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Diabetes genes and prostate cancer in the Atherosclerosis Risk in Communities study

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Abstract

There is a known inverse association between type 2 diabetes (T2D) and prostate cancer (PrCa) that is poorly understood. Genetic studies of the T2D-PrCa association may provide insight into the underlying mechanisms of this association. We evaluated associations in the Atherosclerosis Risk in Communities study between PrCa and nine T2D single nucleotide polymorphisms (SNPs) from genome-wide association (GWA) studies of T2D (in *CDKAL1*, *CDKN2A/B*, *FTO*, *HHEX*, *IGF2BP2*, *KCNJ11*, *PPARG*, *SLC30A8*, and *TCF7L2*) and four T2D SNPs from pre-GWA studies (in *ADRB2*, *CAPN10*, *SLC2A2*, and *UCP2*). From 1987–2000, there were 397 incident PrCa cases among 6,642 men aged 45–64 years at baseline. We used race-adjusted Cox proportional hazards models to estimate associations between PrCa and increasing number of T2D risk-raising alleles. PrCa was positively associated with the *CAPN10* rs3792267 G allele (hazard ratio [HR]=1.20; 95% confidence interval [CI]=1.00, 1.44) and inversely associated with the *SLC2A2* rs5400 Thr110 allele (HR=0.85; 95% CI=0.72, 1.00), the *UCP2* rs660339 Val55 allele (HR=0.84; 95% CI=0.73, 0.97) and the *IGF2BP2* rs4402960 T allele (HR=0.79; 95% CI=0.61, 1.02; blacks only). The *TCF7L2* rs7903146 T allele was inversely associated with PrCa using a dominant genetic model (HR=0.79; 95% CI=0.65, 0.97). Further knowledge of T2D gene-PrCa mechanisms may improve understanding of PrCa etiology.

Keywords

Diabetes Mellitus; Type 2; Genetics; Risk; Polymorphism; Single Nucleotide; Prostatic Neoplasms

Introduction

Meta-analysis shows that men with type 2 diabetes (T2D) have a 16% reduction in their risk of prostate cancer (PrCa) (1), but the basis for this association is unclear. Genetic variation is thought to contribute to both diseases, and common genetic variation may explain part of the association between T2D and PrCa. Recently, genome-wide association (GWA) studies of PrCa have found susceptibility loci on ten different chromosomal regions (reviewed in 2). Interestingly, two of the genes implicated in GWA studies of PrCa also show evidence of association with T2D on a genome-wide significance level (3,4), providing support for a shared genetic contribution to the risk of T2D and PrCa. These shared associations for *HNF1B*, located on 17q and *JAZF1*, located on 7q21, were discussed by Frayling *et al.* (5) in the context of the

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T2D-PrCa link and it was suggested that exploring variation in other T2D genes in association with PrCa is warranted.

Despite inconsistencies across studies, the pre-GWA literature has nevertheless put forth some important candidate variants for T2D. SNPs in *ADRB2* (Glu27Gln; rs1042714) (6) and *CAPN10* (rs3792267) (6,7) have been associated with T2D in meta-analyses, a SNP in *SLC2A2* (Thr110Ile; rs5400) was recently identified and replicated in large case-control studies of T2D (8,9), and a SNP in *UCP2* (Ala55Val; rs660339) was associated with incident diabetes in a large cohort study (10). Examining these T2D variants from GWA studies and pre-GWA literature in association with PrCa may provide further knowledge of PrCa etiology.

We evaluated nine T2D SNPs with evidence for genome-wide significance in or near *CDKAL1*, *CDKN2A/B*, *FTO*, *HHEX*, *IGF2BP2*, *KCNJ11*, *PPARG*, *SLC30A8*, and *TCF7L2* and four T2D candidate SNPs from pre-GWA studies in *ADRB2*, *CAPN10*, *SLC2A2*, and *UCP2*) in association with prostate cancer in the bi-racial Atherosclerosis Risk in Communities (ARIC) Study. These 13 SNPs were previously genotyped in ARIC. Because of the inverse association between T2D and PrCa, we hypothesized that the T2D risk-raising allele for each SNP would be associated with a reduced risk of PrCa.

