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Does diabetes mellitus modify the association between 17q12 risk variant and prostate cancer aggressiveness?

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Abstract

Objective—To examine further the relationship between diabetes mellitus (DM), genotype and prostate cancer aggressiveness. Specifically, we sought to evaluate for effect modification between DM, a newly discovered prostate cancer susceptibility locus on chromosome 17q12 (single nucleotide polymorphism rs4430796) and prostate cancer features.

Patients and methods—In 593 genotyped men treated with radical prostatectomy (RP), we examined RP features stratified by DM and rs4430796 carrier status.

Results—Despite a significantly higher body mass index among patients with DM, individual pathological features were similar between men with and without DM. Using a dominant model, 17q12 carriers were less likely to have DM and more likely to have a RP Gleason score of ≥ 7 . However, the presence or absence of DM did not modify the relationship between 17q12 susceptibility alleles and pathological features.

Conclusion—Among 17q12 risk allele carriers, there was no significant relationship between DM and adverse tumour features. However, there were relatively few men with DM (7%) in our RP cohort, particularly compared with its 21% prevalence in the USA population aged > 60 years. It is unclear whether this reflects selection bias, genetic protection from prostate cancer among patients with DM, or both. Despite these limitations, the present data suggest that DM alone does not appear to modify any association between 17q12 risk alleles with prostate cancer features.

Keywords

17q12; single nucleotide polymorphism; diabetes; prostate cancer; aggressiveness

Introduction

Diabetes mellitus (DM) and prostate cancer are very common conditions in the contemporary ageing population. It has been estimated that DM affects $\approx 14\%$ of USA men aged 50–74 years and 20.9% of the population aged > 60 years [1,2]. Prostate cancer is the most common noncutaneous cancer in USA men, and there were an estimated 186 320 new cases in 2008 [3]. According to data from the American Cancer Society, the lifetime risk of developing prostate cancer is one in every six men (17%).

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Conflict of Interest

William J. Catalona is a consultant, investigator and speaker for DECODE Genetics Inc. and Beckman Coulter Inc.

DM is strongly associated with a wide variety of medical problems. For example, the Framingham Study showed a two- to three-fold increased risk of cardiovascular disease among patients with DM [4]. DM is well-established cause of nephropathy, neuropathy and retinopathy [5]. It also increases the risk of numerous infections, chronic ulcer formation and several malignancies, including those of the pancreas, breast, liver, endometrium, and colon [6].

By contrast, there is a growing body of evidence suggesting that DM may actually be protective against prostate cancer and that a longer duration of DM may lead to further risk reduction [2]. For example, Kasper and Giovannucci [7] performed a meta-analysis of 19 studies on this subject published between 1971 and 2005. They reported that the pooled relative risk for prostate cancer among diabetics was 0.84 (95%CI 0.76–0.93), indicating that patients with DM have nearly a 20% lower risk of developing prostate cancer. Less is known about the relationship between DM and prostate cancer aggressiveness.

In addition, the mechanism through which DM and prostate cancer are related has not been fully elucidated. Differential screening practices, diet, exercise, and hormone levels are all potentially involved. For example, DM progressively leads to lower circulating levels of insulin and insulin-like growth factor-1, both of which have been shown to increase prostate cancer risk [8]. Bioavailable testosterone levels are also decreased in patients with DM [9], representing another potential hormonal link between the two conditions.

Finally, DM and prostate cancer may be associated on a genetic basis. Indeed, Gudmundsson *et al.* [10] recently identified a prostate cancer susceptibility allele, rs4430796, on chromosome 17q12. It is located within the transcription factor 2 (*TCF2*) gene, which is protective against type 2 DM. For example, in 3490 cases and 14 345 controls of American or European descent, the rs4430796 single nucleotide polymorphism was associated with a 1.22-fold increased odds ratio (OR) for prostate cancer (95%CI 1.15–1.30; $P < 0.001$); whereas, the OR of type 2 DM was 0.91 (95%CI 0.87–0.94; $P < 0.001$). Furthermore, our group recently reported that the rs4430796 allele was significantly associated with high-grade disease (Gleason score ≥ 7) at radical prostatectomy (RP) [11].

In light of these new findings, our objective was to examine further the relationship between DM and prostate cancer aggressiveness. Specifically, we sought to evaluate for effect modification between DM, rs4430796, and prostate cancer features.

Patients and methods

From 2002 to 2006, 987 Caucasian men underwent RP for clinically localized prostate cancer by a single surgeon (W.J.C.). Of these men, 616 were genotyped in collaboration with deCODE Genetics, Inc. in Reykjavik, Iceland. Data on DM status was available for 593 of these men who constituted the final study population. For patients with a history of DM, data on the type of diabetes (type 1 vs type 2), hypoglycaemic medication use, and fasting glucose measurements were retrospectively obtained from the medical records. All participants provided written informed consent, and the study protocol was approved by the Institutional Review Board.

