Prostate cancer genetic propensity risk score may modify the association between this tumour and type 2 diabetes mellitus (MCC-Spain study)

Running title: Genetic susceptibility modifies Type 2 diabetes mellitus and prostate cancer association.

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ABSTRACT

BACKGROUND: Some studies have reported an inverse association between type 2 diabetes mellitus (T2DM) and prostate cancer (PCa), but results on this issue are still inconsistent. In this study, we evaluate whether this heterogeneity might be related to differences in this relationship by tumour or by individual genetic susceptibility to PCa.

METHODS: We studied 1047 incident PCa cases and 1379 randomly selected controls, recruited in 7 Spanish provinces for the population-based MCC-Spain case-control. Tumour were classified by aggressiveness according to the International Society of Urological Pathology (ISUP), and we constructed a PCa polygenic risk score (PRS) as proxy for genetic susceptibility. The epidemiological questionnaire collected detailed self-reported data on T2DM diagnosis and treatment. The association between T2DM status and PCa was studied by fitting mixed logistic regression models, and, for its association by aggressiveness of PCa, with multinomial logistic regression models. To evaluate the possible modulator role of PRS in this relationship, we included the corresponding interaction term in the model, and repeated the analysis stratified by PRS tertiles.

RESULTS: Globally, our results showed an inverse association between T2DM and overall PCa limited to grade 1 tumours ($OR_{ISUP=1}$: 0.72; 95%CI: 0.53–0.98), which could be compatible with a detection bias. However, PCa risk also varied with duration of diabetes treatment -inversely to metformin and positively with insulin-, without differences by aggressiveness. When we considered genetic susceptibility, T2DM was more strongly associated with lower PCa risk in those with lower PRS ($OR_{tertile\ 1}$: 0.31; 95%CI: 0.11-0.87), independently of ISUP grade.

CONCLUSIONS: Our findings reinforce the need to include aggressiveness and susceptibility of PCa, and T2DM treatments in the study of the relationship between both diseases.

Key words: prostate cancer; diabetes mellitus; ISUP grade; metformin; genetic susceptibility; MCC-Spain.

Introduction

Prostate cancer (PCa) is a public health problem in terms of incidence and mortality, with almost 1.3 million new cases and 359,000 deaths worldwide in 2018. In fact, it was the most frequently diagnosed cancer and the fourth-leading cause of cancer death for men in 2018[1]. Age, race, and genetic susceptibility—with estimates of PCa heritability at 57%—are non-modifiable risk factors for PCa[2–5]. In contrast, the relationship of other lifestyles exposures, such as smoking or diet, on PCa has limited evidence, excepting obesity, classified as probable risk factor for advanced PCa[6]. Therefore, its aetiology remains largely unknown, limiting the possibilities of primary prevention. As PCa burden is expected to increase in the future[7], the identification of modifiable factors related with this disease is a real need.

PCa is a heterogeneous disease with different behaviour depending on aggressiveness; however, aetiological research has specific difficulties due to variability in prevalence of PSA testing, associated to detection of low-grade tumors[8,9]. Therefore, considering tumour aggressiveness in the search of risk factors for PCa is a critical issue.

Diabetes mellitus is one of the putative risk factors for PCa, as it is an established risk factor for breast or colorectal cancer[10]. However, several reviews have reported an inverse association of PCa with type 2 diabetes mellitus (T2DM)[10–12], with moderate to high heterogeneity among studies, while the reasons for lower rates of PCa in diabetic men remain still unclear.

A possible source of this heterogeneity can be a different relationship according to aggressiveness. Some studies have not found differences by grade of disease[12–14], whereas other authors have reported a higher risk of high-grade disease in patients with T2DM[15]. The most recent studies have found that lower rates in T2DM patients was limited to low/intermediate-grade PCa, with detection bias as a plausible explanation for

this relationship[16–19]. However, none of these studies evaluated whether genetic susceptibility to PCa may play a modifying role in this complex association. On the other hand, there is some evidence that the use and duration of pharmacological treatments habitually used for T2DM control may modulate its association with PCa[20,21]. To date, research results for these points are controversial[10,13,22,23].