Materials and Methods

The Atherosclerosis Risk in Communities (ARIC) study

ARIC is a longitudinal cohort study designed to understand the natural history of cardiovascular disease. From 1987–1989, 7,082 men and 8,710 women aged 45 to 64 were enrolled from four US communities (Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland). Structured interviewer-administered questionnaires and in-depth clinical exams were conducted at baseline and in three year intervals after baseline (1990–1992, 1993–1995, and 1996–1998). Annual telephone interviews were also conducted to ascertain medical events.

Fasting blood samples were drawn from the antecubital vein into serum separator tubes. Serum glucose was measured using the hexokinase/glucose-6-phosphate dehydrogenase method on a Coulter DACOS device (Beckman Coulter, Fullerton, CA). Serum insulin was measured by radioimmunoassay (Insulin kit; Cambridge Medical Diagnosis, Bilerica, MA) with a 7 pmol/l limit of detection and 33% cross-reactivity with proinsulin. The reliability of these assays was 0.84 for glucose and 0.81 for insulin, as measured over a 4-week period. Further details describing blood chemistry procedures can be found elsewhere (11). Prevalent diabetes at baseline was defined as fasting blood glucose ≥126 mg/dL, non-fasting blood glucose ≥200 mg/dL, self-reported physician-diagnosed diabetes, or use of diabetes medications in the previous two weeks. At baseline, 12% of participants had prevalent diabetes.

Prostate cancer ascertainment

Ascertainment of cancer cases has been described previously (12) and is summarized here. Participants who self-reported a history of prevalent cancer at baseline were excluded from this analysis. Incident cases of PrCa were detected through linkage with state or county cancer registries covering Minneapolis, Forsyth County, Washington County, and Jackson (after 1995). Before 1995, cancer cases were determined using hospital surveillance in Jackson. Annual hospital surveillance was used in all four communities to supplement cancer registry information. For cancer-related hospital discharges not previously identified by the cancer registries, medical records were retrieved and reviewed for inclusion. Participants were also asked to report dates and locations for all hospitalizations during annual telephone interviews. Cases determined through hospital surveillance or cancer-related hospitalizations were

included in the dataset after verification. We checked all causes of death in people who died before 2001, as an indicator of missed cases, and only found four additional prostate cancer cases among the deaths (12). Primary cancer site and date of diagnosis were available for all confirmed cases from January, 1987 through December, 2000. There were 397 incident PrCa cases (268 whites, 129 blacks) over an average of 11 years of follow-up. PrCa-free survival time was calculated from the date of baseline study examination to the date of PrCa diagnosis, or until death, loss to follow-up, or December 31, 2000 for those not developing PrCa. Participants reported family history of cancer in first degree relatives in a telephone interview near the third visit. Participants were classified as having 0, ≥1, or unknown number of first degree relatives with PrCa. Information on screening practices, cancer stage, cancer grade or Gleason score was not routinely collected.

Genotyping

Genotyping methods are described here in brief. Primer sequences for the genotyping assays will be provided upon request. Genotyping of *ADRB2* rs1042714 was performed using the Pyrosequencing PSQ HS 96 instrument (Biotage AB; Uppsala, Sweden). Primers were purchased from Integrated DNA Technologies (IDT) (Coralville, IA) and the PSQ HS 96 instrument was used for detection. Genotype calling was performed automatically with the Pyrogram® generating software. Genotyping of the *UCP2* rs660339 polymorphism was done using a TaqMan assay (Applied Biosystems) with allele detection and genotype calling with the ABI 7700 and the Sequence Detection System software (Applied Biosystems). The remaining SNPs were genotyped using the TaqMan Assay-on-Demand system (Applied Biosystems; Foster City, CA). Allele detection and genotype calling were performed using the ABI 7900HT and the Sequence Detection System Software (Applied Biosystems). Genotype call rates were >90% for each SNP and sample completion rates averaged 100%.