DNA samples were isolated from whole blood, and genotyping was performed using the Centaurus (Nanogen) platform, as previously described [12,13]. In the present study, we specifically assayed for the presence of the T-allele variant of rs4430796 on 17q12 that has previously been associated with a higher risk for prostate cancer and a lower risk for DM.

Clinical and pathological features were compared using chi-square and Fisher's exact tests, stratified by DM status and genotype. All analyses were performed separately using

dominant (heterozygotes classified as carriers) and recessive inheritance models (heterozygotes classified as non-carriers) for 17q12 carrier status. We defined a positive family history as at least one affected first-degree relative. We also calculated the rates of biochemical progression for the subset of patients with at least 1 year of follow-up, wherein biochemical progression was defined as a postoperative PSA level of > 0.2 ng/mL.

Results

Clinical features and treatment outcomes for the overall population

In the overall population of 593 men, the mean (range) age was 59(37–75) years and the mean (range) body mass index (BMI) was 27.2 (17.4–41.3) kg/m². In all, 553 (93%) men did not have DM and 40 (7%) had DM, of which 39 (98%) had type 2 DM. Among the patients with type 2 DM, 15 (39%) were diet-controlled and the remainder (62%) used oral hypoglycaemic agents. Fasting glucose levels were similar between patients with diet-controlled vs medication-controlled DM (157 vs 163 mg/dL, $P = 0.36$).

The median (range) PSA level at diagnosis was 5.0 (0.27–47.9) ng/mL, and 173 (29%) had at least one affected first-degree relative. The biopsy Gleason score was ≤ 6 in 412 (70%) and ≥ 7 in 181 (31%) men. The clinical stage was $\leq$ T1c in 421 (70%), T2 in 164 (28%), T3 in four (1%) patients, and missing in 4 (1%) patients..

At the time of RP, 465 (78%) men had organ-confined disease. Positive surgical margins and extracapsular extension were present in 102 (17%) and 121 (20%), respectively. There were 27 (5%) patients with seminal vesicle invasion and five (1%) with pelvic lymph node metastases. The RP Gleason score was ≥ 7 in 285 (48%). Among 426 men with at least 1 year of follow-up, biochemical progression occurred in 25 (6%).

DM and prostate cancer features

Table 1 compares the demographics and pathology findings between men with and without DM. The men with DM were significantly older and had a higher BMI; whereas, all other clinical and pathological features were similar.

17q12 and prostate cancer features

Using a dominant model, 492 (83%) of the study population were considered carriers. Non-carriers had a significantly higher BMI than carriers. Despite otherwise similar clinical characteristics, 17q12 carriers were significantly more likely to have an RP Gleason score of ≥ 7 (50% vs 39%, $P = 0.041$).

Using a recessive model for carrier status, 190 (32%) men were carriers of the 17q12 susceptibility allele. Carriers were significantly more likely to have clinical stage of $\geq$ T2 disease ($P = 0.019$). However, all other clinical and pathological features were similar (data not shown).

Association of genotype and DM with prostate cancer features (dominant model)

Using the dominant model, 31 (6%) of carriers had DM and 461 (94%) did not. By comparison, nine (9%) of the non-carriers had DM and 92 (91%) did not, suggesting that carriers in this cohort were 29% less likely to have DM. Notably, 17q12 carrier status was similar between patients with DM who were diet-controlled vs medication-controlled ($P = 0.43$).

Overall, carriers with DM were significantly older and had a higher mean BMI (Table 2). However, prostate cancer features including Gleason score were similar between carriers with and without DM.

Among 17q12 non-carriers, patients with DM tended to have a higher BMI and were less likely to report a positive family history of prostate cancer, compared with those without DM. Nevertheless, clinico-pathological tumour features were similar between non-carriers irrespective of DM status (Table 2).

Association of genotype and DM with prostate cancer features (recessive model)

Using a recessive model for 17q12, 10 (5%) carriers and 30 (7%) non-carriers had DM. As before, DM carriers had a significantly higher BMI and tended to have a higher percentage with positive margins than carriers without DM ($P = 0.09$). Nevertheless, the pathological features and early biochemical progression rates did not differ between carriers with and without DM. Among 17q12 non-carriers, DM was also associated with a higher BMI and clinical stage. However, there were no other significant differences in pathological outcomes (data not shown).

Discussion

Numerous studies have shown that DM may be associated with a decreased risk of prostate cancer [7]; however, less is known about its relationship with treatment outcomes. Interestingly, DM is associated with obesity, which has been linked with adverse prostate cancer features and a higher rate of biochemical recurrence [14,15]. Despite this, in the present study there was no significant association between DM and pathological features at RP.

The present results are in agreement the study of Chan *et al.* [16] in men from the CaPSURE database. Among patients treated by RP and radiation therapy, they reported no significant differences in recurrence-free survival based upon DM status ($P = 0.45$ and $P = 0.08$, respectively).

