

Research Article

Diabetes Genes and Prostate Cancer in the Atherosclerosis Risk in Communities Study

Tamra E. Meyer¹, Eric Boerwinkle¹, Alanna C. Morrison¹, Kelly A. Volcik¹, Maureen Sanderson¹, Ann L. Coker¹, James S. Pankow², and Aaron R. Folsom²

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 from genome-wide association studies of T2D (in *CDKAL1*, *CDKN2A/B*, *FTO*, *HHEX*, *IGF2BP2*, *KCNJ11*, *PPARG*, *SLC30A8*, and *TCF7L2*) and four T2D single nucleotide polymorphisms from pre-genome-wide association studies (in *ADRB2*, *CAPN10*, *SLC2A2*, and *UCP2*). From 1987 to 2000, there were 397 incident PrCa cases among 6,642 men ages 45 to 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. *Cancer Epidemiol Biomarkers Prev*; 19(2); 558-65. ©2010 AACR.

Introduction

Meta-analysis shows that men with type 2 diabetes (T2D) have a 16% reduction in their risk of prostate cancer (PrCa; ref. 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 in 10 different chromosomal regions (reviewed in ref. 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 T2D-PrCa link and it was suggested that exploring variation in other T2D genes in association with PrCa is warranted.

Authors' Affiliations: ¹Human Genetics Center and Division of Epidemiology, University of Texas Health Science Center at Houston, Houston, Texas and ²Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota

Corresponding Author: Eric Boerwinkle, Human Genetics Center, The University of Texas Health Science Center at Houston, School of Public Health, 1200 Herman Pressler, E447 Houston, TX 77030. Phone: 713-500-9816; Fax: 713-500-0900. E-mail: Eric.Boerwinkle@uth.tmc.edu

doi: 10.1158/1055-9965.EPI-09-0902

©2010 American Association for Cancer Research.

Despite inconsistencies across studies, the pre-GWA literature has nevertheless put forth some important candidate variants for T2D. Single nucleotide polymorphisms (SNP) in *ADRB2* (Glu27Gln; rs1042714; ref. 6) and *CAPN10* (rs3792267; refs. 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 biracial 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 ARIC Study

ARIC is a longitudinal cohort study designed to understand the natural history of cardiovascular disease. From

1987 to 1989, 7,082 men and 8,710 women ages 45 to 64 were enrolled from four communities in the United States (Forsyth County, NC; Jackson, MI; suburban Minneapolis, MN; and Washington County, MD). Structured interviewer-administered questionnaires and in-depth clinical exams were conducted at baseline and at 3-y 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). Serum insulin was measured by RIA (Insulin kit; Cambridge Medical Diagnosis) 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-wk period. Further details describing blood chemistry procedures can be found elsewhere (11). Prevalent diabetes at baseline was defined as a fasting blood glucose level of ≥ 126 mg/dL, a nonfasting blood glucose level of ≥ 200 mg/dL, self-reported physician-diagnosed diabetes, or use of diabetes medications in the previous 2 wk. 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 data set 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 to December 2000. There were 397 incident PrCa cases (268 whites and 129 blacks) over an average of 11 y 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 done using the Pyrosequencing PSQ HS 96 instrument (Biotage AB). Primers were purchased from Integrated DNA Technologies (IDT) and the PSQ HS 96 instrument was used for detection. Genotype calling was done 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). Allele detection and genotype calling were done 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 (HR) and 95% confidence intervals (CI) for incident PrCa were calculated using Cox proportional hazards regression in STATA for prevalent diabetes, insulin, and glucose levels (among nondiabetics who fasted for at least 8 h) 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 because 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 (χ^2 test, $P < 0.05$) for all but the *TCF7L2* and *UCP2* SNPs. SNPs were consistent with Hardy-Weinberg expectations (χ^2 test, $P \geq 0.05$) 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 nondiabetics 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

Table 1. SNPs associated with T2D

Gene	Common SNP name	dbSNP ID	Risk allele*	Allele frequency [†]			Location	Function
				Whites	Blacks	P [‡]		
<i>ADRB2</i>	Glu27Gln	rs1042714	G	0.44	0.19	≤0.001	5q31-32	β2-Adrenergic receptor
<i>CAPN10</i>		rs3792267	G	0.74	0.86	≤0.001	2q37.3	Calcium-dependent cysteine protease
<i>CDKAL1</i>		rs7754840	C	0.32	0.58	≤0.001	6p22.3	Cyclin dependent kinase 5 regulatory subunit associated protein 1-like 1
<i>CDKN2A/B</i>		rs10811661	T	0.83	0.93	≤0.001	9p21	Cyclin-dependent kinase 4 inhibitor; tumor suppressor
<i>FTO</i>		rs8050136	A	0.41	0.45	≤0.001	16q12.2	Fat mass and obesity-associated protein
<i>HHEX</i>		rs1111875	C	0.60	0.79	≤0.001	10q23.33	Hematopoietically expressed homeo box
<i>IGF2BP2</i>		rs4402960	T	0.32	0.51	≤0.001	3q27.2	Insulin-like growth factor 2 mRNA binding protein
<i>KCNJ11</i>	Glu23Lys	rs5219	T	0.37	0.07	≤0.001	11p15.1	Integral membrane protein in a K ⁺ signaling channel
<i>PPARG</i>	Pro12Ala	rs1801282	C	0.88	0.98	≤0.001	3p25	Nuclear ligand-dependent transcription factor
<i>SLC2A2</i>	Thr110Ile	rs5400	G	0.86 [§]	0.55	≤0.001	3q26.1-26.2	Facilitative glucose transporter
<i>SLC30A8</i>		rs13266634	C	0.69	0.91	≤0.001	8q24.11	Zinc transporter
<i>TCF7L2</i>		rs7903146	T	0.30	0.30	0.30	10q25.3	Transcription factor activated in Wnt pathway
<i>UCP2</i>	Ala55Val	rs660339	C	0.59	0.56	0.02	11q13	Mitochondrial transporter protein involved in energy metabolism

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

[†]Risk allele frequency in whites and blacks from the ARIC study, United States (1987-1989).