Analysis

From 7,082 men in ARIC, we excluded races other than black or white (n=23) or blacks from Minneapolis and Washington County (n=29) due to small numbers. After further excluding those with any baseline cancer (n=310), those without information on baseline cancer (n=68), those who refused participation in genetic or cancer studies (n=8) and those missing survival time (n=2), 6,642 men (1,560 blacks and 5,082 whites) remained for this analysis. Crude hazard ratios (HRs) and 95% confidence intervals (CIs) for incident PrCa were calculated using Cox Proportional Hazards regression in STATA™ (College Station, TX) for prevalent diabetes, insulin and glucose levels (among non-diabetics who fasted for at least 8 hours) and traditional PrCa risk factors (age, race, and family history of PrCa). Because of the inverse T2D-PrCa association in the literature (1), we hypothesized that the T2D risk-raising allele would be associated with a reduced risk of PrCa. Therefore, SNPs were coded in additive genetic form (i.e., 0, 1, or 2 risk-raising alleles) using the T2D risk allele identified in previous studies. For each SNP, allele frequencies and departures from Hardy-Weinberg Equilibrium were determined separately by race. The SNPs were tested for association with PrCa in race-adjusted or race-specific Cox models using additive genetic models since additive models have been shown to perform well even when the underlying inheritance model is dominant or recessive (13,14). Interactions between the SNPs and age, race, family history, prevalent diabetes, fasting glucose levels and fasting insulin levels were evaluated using the likelihood ratio test comparing models with and without a multiplicative SNP*risk factor interaction term. We included SNPs that were statistically significant in univariable tests ($P<0.05$) in a multivariable Cox model with prevalent diabetes and traditional PrCa risk factors (age, race, and family history of PrCa). We further evaluated SNPs in models with fasting insulin and glucose to see if adding these traits attenuated SNP effects.

Results

Frequencies of the T2D risk-raising alleles in ARIC blacks and whites are reported in Table 1. Risk allele frequencies differed significantly by race (chi-square test *P*-value<0.05) for all but the *TCF7L2* and *UCP2* SNPs. SNPs were consistent with Hardy-Weinberg expectations (chi-square test *P*-value ≥0.05) except for the *SLC2A2* Thr110Ile SNP in white males (*P*=0.01). However, the *SLC2A2* SNP was consistent with Hardy-Weinberg expectations in white males and females combined in ARIC (*P*=0.17).

Crude HR and 95% CI for incident PrCa in association with traditional PrCa risk factors (age, race, and family history of PrCa), prevalent diabetes, and fasting glucose and insulin among non-diabetics are presented in Table 2. These factors were determined at baseline except for family history of PrCa, which was collected around the third study visit. The traditional risk factors were strongly associated with PrCa in this sample. There was also a significant association with unknown family history of PrCa. The rate of PrCa was lower in men with prevalent diabetes (HR=0.81), although the association was not statistically significant (*P*=0.23). There was no association between fasting glucose or insulin levels and risk of PrCa among men without prevalent diabetes.