Another area of current investigation involves several germ-line DNA sequence variants that recently have been linked to prostate cancer susceptibility. Specifically, three regions on chromosome 8q24 and two regions on chromosome 17 appear to increase the risk of prostate cancer in a multiplicative fashion [17]. As discussed, one of these alleles (rs4430796 on chromosome 17q12) is located within the same region that is associated with decreased susceptibility to type 2 DM [10]. Because this 17q12 risk allele was also associated with high-grade disease in a previous analysis from our group [11], we conducted a stratified analysis to look for a potential interaction with DM.

Indeed, in the present study there was no evidence of effect modification by DM. In our surgical cohort, clinical and pathological characteristics were similar among 17q12 carriers regardless of DM status. Likewise, among non-carriers of the 17q12 risk allele, we were unable to identify any systematic differences in disease features between those with and without DM.

There are several limitations to the present study. The study population was drawn from a RP series. Because all participants had a known diagnosis of prostate cancer, we were not able to evaluate the risk of prostate cancer among community men with or without DM. In addition, the present series had a relatively small proportion of patients with DM compared with the prevalence in the USA population, which limited the statistical power of the study.

Although this could be due in part to the lower risk of prostate cancer among patients with DM, selection bias also might have played a role.

Other limitations of the present study are that virtually all the patients with DM had type 2 DM, and data on the duration of DM or hormonal profiles were not available. Finally, the proportion of 17q12 ‘carriers’ and associated pathological features were different, depending upon whether a dominant or recessive model was used. It was previously suggested that a recessive model fit this locus best in a Swedish population [17]. Because this finding has not yet been confirmed in different ethnic groups, we performed the analysis using different inheritance models for completeness.

In conclusion, despite evidence that DM decreases prostate cancer risk, there was no significant association between DM and prostate cancer aggressiveness in the present cohort. As we have previously reported, the 17q12 prostate cancer susceptibility allele was associated with a greater likelihood of high-grade disease in the RP specimen using a dominant inheritance model. Moreover, carriers of the 17q12 risk allele were less likely to report a history of DM. Nevertheless, prostate cancer features in both carriers and non-carriers appear to be unaffected by DM status.

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Abbreviations

DM	diabetes mellitus
RP	radical prostatectomy
BMI	body mass index

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Table 1

Comparison of clinico-pathological prostate cancer features between patients with and without DM

Variable	DM	No DM	P
N	40	553	
Mean:			
Age, years	61.2	59.0	0.047
BMI, kg/m ²	30.22	27.03	< 0.001
PSA level, ng/mL	6.38	5.89	0.461
N (%):			
Family history of prostate cancer	11 (28)	162 (30)	0.733
Biopsy Gleason $\geq$ 7	14 (36)	167 (31)	0.479
Clinical stage $\leq$ T1C	32 (80)	389 (70)	0.119
Organ-confined	32 (80)	433 (78)	0.801
Positive margins	7 (18)	95 (17)	0.958
Extracapsular extension	7 (18)	114 (21)	0.637
Seminal vesicle invasion	3 (8)	24 (4)	0.417
Positive nodes	0	5 (1)	1.0
RP Gleason $\geq$ 7	24 (60)	261 (48)	0.125

Table 2
Comparison of demographics and RP features by DM status in 17q12 carriers and non-carriers using a dominant model

Variable	Carrier			Non-carrier		
	DM	No DM	P	DM	No DM	P
N	31	461		9	92	
Mean:						
Age, years	61.5	59.0	0.050	60.1	58.6	0.545
BMI, kg/m ²	30.24	26.86	< 0.001	30.16	27.88	0.079
PSA level, ng/mL	6.52	5.88	0.411	5.92	5.93	0.992
Follow-up, years	2.2	2.5	0.226	2.6	2.3	0.183
N (%):						
Family history of prostate cancer	11 (36)	128 (29)	0.407	0	34 (38)	0.025
Biopsy Gleason $\geq$ 7	10 (32)	146 (32)	0.971	4	21 (23)	0.108
Clinical stage $\leq$ T1c	23 (77)	321 (70)	0.415	9	68 (74)	0.110
Organ-confined	25 (81)	359 (78)	0.718	7	74 (80)	1.0
Positive margins	7 (23)	79 (17)	0.440	0	16 (17)	0.348
Extracapsular extension	5 (16)	98 (21)	0.497	2	16 (17)	0.660
Seminal vesicle invasion	2 (7)	19 (4)	0.635	1	5 (5)	0.437
Positive nodes	0	4 (1)	1.0	0	1 (1)	1.0
RP Gleason $\geq$ 7	19 (61)	227 (50)	0.202	5	34 (37)	0.306
Biochemical progression	1 (5)	19 (6)	1.0	0	5 (7)	1.0