For the above reasons and unanswered questions, the objective of this study was to evaluate the association between T2DM and PCa, taking into account tumour aggressiveness and individual genetic susceptibility for PCa, as well as the type and duration of diabetes treatment.

Methods

Study participants

MCC-Spain is a population-based multicase-control study designed to explore the influence of environmental factors and their interaction with genetic factors in the aetiology of different tumours (cases of breast, colorectal, prostate, gastric cancer, and chronic lymphocytic leukaemia). Simultaneously of cases and controls was carried out between September 2008-December 2013. Detailed information on the study design has been previously published[24]. Study protocol was approved by the Ethics committees of the participating institutions. All participants signed an informed consent.

Briefly, for this study, participating cases were all incident cases of histologically confirmed PCa (International Classification of Diseases 10th Revision:C61,D07.5) with a Gleason score ≥6 (N=1090) identified through the medical registries of the participant hospitals in 7 Spanish provinces (Asturias, Barcelona, Cantabria, Granada, Huelva, Madrid, and Valencia) during the recruitment period. Controls were randomly selected from the general practitioner lists of selected primary healthcare centres within the catchment areas of the collaborating hospitals. This identification was possible because

the Spanish National Health System has universal access with a general practitioner assigned to each user. Therefore, a single set of population-based controls, frequency-matched to the overall distribution of cases by age in 5-year intervals, sex, and study region were selected. Eligibility criteria for all participants were: 1) age 20-85 years, 2) residence in the catchment area ≥6 months prior to recruitment, and 3) able to answer the epidemiological questionnaire. They study personnel invited them to participate by phone. We recruited 1493 male controls without previous history of PCa. The response rate was 67.4% for cases and 52.2% for controls.

From the confirmed PCa cases, we excluded those participants reporting a diagnosis of diabetes ≤1 year before the interview, (n=23:9 cases;14 controls) to allow for a minimum latency period, as well as those diagnosed with diabetes before the age of 40 (n=27:7 cases;20 controls), as this subgroup might include type 1 diabetes mellitus cases. We also excluded participants lacking information on diabetes or on potential confounding variables (education level and family history of PCa) (n=107:27 cases;80 controls), leading to a final sample size of 1047 incident cases and 1379 controls (**Figure 1**).

Study variables

Trained examiners performed the interviews for all participants. We used a structured computerised questionnaire that included socio-demographic factors, anthropometric variables, lifestyle behaviours, family history of cancer, and self-reported history of previous diseases and treatments. Interviewers were blinded to any previous hypothesis.

For this analysis, we classified study participants as having T2DM if they answered positively to the question “has your doctor ever told you that you have diabetes?”. Time since diabetes diagnosis was calculated by subtracting the age at T2DM diagnosis from

the age at the interview. We also collected data on self-reported medical treatment of T2DM, differentiated to main groups: insulin and analogues (A10A) and blood glucose-lowering drugs, excluding insulin (A10B)[25]. According to the last treatment received ≥1 year, participants were sub-classified into three categories: 1) conservative therapy, 2) oral hypoglycaemic agents, and 3) insulin, regardless of the use oral hypoglycaemic agents. The duration of treatments (in years) for metformin, insulin, and sulfonylurea use was calculated through the questions: "In what year/at what age did you start taking treatment X?", "Are you still taking the treatment?", and "At what year/at what age did you stop taking treatment X?".

PCa was classified according International Society of Urological Pathology (ISUP)[26]. Ten PCa cases could not be classified due to lack of information. For sample size reasons, grades 4 and 5 were analysed jointly. We also explored this association with other categorisation (ISUP 1vs.2vs.3-5; American Joint Committee on Cancer (AJCC) 8th ed.: I-IIA vs IIB-IV).

The genotyping of the participants with available DNA (694 cases and 1,010 controls) was performed by the Centro Nacional de Genotipado (CEGEN-ISCIII). They used the Infinium Human Exome BeadChip (Illumina, San Diego, USA), with >200,000 coding markers, plus 5000 additional custom SNPs selected from genes of interest or from previous genome-wide association studies (GWAS). We constructed a Polygenic Risk Score (PRS) to classify our participants according to their genetic polymorphic susceptibility to PCa (see Supplementary Table S1 and Gómez-Acebo, I. et al.[27]).