The race-adjusted and race-specific associations between incident PrCa and the 13 T2D SNPs are reported in Table 3. The T2D risk-raising allele was associated with an increased risk of PrCa for the *CAPN10* rs3792267 SNP (race-adjusted HR=1.20; 95% CI: 1.00, 1.44) but a reduced risk of PrCa for the *SLC2A2* Thr110Ile (race-adjusted HR=0.85; 95% CI: 0.72, 1.00) and *UCP2* Ala55Val (race-adjusted HR=0.84; 95% CI: 0.73, 0.97) SNPs. There was a suggestive association with PrCa for the *TCF7L2* rs7903146 T allele using an additive genetic model (race-adjusted HR=0.88; 95% CI: 0.75, 1.03), so we evaluated dominant and recessive models. Having at least one copy of the T allele was associated with a 21% reduction in risk (race-adjusted HR=0.79; 95% CI: 0.65, 0.97) as compared to having no copies of the T allele. Having two copies of the T allele compared to one or fewer copies was not associated with PrCa risk (race-adjusted HR=1.05; 95% CI: 0.74, 1.49). There was a suggestive inverse association between PrCa and the *IGF2BP2* rs4402960 T allele in blacks (HR=0.79; 95% CI: 0.61, 1.02) but not in whites (HR=0.98; 95% CI 0.81, 1.18). Formal tests of effect modification by race showed no significant differences in effects sizes by race for the *IGF2BP2* SNP or any of the other SNPs evaluated in this study. Nevertheless, we also present race-specific effects since there may still be underlying population stratification. There were no associations between PrCa and the other SNPs evaluated in this sample. Effect sizes for the SNPs in non-diabetics were not substantially different from those for the whole population (data not shown) and were based on a smaller sample size. Furthermore, there were no statistically significant interactions between the SNPs and prevalent diabetes, so we report only the estimates for the whole population. There were also no statistically significant interactions between the SNPs and age, family history of PrCa or fasting glucose or insulin among non-diabetics (data not shown).

Results for the multivariable model of *CAPN10* rs3792267, *SLC2A2* Thr110Ile, *TCF7L2* rs7903146, *UCP2* Ala55Val, age, race, family history of PrCa and prevalent diabetes are included in Table 4. In this model, each factor was adjusted for all other factors in the model. The HR for prevalent diabetes decreased by 23% from the crude estimate (HR=0.62; 95% CI: 0.43, 0.89), mostly due to the addition of age and race (data not shown). Overall, the estimates for family history of PrCa were attenuated after adjustment for the other variables, and this was mostly due to the addition of age and race (data not shown). However, in blacks, the association with family history of PrCa was strengthened slightly in the multivariable model after addition of the SNPs. The associations for age, race and the SNPs did not change substantially from the crude estimates (race-adjusted estimates for the SNPs). We also

evaluated the SNPs in models with fasting insulin and glucose among participants without diabetes. Results for the SNPs were similar to the results when diabetes was included in the model and were based on fewer people so we only present results after adjustment for diabetes.

Discussion

There is an established inverse association between T2D and PrCa (1) that is poorly understood. To enhance understanding of mechanisms underlying the T2D-PrCa association, we examined PrCa risk in association with 13 T2D SNPs previously genotyped in ARIC. The SNPs chosen were associated with T2D in GWA studies (15), in meta-analyses (6,7)or were located in strong biological candidate genes and were recently associated with T2D in large studies (8–10). We found significant associations (P<0.05) for four of the 13 T2D SNPs (*CAPN10* rs3792267, *SLC2A2* Thr110Ile, *TCF7L2* rs7903146 and *UCP2* Ala55Val) and PrCa risk in the ARIC study, and a borderline significant association for the *IGF2BP2* SNP in blacks. Results for the other T2D SNPs with PrCa in ARIC were null. These null results should be confirmed in larger studies since power to detect moderate effects was limited (<80%) for several SNPs.

