala, Sweden. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

Results and views of the present study represent the authors and are not necessarily any official views of the MPA.

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References

1. Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Madarnas Y, et al. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. J Clin Oncol 2002;20:42–51.
2. Ortiz AP, Thompson CL, Chak A, Berger NA, Li L. Insulin resistance, central obesity, and risk of colorectal adenomas. Cancer 2012;118: 1774–81.
3. Hsing AW, Gao YT, Chua S Jr, Deng J, Stanczyk FZ. Insulin resistance and prostate cancer risk. J Natl Cancer Inst 2003;95:67–71.
4. Barnard RJ, Aronson WJ, Tymchuk CN, Ngo TH. Prostate cancer: another aspect of the insulin-resistance syndrome? Obes Rev 2002;3:303–8.
5. Stocks T, Lukanova A, Rinaldi S, Biessy C, Dossus L, Lindahl B, et al. Insulin resistance is inversely related to prostate cancer: a prospective study in Northern Sweden. Int J Cancer 2007;120:2678–86.
6. Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. JAMA 1995;273:1605–9.
7. Strickler HD, Wylie-Rosett J, Rohan T, Hoover DR, Smoller S, Burk RD, et al. The relation of type 2 diabetes and cancer. Diabetes Technol Ther 2001;3:263–74.
8. Hu FB, Manson JE, Liu S, Hunter D, Colditz GA, Michels KB, et al. Prospective study of adult onset diabetes mellitus (type 2) and risk of colorectal cancer in women. J Natl Cancer Inst 1999;91:542–7.
9. Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 2006;15:2056–62.
10. Bonovas S, Filioussi K, Tsantes A. Diabetes mellitus and risk of prostate cancer: a meta-analysis. Diabetologia 2004;47:1071–8.
11. Gong Z, Neuhouser ML, Goodman PJ, Albanes D, Chi C, Hsing AW, et al. Obesity, diabetes, and risk of prostate cancer: results from the prostate cancer prevention trial. Cancer Epidemiol Biomarkers Prev 2006;15:1977–83.
12. Kasper JS, Liu Y, Giovannucci E. Diabetes mellitus and risk of prostate cancer in the health professionals follow-up study. Int J Cancer 2009;124:1398–403.
13. Rodriguez C, Patel AV, Mondul AM, Jacobs EJ, Thun MJ, Calle EE. Diabetes and risk of prostate cancer in a prospective cohort of US men. Am J Epidemiol 2005;161:147–52.
14. Zhu K, Lee IM, Sesso HD, Buring JE, Levine RS, Gaziano JM. History of diabetes mellitus and risk of prostate cancer in physicians. Am J Epidemiol 2004;159:978–82.
15. Coker AL, Sanderson M, Zheng W, Fadden MK. Diabetes mellitus and prostate cancer risk among older men: population-based case-control study. Br J Cancer 2004;90:2171–5.
16. Van Hemelrijck M, Wigertz A, Sandin F, Garmo H, Hellstrom K, Fransson P, et al. Cohort profile: the National Prostate Cancer Register of Sweden and Prostate Cancer data Base Sweden 2.0. Int J Epidemiol. 2012 May 4. [Epub ahead of print].
17. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol 2009;24:659–67.
18. Hagel E, Garmo H, Bill-Axelson A, Bratt O, Johansson JE, Adolfsson J, et al. PCBaSe Sweden: a register-based resource for prostate cancer research. Scand J Urol Nephrol 2009;43:342–9.
19. Cederholm J, Zethelius B, Nilsson PM, Eeg-Olofsson K, Eliasson B, Gudbjornsdottir S. Effect of tight control of HbA1c and blood pressure on cardiovascular diseases in type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR). Diabetes Res Clin Pract 2009;86:74–81.
20. Hoelzel W, Weykamp C, Jeppsson JO, Miedema K, Barr JR, Goodall I, et al. IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study. Clin Chem 2004;50:166–74.
21. Calton BA, Chang SC, Wright ME, Kipnis V, Lawson K, Thompson FE, et al. History of diabetes mellitus and subsequent prostate cancer risk in the NIH-AARP Diet and Health Study. Cancer Causes Control 2007;18:493–503.
22. Turner EL, Lane JA, Donovan JL, Davis MJ, Metcalfe C, Neal DE, et al. Association of diabetes mellitus with prostate cancer: nested case-control study (Prostate testing for cancer and treatment study). Int J Cancer 2011;128:440–6.
23. Jonsson H, Holmstrom B, Duffy SW, Stattin P. Uptake of prostate-specific antigen testing for early prostate cancer detection in Sweden. Int J Cancer 2011;129:1881–8.
24. Fukui M, Tanaka M, Kadono M, Imai S, Hasegawa G, Yoshikawa T, et al. Serum prostate-specific antigen levels in men with type 2 diabetes. Diabetes Care 2008;31:930–1.
25. Werny DM, Saraiya M, Gregg EW. Prostate-specific antigen values in diabetic and nondiabetic US men, 2001–2002. Am J Epidemiol 2006;164:978–83.
26. Wallner LP, Morgenstern H, McGree ME, Jacobson DJ, St Sauver JL, Jacobsen SJ, et al. The effects of type 2 diabetes and hypertension on changes in serum prostate specific antigen levels: results from the Olmsted County study. Urology 2011;77:137–41.
27. Banez LL, Hamilton RJ, Partin AW, Vollmer RT, Sun L, Rodriguez C, et al. Obesity-related plasma hemodilution and PSA concentration among men with prostate cancer. JAMA 2007;298:2275–80.
28. Culp S, Porter M. The effect of obesity and lower serum prostate-specific antigen levels on prostate-cancer screening results in American men. BJU Int 2009;104:1457–61.
29. Lee SE, Hong SK, Park HZ, Chang JS, Yoon CY, Byun SS, et al. Higher body mass index is associated with lower risk of prostate cancer detection via multi ($\geq$ 12)-core prostate biopsy in Korean men. Urology 2010;76:1063–6.
30. Scales CD Jr, Curtis LH, Norris RD, Schulman KA, Dahm P, Moul JW. Relationship between body mass index and prostate cancer screening in the United States. J Urol 2007;177:493–8.
31. Fowke JH, Signorello LB, Underwood W III, Ukoli FA, Blot WJ. Obesity and prostate cancer screening among African-American and Caucasian men. Prostate 2006;66:1371–80.
32. Wu C, Moreira DM, Gerber L, Rittmaster RS, Andriole GL, Freedland SJ. Diabetes and prostate cancer risk in the REDUCE trial. Prostate Cancer Prostatic Dis 2011;14:326–31.
33. Colangelo LA, Ouyang P, Liu K, Kopp P, Golden SH, Dobs AS, et al. Association of endogenous sex hormones with diabetes and impaired fasting glucose in men: multi-ethnic study of atherosclerosis. Diabetes Care 2009;32:1049–51.
34. Albanes D, Weinstein SJ, Wright ME, Mannisto S, Limburg PJ, Snyder K, et al. Serum insulin, glucose, indices of insulin resistance, and risk of prostate cancer. J Natl Cancer Inst 2009;101:1272–9.
35. Ma J, Li H, Giovannucci E, Mucci L, Qiu W, Nguyen PL, et al. 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 2008;9:1039–47.
36. LeRoith D, Roberts CT Jr. The insulin-like growth factor system and cancer. Cancer Lett 2003;195:127–37.