Statistical Analyses

The association between T2DM status and PCa was studied by fitting mixed logistic regression models. To evaluate the association between T2DM and aggressiveness of

PCa (ISUP1/ISUP2/ISUP3/ISUP4-5), we adjusted mixed multinomial logistic regression models, with controls as reference category. In both analyses, we included as putative confounding factors, age (continuous), education level (no studies-primary/secondary/high school), body mass index (BMI) one year before the interview (normal/overweight versus obesity), family history of PCa (none/second-grade/first-degree) as fixed effects terms, and interviewers as a random effect term. As a sensitivity analysis, we tested other models, adjusting also by smoking (never/ex-smoker/smoker), family history of diabetes (none/second-degree/first-degree), and physical exercise (metabolic equivalents accumulated throughout life).

To study whether diabetes treatment could be associated with PCa incidence, first, we evaluated the risk of PCa associated with each treatment regimen (conservative, oral medication, insulin+/-oral medication) using population without diabetes as reference category. Then, we quantified the association between time of use of specific antidiabetic drugs (metformin, insulin, sulfonylureas) and PCa among diabetic subgroup. In both cases, we used mixed multivariate multinomial logistic regression models with interviewers as random effect term and included the previously adjusted variables.

Finally, we evaluated the role of genetic susceptibility in the relationship between diabetes and PCa for all cases and by aggressiveness of PCa. We combined ISUP 3-5 due to the lower number of participants with genotyping data. We classified cases and controls according to PRS tertiles in controls; models were similar to those explained, including the corresponding interaction term to test the possible modifying role of PRS or stratified by this variable.

Results

Table 1 shows the main characteristics of the studied participants. According to ISUP classification, 44.8% of PCa cases had grade 1, decreasing this proportion to 35.3% in diabetic men (versus 46.3% in non-diabetic men). Compared to controls, PCa cases had a higher frequency of studies lower than secondary level (62.2% versus 51.1% of controls), family history of PCa (19.8% versus 7.4% of controls), and of having had PSA testing (96.5% versus 71.5% of controls). Men with T2DM were older, had a higher prevalence of obesity, and familiar history of T2DM, both in cases and controls. Non-diabetic men reported more first-degree relatives with PCa within cases (18.2% versus 8.1% of men with T2DM), and lower prostate-specific antigen (PSA) testing within controls (70.1% versus 78.2% of men with T2DM). Regarding duration of T2DM, on average, controls reported to have this disease for around one year more than cases. Description of other clinical characteristics of PCa cases appears in Supplementary Table S2.

Table 2 shows the associations between diabetes status, diabetes management and PCa risk, overall and by ISUP categories. After multivariate analysis, participants with T2DM seemed to have a protective association with PCa risk compared to those without diabetes (OR:0.78;95% CI:0.60–1.02). However, when ISUP grade was considered, this negative relationship was only found in grade 1: OR:0.72(95%CI:0.53–0.98). Regarding duration of treatment, an inverse association between the number of years of metformin treatment and overall PCa was observed ($OR_{per\ year}$:0.90;95%CI:0.85–0.96). Conversely, a small increase in the rates of PCa appeared with each longer duration of insulin use. In both treatments, there were no relevant differences by level of aggressiveness.

The sensitivity analyses showed similar findings (Supplementary Table S3 and S4).

According to PRS, cases with lower genetic susceptibility (tertile 1) were older, had a lower prevalence of T2DM, and lower PSA levels at diagnosis (Supplementary Table

S5). The results of the association between T2DM and PCa by genetic susceptibility to PCa is presented in **Table 3**. There were differences by tertile of PRS in all aggressiveness categories: the lower the genetic predisposition to PCa, the stronger the inverse association between T2DM and PCa.