Meta-analysis of 19 studies has shown a 16% reduction in risk of PrCa among men with diabetes (1). An inverse association between T2D and PrCa was also observed in ARIC (HR 0.73; 95% CI 0.51–1.05) (12) with a magnitude of effect similar to the summary estimate reported for 10 studies with good adjustment for potential confounders (1). Given this established inverse association between T2D and PrCa, we hypothesized *a priori* that the T2D risk-raising alleles for the SNPs would be inversely associated with PrCa. The associations with PrCa were in the direction expected for the *IGF2BP2*, *SLC2A2*, *TCF7L2* and *UCP2* SNPs, but surprisingly, the G allele of the *CAPN10* SNP predicted an increased risk of both T2D (18) and PrCa (this report) in ARIC. The PrCa associations with the T2D risk-raising alleles were of similar or stronger magnitude than the associations reported in the literature for T2D for three of the five SNPs. In a large Finnish sample, the *SLC2A2* rs5400 G allele was associated with a 14% increase in risk of T2D (9) while we found a 24% reduction in risk of PrCa in ARIC whites. The *CAPN10* rs3792267 G allele was associated with a 9% increase in risk of T2D in a summary measure from 20 samples of multiple racial/ethnic origins (7) compared to a 20% increase in risk of PrCa associated with the G allele in ARIC after adjusting for race. For the *UCP2* rs660339 SNP, there was a 16% increase in risk of T2D associated with the C allele summarized over four studies of whites or Japanese individuals (6) compared to a 16% reduction in risk of PrCa associated with the C allele in whites and blacks combined in ARIC. Of the T2D SNPs, the *TCF7L2* rs7903146 variant demonstrates the strongest allelic association with T2D (OR = 1.37 per T allele) (15), but we found no published reports of T2D and the *TCF7L2* SNP using a dominant model or for the association between T2D and the *IGF2BP2* SNP in blacks. In our sample of men without prevalent cancer from ARIC, having at least one copy of the *TCF7L2* rs7903146 T allele was associated with a 48% increase in prevalent T2D after adjustment for race compared to a 21% reduction in risk of PrCa, and the *IGF2BP2* rs4402960 T allele was associated with a 16% increase in prevalent T2D compared to 21% reduction in risk of PrCa in blacks from our sample.

The prevailing hypothesis to explain the T2D-PrCa association is that the reduction in insulin, insulin-like growth factor-1 (IGF1), and testosterone levels over time in men with diabetes ameliorates the oncogenic effects of these hormones in the prostate (16). Other T2D-related factors such as medications and complications from diabetes could also be involved in the reduced risk of PrCa seen in diabetic men. Diabetes-related genes may influence PrCa through 1) a pathway that proceeds through diabetes and the concomitant “diabetic environment” and/or 2) by influencing both diabetes and PrCa through pleiotropic effects of the genes. Most studies have shown a stronger reduction in risk of PrCa associated with duration of T2D (17–20), which provides strong support for the contribution of the “diabetic environment”.

However, our observation that the *SLC2A2*, *CAPN10*, *UCP2*, and *IGF2BP2* SNPs showed a magnitude of association with PrCa that was similar to, or even stronger than, the associations reported for T2D, combined with our observation that the SNP-PrCa associations were unchanged after adjusting for T2D, suggests that at least some of the T2D-related SNPs may contribute to both diseases through pleiotropic mechanisms. The true causal relationship between T2D and PrCa is likely a complex interrelationship between the "diabetic environment" and pleiotropic genetic effects.

Interestingly, several of the T2D genes that were associated with PrCa in this report have been previously implicated in neoplastic processes such as cell proliferation, cell migration, or the oxidative stress response. Calpains, such as CAPN10, code for serine proteases that have been found to play a role in cell cycle control and cell migration(21). IGF2BP2 belongs to a family of mRNA-binding proteins that traffic untranslated insulin-like growth factor II (IGF2) mRNA (22). IGF2 binding proteins have been implicated in cell motility, cell proliferation and cancer (reviewed in 23, 24). TCF7L2 belongs to a family of transcription factors involved in apoptosis, differentiation, and migration (25). The UCP2 protein is involved in uncoupling of oxidative phosphorylation and is known to help regulate the oxidative stress response (26,27). The *SLC2A2* gene codes for GLUT2, a protein involved in monitoring blood glucose concentrations and glucose transport across the plasma membrane (28). We found no reports to suggest a mechanistic role for GLUT2 in cancer, but copy number gains in the region containing *SLC2A2* on chromosome 3q have been reported in several PrCa studies (29–31) suggesting that *SLC2A2* may be involved in PrCa progression.