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37. Yu H, Rohan T. Role of the insulin-like growth factor family in cancer development and progression. J Natl Cancer Inst 2000;92:1472–89.
38. Polychronakos C, Janthly U, Lehoux JG, Koutsilieris M. Mitogenic effects of insulin and insulin-like growth factors on PA-III rat prostate adenocarcinoma cells: characterization of the receptors involved. Prostate 1991;19:313–21.
39. Mucci LA, Powolny A, Giovannucci E, Liao Z, Kenfield SA, Shen R, et al. Prospective study of prostate tumor angiogenesis and cancer-specific mortality in the health professionals follow-up study. J Clin Oncol 2009;27:5627–33.
40. Zhang W, Hu R. Why does diabetes offer protective effects against prostate cancer? The possible role of its microvascular complications. Med Hypotheses 2010;74:242–3.
41. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, et al. The influence of finasteride on the development of prostate cancer. N Engl J Med 2003;349:215–24.
42. Lima N, Cavaliere H, Knobel M, Halpern A, Medeiros-Neto G. Decreased androgen levels in massively obese men may be associated with impaired function of the gonadostat. Int J Obes Relat Metab Disord 2000;24:1433–7.
43. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia 2009;52:1766–77.
44. van Staa TP, Patel D, Gallagher AM, de Bruin ML. Glucose-lowering agents and the patterns of risk for cancer: a study with the General Practice Research Database and secondary care data. Diabetologia 2011;55:654–55.
45. Carstensen B, Witte DR, Friis S. Cancer occurrence in Danish diabetic patients: duration and insulin effects. Diabetologia 2011;55:948–58.
46. Stattin P, Johansson R, Lodnert R, Andren O, Bill-Axelsson A, Bratt O, et al. Geographical variation in incidence of prostate cancer in Sweden. Scand J Urol Nephrol 2005;39:372–9.

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