Discussion

Our results provide new information that highlights the complexity of the relationship between T2DM and PCa. On the one hand, our results suggest that T2DM might be a protective factor for PCa, but this inverse relationship may be limited only to low-grade PCa. On the other hand, it seems that genetic susceptibility plays a modulating role in the association between T2DM and this tumour, with lower risks of PCa among those with low PRS, independent of tumour grade. Our findings also show that prolonged use of metformin reduced the PCa rates and the years of use of insulin produce a small increase in risk, without clear differences by ISUP grade.

To date, the mechanistic pathways that may explain a possible protective association between both diseases are unclear. Some authors have reported that diabetic men may have lower levels of certain hormonal factors (i.e., testosterone, insulin, and IGF-1) involved in the development of aggressive prostate cancers[28]; others have suggested that lifestyle changes after diabetes diagnosis might contribute to reducing the risk of PCa[28], although there are no indisputable preventive factors associated with this tumour. However, as in our case, most recent reports have found that the inverse association of T2DM was limited to low-grade prostate tumours[16–18], and attributed this to detection bias. PSA levels seem to be lower in men with diabetes than in those without this illness, perhaps due to lower testosterone levels[29], placing diabetic men with prostatic tumours under the established PSA cut-off point for biopsy more often. Thus, T2DM may appear ‘protective’ for those indolent low-grade PCa usually detected by PSA

239 screening. If so, diabetic subjects would have a higher proportion of aggressive tumours
240 than non-diabetics, as we observe in our study.

241 However, the inclusion of genetic data in the analysis adds new information to the
242 picture. We observed a differential effect of T2DM depending on the genetic
243 susceptibility of men to PCa. According to our data, the potential protective effect of
244 T2DM is stronger in men with a lower PRS across all aggressiveness categories. While
245 detection bias might still play a certain role, as some authors have reported lower levels
246 of PSA in men with a lower PRS[30,31], our results also support the existence of a real
247 protective association between T2DM and PCa among men with lower genetic risk of
248 PCa. These data are in line with the "genetic theory" that suggests an inverse genetic
249 link between both pathologies[28,32]. In this sense, other authors have reported a lower risk
250 of PCa among individuals with higher genetic susceptibility to T2DM[33–35].

251 In regard to the duration of specific treatments, our data provide additional evidence that
252 a higher number of years using metformin may be protective against PCa. In this sense,
253 experimental studies have found that this biguanide could have anti-ageing and anti-
254 cancer effects through many actions[36]. Nevertheless, results are not uniform; in fact,
255 recent meta-analyses reporting no association between duration of metformin use and
256 PCa[37–39] have been shown to be affected by high heterogeneity and publication bias.

257 On the contrary, we observed a small positive association for each year of insulin use
258 and PCa. This is compatible with the reported effect of insulin in the viability of PCa
259 cells[40]. However, studies have been more focused on the effect of its use than on its
260 duration, and they have yielded inconsistent findings with a meta-analysis declaring no
261 association[41], another indicating increased risk,[42] and recent original articles finding a
262 protective relationship[13,19]. Time of exposure to antidiabetic agents may also be an
263 additional source of heterogeneity[21].

One of the strengths of this multicentre study is its population-based character, making the results more generalisable. Moreover, the prevalence of comorbidities such as diabetes and obesity in the control group (15.7% and 24.6% respectively) were similar to those published in previous studies[43,44], reinforcing the representativeness of our study sample. In addition, the availability of clinical and histological information allowed us to classify tumours according to ISUP grade. Another added value of this study is the evaluation of PCa risk in regard to both T2DM treatment type and duration, an approach that, to our knowledge, very few observational studies have previously done, as well as the availability of genetic data for most of the participants.