A few studies have previously examined the association between PrCa and the *TCF7L2* and *PPARG* SNPs included in this report. Ilir Agalliu and colleagues (32) found no association between overall PrCa and a SNP in strong linkage disequilibrium with the rs7903146 SNP, but did see an association with advanced PrCa. The null association for the *PPARG* Pro12Ala SNP in this report is consistent with the null association reported by Paltoo and colleagues (33). However, Zmuda *et al.* (34) found an increased risk of PrCa in carriers of the *PPARG* Ala12 allele in men with BMI >27.2 kg/m^2. We found no evidence of an interaction between the Pro12Ala SNP and obesity in ARIC (data not shown).

Since we are one of the first to report associations between these T2D SNPs and risk of PrCa, our findings should be confirmed by others in independent studies. Furthermore, we performed multiple tests and had low power for some of our tests, so some of our results may be false positives or negatives. A major limitation to consider when interpreting our results is the lack of information on stage and grade of PrCa, which prevented us from evaluating the T2D SNPs in association with PrCa aggressiveness. It will be important to evaluate these SNPs in association with PrCa aggressiveness in other studies since the T2D-PrCa association has previously been shown to differ by disease stage or grade in some (17,19,35–38), but not all studies (20,39–40). Moreover, several of these T2D genes have been implicated in processes related to cell motility and migration, so it will be important to evaluate associations with advanced or metastatic disease. Despite these limitations, our findings for these T2D SNPs and PrCa in ARIC are intriguing, and we add additional evidence for a shared genetic component between T2D and PrCa that was recently highlighted in the overlapping *HNF1B* and *JAZF1* findings from GWA studies (2–5).

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Table 1

Single Nucleotide Polymorphisms Associated With Type 2 Diabetes

Gene	Common SNP Name	dbSNP ID	Risk Allele[a]	Allele Frequency[b]			Location	Function
				Whites	Blacks	*P*-value[c]		
ADRB2	Glu27Gln	rs1042714	G	0.44	0.19	≤0.001	5q31-32	beta-2-adrenergic receptor
CAPN10		rs3792267	G	0.74	0.86	≤0.001	2q37.3	calcium-dependent cysteine protease
CDKAL1		rs7754840	C	0.32	0.58	≤0.001	6p22.3	cyclin dependent kinase 5 regulatory subunit associated protein 1-like 1
CDKN2A/B		rs10811661	T	0.83	0.93	≤0.001	9p21	cyclin dependent kinase 4 inhibitor; tumor suppressor
FTO		rs8050136	A	0.41	0.45	≤0.001	16q12.2	fat mass and obesity-associated protein
HHEX		rs1111875	C	0.60	0.79	≤0.001	10q23.33	hematopoietically expressed homeo box
IGF2BP2		rs4402960	T	0.32	0.51	≤0.001	3q27.2	Insulin-like growth factor 2 mRNA binding protein
KCNJ11	Glu23Lys	rs5219	T	0.37	0.07	≤0.001	11p15.1	integral membrane protein in a K^+ signaling channel
PPARG	Pro12Ala	rs1801282	C	0.88	0.98	≤0.001	3p25	nuclear ligand-dependent transcription factor
SLC2A2	Thr110Ile	rs5400	G	0.86[d]	0.55	≤0.001	3q26.1-26.2	facilitative glucose transporter
SLC30A8		rs13266634	C	0.69	0.91	≤0.001	8q24.11	zinc transporter
TCF7L2		rs7903146	T	0.30	0.30	0.30	10q25.3	transcription factor activated in Wnt pathway
UCP2	Ala55Val	rs660339	C	0.59	0.56	0.02	11q13	mitochondrial transporter protein involved in energy metabolism

[a] Risk-raising allele for type 2 diabetes reported by the majority of previous studies.

[b] Risk allele frequency in whites and blacks from the Atherosclerosis Risk in Communities study, United States, 1987–1989.

[c] P-value for chi-square test of allele frequencies by race.

[d] $P<0.05$ for Hardy-Weinberg equilibrium test.

Table 2

Crude HR and 95% CI for Traditional PrCa Risk Factors and Diabetes-related Traits in Men From the ARIC Study, United States, 1987–1989 or 1994–1996

	Overall (N=6,642)				Whites (N=5,082)				Blacks (N=1,560)			
Risk Factor	**N**	**PrCa events**	**HR**	**95% CI**	**N**	**PrCa events**	**HR**	**95% CI**	**N**	**PrCa events**	**HR**	**95% CI**
Age at baseline (y)	6,642	397	1.10[d]	1.08, 1.12	5,082	268	1.11[d]	1.09, 1.14	1,560	129	1.10[d]	1.07, 1.13
Race												
White	5,082	268	Ref									
Black	1,560	129	1.72[d]	1.40, 2.12								
Family history of PrCa[a]												
No	5,803	283	Ref		4,082	211	Ref		1,001	72	Ref	
Yes	374	42	2.06[d]	1.49, 2.85	306	31	2.00[d]	1.37, 2.91	68	11	2.34[e]	1.24, 4.41
Unknown	1,185[b]	72	1.69[e]	1.31, 2.20	694	26	1.14	0.76, 1.71	491	46	1.96[d]	1.35, 2.84
Prevalent diabetes												
No	5,798	358	Ref		4,559	247	Ref		1,239	111	Ref	
Yes	792	35	0.81	0.57, 1.14	509	19	0.76	0.48, 1.21	283	16	0.72	0.42, 1.21
Fasting glucose (mmol/L)[c]	5,659	346	0.93	0.76, 1.15	4,467	238	1.08	0.83, 1.39	1,192	108	0.79	0.56, 1.11
Fasting insulin (pmol/L)[c]	5,659	346	1.00	1.00, 1.00	4,467	238	1.00	1.00, 1.00	1,192	108	1.00	1.00, 1.00

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; HR, hazard ratio; PrCa, prostate cancer.

[a] Family history was collected from 1994–1996. Others were collected from 1987–1989.

[b] 290 subjects were did not participate in the telephone interview from 1994–1996 and were therefore classified as unknown.

[c] Among men without prevalent diabetes

[d] $P<0.001$.

[e] $P<0.01$.

Table 3

Race-adjusted and Race-specific HR and 95% CI for Diabetes SNPs and Incident PrCa in ARIC Study Men, United States, 1987–2000

	Overall				Whites				Blacks				
Gene	**N**	**PrCa events**	**HR[a, b]**	**95% CI**	**N**	**PrCa events**	**HR[a]**	**95% CI**	**N**	**PrCa events**	**HR[a]**	**95% CI**	***P*-interaction**
ADRB2	6,122	365	1.04	0.89, 1.21	4,778	253	1.06	0.89, 1.27	1,344	112	--[d]	--[d]	0.43
CAPN10	6,240	380	1.20[g]	1.00, 1.44	4,807	257	1.29[g]	1.05, 1.60	1,433	123	0.95	0.67, 1.36	0.51
CDKAL1	6,266	379	1.01	0.87, 1.18	4,819	256	1.01	0.84, 1.22	1,447	123	1.01	0.79, 1.30	0.92
CDKN2A/B	6,304	381	1.07	0.87, 1.33	4,856	259	1.12	0.89, 1.42	1,448	122	0.83[c]	0.50, 1.37	0.24
FTO	6,253	379	1.04	0.91, 1.20	4,819	256	1.11	0.94, 1.32	1,434	123	0.91	0.71, 1.17	0.42
HHEX	6,264	382	0.96	0.82, 1.11	4,824	258	0.94	0.79, 1.13	1,440	124	0.99	0.73, 1.33	0.46
IGF2BP2	6,234	377	0.91	0.78, 1.06	4,816	255	0.98	0.81, 1.18	1,418	122	0.79[h]	0.61, 1.02	0.53
KCNJ11	6,209	381	0.97	0.82, 1.15	4,795	257	1.01	0.84, 1.20	1,414	124	--[d]	--[d]	0.06
PPARG	6,211	374	0.93[c]	0.70, 1.22	4,731	248	0.94[c]	0.70, 1.26	1,480	126	0.84[c]	0.37, 1.90	0.81
SLC2A2	6,279	384	0.85[h]	0.72, 1.00	4,859	262	0.76[g]	0.60, 0.94	1,420	122	0.97	0.76, 1.24	0.38
SLC30A8	6,224	374	0.97	0.82, 1.16	4,820	255	1.01	0.84, 1.21	1,404	119	0.77[c]	0.50, 1.20	0.27
TCF7L2[e]	6,215	379	0.88	0.75, 1.03	4,770	256	0.87	0.72, 1.06	1,445	123	0.89	0.67, 1.18	0.30
UCP2	6,235	379	0.84[g]	0.73, 0.97	4,827	258	0.84[g]	0.70, 0.99	1,408	121	0.85	0.66, 1.10	0.22