This study also has several limitations. First, it is difficult to differentiate the effects of T2DM treatment from those of the disease itself. While there are biologic reasons for metformin to reduce risk, this may be a proxy for the results seen with diabetes duration as most of the participants with diabetes took metformin. Second, as diabetes history and treatment were self-reported, they might be affected by recall bias, a very relevant issue in case-control studies; however, its effect might be attenuated by the fact that the possible relationship between PCa and T2DM is not common knowledge. An additional third problem is the possible presence of unknown diabetes, mainly among controls; according to the International Diabetes Federation[45] around 40.7% of the European diabetic population do not know they are. In contrast, in PCa cases, undetected T2DM is probably discovered along the diagnostic process of the tumour. Thus, this underdiagnosis of diabetes, probably more pronounced in controls, would suggest that we might be underestimating the real association between T2DM and PCa. Fourth, our dataset did not allow us to differentiate between type-1 or type-2 diabetes mellitus, although we tried to minimise the probability of including cases of type-1 diabetes by excluding diabetes diagnosed before the age of 40. Fifth, we took into account some

potential confounders when analysing the association between diabetes and PCa, but residual confounding could influence our results. Finally, the reduced number of participants on medications other than metformin resulted in limited power to assess associations with PCa by grade.

In conclusion, our results suggest that T2DM might be a protective factor for PCa. We cannot rule out the existence of a detection bias, but the variation of the risk according to PCa genetic susceptibility may suggest a biological base in the relationship between both diseases. Further research is needed to confirm these results and to continue clarifying the mechanisms of this complex association.

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Availability of Data and Materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author Contributions

B. P.-G., M. K., M. P. and J.J.J.-M. conceptualisation and design of the study; R. B.-R. and E. G.-E. formal analysis of data; N. F. L. B., R. O.-R., M. V.-E., G. F.-T., P. F.-N., L. C., V. L., I. G.-A., data curation; B. P.-G., G. C.-V., J. L., J.A., and J.J.J.-M. funding acquisition; G. C.-V., N. A., M. K., and M. P. project administration; R. B.-R., E. G.-E., B. P.-G., and J.J.J.-M first draft of this paper. All authors read and approved the final version of the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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Figure and table legends

Figure 1. Participant's flowchart.

Table 1. Main characteristics of the study participants by type 2 diabetes mellitus (T2DM) and cancer status.

Table 2. Association between diabetes and diabetes treatment with prostate cancer risk, overall and by International Society of Urological Pathology (ISUP) grading of prostate cancer. Numbers may differ due to lack of information on ISUP scores in some participants.

Table 3. Association between type 2 diabetes mellitus and prostate cancer by genetic susceptibility to prostate cancer.

Figure 1. Participant's flowchart.

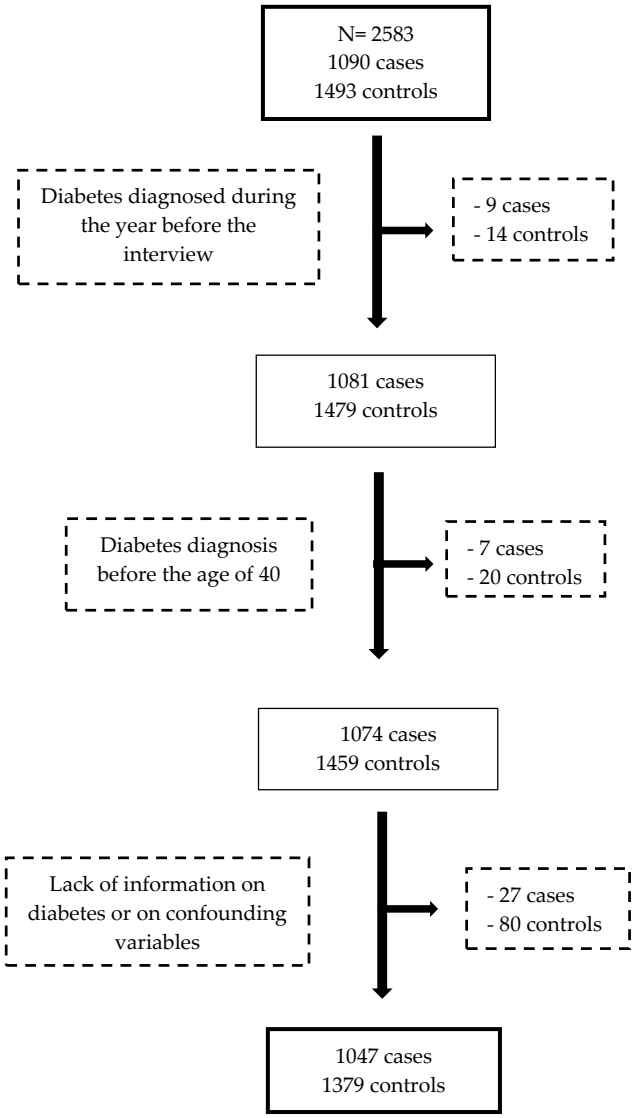

Table 1. Main characteristics of the study participants by type 2 diabetes mellitus (T2DM) and cancer status.

Study variables		Cases			Controls		
		Total (n= 1047)	**No T2DM (n=911)**	**T2DM (n=136)**	**Total (n= 1379)**	**No T2DM (n=1162)**	**T2DM (n=217)**
Age, mean (SD[a])		65.9 (7.4)	65.7 (7.4)	67.3 (7.2)	66.4 (8.6)	65.9 (8.7)	69.2 (6.8)
Education level, n (%)	<Secondary	651 (62.2)	555 (60.9)	96 (70.6)	705 (51.1)	588 (50.6)	117 (53.9)
	Secondary	233 (22.2)	207 (22.7)	26 (19.1)	377 (27.3)	324 (27.9)	53 (24.4)
	>High School	163 (15.6)	149 (16.4)	14 (10.3)	297 (21.6)	250 (21.5)	47 (21.7)
Body mass index (kg/m^2), n (%)	<25	266 (25.3)	244 (26.8)	22 (16.2)	351 (25.4)	314 (27.0)	36 (16.6)
	25–30	533 (50.7)	467 (51.2)	65 (47.8)	689 (49.9)	580 (49.9)	109 (50.2)
	>30	253 (24.1)	200 (22.0)	49 (36.0)	341 (24.6)	268 (23.1)	72 (33.2)
Family history prostate cancer, n (%)	No	840 (80.2)	719 (78.9)	121 (89.0)	1277 (92.6)	1074 (92.4)	203 (93.5)
	Second-degree	30 (2.9)	26 (2.9)	4 (2.9)	17 (1.2)	16 (1.4)	1 (0.5)
	First-degree	177 (16.9)	166 (18.2)	11 (8.1)	85 (6.2)	72 (6.2)	13 (6.0)
Family history diabetes, n (%)	No	714 (68.2)	653 (71.7)	61 (44.8)	957 (69.5)	853 (73.5)	104 (48.1)
	Second-degree	31 (3.0)	24 (2.6)	7 (5.2)	61 (4.4)	55 (4.7)	6 (2.8)
	First-degree	302 (28.8)	234 (25.7)	58 (50.0)	359 (26.1)	253 (21.8)	106 (49.1)
	Missing	-	-	-	2	1	1
Screening last 5 years PSA testing, n (%)	No	37 (3.5)	30 (3.3)	7 (5.1)	356 (28.5)	311 (29.9)	45 (21.8)
	Yes	1004 (96.5)	875 (96.7)	129 (94.9)	891 (71.5)	730 (70.1)	161 (78.2)
	Missing	6	6	-	132	121	11
T2DM duration (yrs), mean (SD)				8.9 (7.5)			10.4 (8.0)
T2DM treatment, n (%)	Conservative			12 (8.8)			29 (13.4)
	Drugs			124 (91.2)			188 (86.6)
ISUP grade[b], n (%)	1	465 (44.8)	417 (46.3)	48 (35.3)			
	2	300 (28.9)	254 (28.2)	46 (33.8)			
	3	120 (11.6)	100 (11.1)	20 (14.7)			
	4	87 (8.4)	76 (8.4)	11 (8.1)			
	5	65 (6.3)	54 (6.0)	11 (8.1)			
	Missing	10	10	-			

a: standard deviation; b: classified according to International Society of Urological Pathology (ISUP).

Table 2. Association between diabetes and diabetes treatment with prostate cancer risk, overall and by International Society of Urological Pathology (ISUP) grading of prostate cancer. Numbers may differ due to lack of information on ISUP scores in some participants.