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; HR, hazard ratio; PrCa, prostate cancer; SNP, single nucleotide polymorphism.

[a] For additive genotypic model (i.e., 0, 1, or 2 diabetes risk-raising alleles) unless otherwise noted.

[b] Adjusted for race; effect sizes were similar after additional adjustment for age (y), family history (yes, no, unknown), and prevalent diabetes except for the *PPARG* SNP in blacks (fully-adjusted HR=0.97, 95% CI=0.39, 2.37).

[c] Comparing two copies of risk allele to less than two copies due to low frequency of non-risk homozygotes.

[d] Estimates not reported since they were based on less than 5 cases homozygous for the diabetes risk-raising allele.

[e] Under a dominant model: overall HR=0.79, 95% CI= 0.65, 0.97, P=0.03; whites HR=0.78, 95% CI=0.61, 0.99, P =0.04; blacks HR=0.83, 95% CI=0.59, 1.19, P=0.32.

[f] P<0.01.

[g] P<0.05.

$^{h}P<0.1$.

Table 4

Multivariable Analysis of Diabetes, Diabetes SNPs and Traditional PrCa Risk Factors in ARIC Study Men, United States, 1987–2000

	Overall		Whites		Blacks	
Risk Factor	**HR[a]**	**95% CI**	**HR[a]**	**95% CI**	**HR[a]**	**95% CI**
CAPN10 (rs3792267)[b]	1.20[g]	0.99, 1.44	1.28[f]	1.03, 1.58	0.95	0.65, 1.39
SLC2A2 (rs5400)[b]	0.85[g]	0.71, 1.01	0.75[f]	0.60, 0.95	0.98	0.76, 1.27
TCF7L2 (rs7903146)[c]	0.84	0.68, 1.03	0.81	0.63, 1.04	0.90	0.62, 1.30
UCP2 (rs660339)[b]	0.83[f]	0.72, 0.96	0.82[f]	0.69, 0.98	0.85	0.65, 1.10
Age (y)	1.11[d]	1.09, 1.13	1.12[d]	1.09, 1.15	1.09[d]	1.06, 1.13
Black race	1.75[d]	1.35, 2.28				
Family history of PrCa						
No	Ref		Ref		Ref	
Yes	1.94[d]	1.39, 2.72	1.78[e]	1.20, 2.65	2.53[e]	1.33, 4.81
Unknown	1.32[g]	1.00, 1.76	1.06	0.69, 1.62	1.70	1.13, 2.52
Prevalent Diabetes	0.62[f]	0.43, 0.89	0.63[g]	0.38, 1.03	0.64	0.36, 1.12

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; HR, hazard ratio; PrCa, prostate cancer; SNP, single nucleotide polymorphism.

[a] Each factor is adjusted for all other factors listed in a multivariable model.

[b] Using an additive genetic model (i.e., 0, 1, or 2 diabetes risk-raising alleles).

[c] Under a dominant genetic model (i.e., 0 or ≥1 diabetes risk-raising alleles).

[d] $P<0.001$.

[e] $P<0.01$.

[f] $P<0.05$.

[g] $P<0.1$.