	Overall[1]			ISUP=1[2]		ISUP=2		ISUP=3		ISUP=4–5		
	n Ca[3]	n Co[4]	OR (95% CI)	n Ca[3]	OR (95% CI)	n Ca[3]	OR (95% CI)	n Ca[3]	OR (95% CI)	n Ca[3]	OR (95% CI)	p-het[5]
No diabetes	911	1162	1.00	417	1.00	254	1.00	100	1.00	130	1.00	
Diabetes	136	217	0.78 (0.60–1.02)	48	0.72 (0.53–0.98)	46	0.99 (0.70–1.42)	20	1.12 (0.65–1.93)	22	0.83 (0.59–1.16)	0.07
Conservative management	12	29	0.48 (0.22–1.04)	2	*	3	*	2	*	5	1.45 (0.69–3.05)	*
Oral hypoglycaemic agents	95	147	0.78 (0.57–1.07)	38	0.87 (0.60–1.25)	33	1.08 (0.70–1.65)	13	1.10 (0.60–2.02)	11	0.62 (0.33–1.14)	0.26
Metformin use (years) **	78	111	0.90 (0.85–0.96)	30	0.93 (0.83–1.05)	28	0.93 (0.83–1.04)	10	0.86 (0.78–0.94)	10	0.93 (0.81–1.07)	0.94
Sulfonylurea use (years)**	36	54	0.97 (0.90–1.05)	14	1.01 (0.94–1.10)	13	0.96 (0.87–1.07)	3	*	6	0.93 (0.85–1.02)	0.36
Insulin (+/- oral hypoglycaemic agents)	29	41	1.01 (0.57–1.78)	8	0.62 (0.36–1.08)	10	1.09 (0.69–1.72)	5	1.47 (0.53–4.07)	6	1.12 (0.53–2.34)	0.10
Insulin use (years)**	24	36	1.05 (0.99–1.11)	7	1.05 (1.01–1.08)	9	1.02 (0.97–1.08)	3	*	5	1.03 (0.94–1.12)	0.39

[1] Mixed logistic regression models. [2] Mixed multinomial logistic regression models. [3] Ca: cases. [4] Co: controls.

*Values are not presented due to the small number of cases in this group. **Based on participants who reported duration of treatment.

Models for diabetes and diabetes management are adjusted for age, education level (no studies-primary/secondary/high school), body mass index (normal/overweight versus obesity), and family history of prostate cancer (none/second-degree/first-degree).

Models for metformin and sulfonylurea further adjusted for insulin treatment (yes/no) and for treatment with the other hypoglycaemic agent (yes/no).

Table 3. Association between type 2 diabetes mellitus and prostate cancer by genetic susceptibility to prostate cancer.

PRS[5]	Overall[1]			ISUP=1[2]		ISUP=2[2]		ISUP=3-5[2]	
	N Ca[3]	n Co[4]	OR (95% CI)	n Ca[3]	OR (95% CI)	n Ca[3]	OR (95% CI)	n Ca[3]	OR (95% CI)
Tertile 1	95	337	0.31 (0.11–0.87)	51	0.30 (0.08–0.97)	21	0.57 (0.14–2.29)	23	0.21 (0.05–0.97)
Tertile 2	222	337	0.55 (0.32–0.95)	93	0.47 (0.21–1.01)	63	0.68 (0.37–1.24)	66	0.67 (0.33–1.37)
Tertile 3	368	336	0.61 (0.38–0.98)	164	0.56 (0.32–0.97)	113	0.94 (0.49–1.78)	91	0.65 (0.40–1.06)
p-het			0.428		0.217		0.815		0.840

[1] Mixed logistic regression models. [2] Mixed multinomial logistic regression models. [3] Ca: cases. [4] Co: controls. [5] Tertiles of the polygenic risk score (PRS). Models for diabetes and diabetes management are adjusted for age, education level (no studies-primary/secondary/high school), body mass index (normal/overweight versus obesity), and family history of prostate cancer (none/second-degree/first-degree).