[‡]P value for χ^2 test of allele frequencies by race.

[§]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)

Risk factor	Overall (n = 6,642)			Whites (n = 5,082)			Blacks (n = 1,560)		
	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* (1.08-1.12)	5,082	268	1.11* (1.09-1.14)	1,560	129	1.10* (1.07-1.13)
Race									
White	5,082	268	Reference						
Black	1,560	129	1.72* (1.40-2.12)						
Family history of PrCa [†]									
No	5,803	283	Reference	4,082	211	Reference	1,001	72	Reference
Yes	374	42	2.06* (1.49-2.85)	306	31	2.00* (1.37-2.91)	68	11	2.34 [‡] (1.24-4.41)
Unknown	1,185 [§]	72	1.69 [‡] (1.31-2.20)	694	26	1.14 (0.76-1.71)	491	46	1.96* (1.35-2.84)
Prevalent diabetes									
No	5,798	358	Reference	4,559	247	Reference	1,239	111	Reference
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)	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)	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)

**P* < 0.001.[†]Family history was collected from 1994 to 1996. Others were collected from 1987 to 1989.[‡]*P* < 0.01.[§]Two hundred and ninety subjects did not participate in the telephone interview from 1994 to 1996 and were therefore classified as unknown.^{||}Among men without prevalent diabetes.

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 with having no copies of the T allele. Having two copies of the T allele compared with 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 effect sizes by race for the *IGF2BP2* SNP or any of the other SNPs evaluated in this study. Nevertheless, we also present race-specific effects because 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 nondiabetics 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 nondiabetics (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 the addition of SNPs. The associations for age, race, and 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 4 of the 13 T2D SNPs (*CAPN10* rs3792267,

SLC2A2 Thr110Ile, *TCF7L2* rs7903146, and *UCP2* Ala55-Val) 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 because 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; ref. 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 (16) 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

Table 3. Race-adjusted and race-specific HR and 95% CI for diabetes SNPs and incident PrCa in men from the ARIC study, United States (1987-2000)

Gene	Overall			Whites			Blacks			P interaction
	N	PrCa events	HR**† (95% CI)	N	PrCa events	HR* (95% CI)	N	PrCa events	HR* (95% CI)	
<i>ADRB2</i>	6,122	365	1.04 (0.89-1.21)	4,778	253	1.06 (0.89-1.27)	1,344	112	— (—)†	0.43
<i>CAPN10</i>	6,240	380	1.20 [§] (1.00-1.44)	4,807	257	1.29 [§] (1.05-1.60)	1,433	123	0.95 (0.67-1.36)	0.51
<i>CDKAL1</i>	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
<i>CDKN2A/B</i>	6,304	381	1.07 (0.87-1.33)	4,856	259	1.12 (0.89-1.42)	1,448	122	0.83 (0.50-1.37)	0.24
<i>FTO</i>	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
<i>HHEX</i>	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
<i>IGF2BP2</i>	6,234	377	0.91 (0.78-1.06)	4,816	255	0.98 (0.81-1.18)	1,418	122	0.79 (0.61-1.02)	0.53
<i>KCNJ11</i>	6,209	381	0.97 (0.82-1.15)	4,795	257	1.01 (0.84-1.20)	1,414	124	— (—)†	0.06
<i>PPARG</i>	6,211	374	0.93 (0.70-1.22)	4,731	248	0.94 (0.70-1.26)	1,480	126	0.84 (0.37-1.90)	0.81
<i>SLC2A2</i>	6,279	384	0.85 (0.72-1.00)	4,859	262	0.76 [§] (0.60-0.94)	1,420	122	0.97 (0.76-1.24)	0.38
<i>SLC30A8</i>	6,224	374	0.97 (0.82-1.16)	4,820	255	1.01 (0.84-1.21)	1,404	119	0.77 (0.50-1.20)	0.27
<i>TCF7L2**</i>	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
<i>UCP2</i>	6,235	379	0.84 [§] (0.73-0.97)	4,827	258	0.84 [§] (0.70-0.99)	1,408	121	0.85 (0.66-1.10)	0.22

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

†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).

‡Estimates not reported because they were based on less than five cases homozygous for the diabetes risk-raising allele.

§ $P < 0.05$.

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

¶ $P < 0.1$.

**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; $P = 0.32$.

Table 4. Multivariable analysis of diabetes, diabetes SNPs, and traditional PrCa risk factors in men from the ARIC study, United States (1987-2000)

Risk factor	Overall	Whites	Blacks
	HR* (95% CI)	HR* (95% CI)	HR* (95% CI)
<i>CAPN10</i> (rs3792267) [†]	1.20 [‡] (0.99, 1.44)	1.28 [§] (1.03-1.58)	0.95 (0.65-1.39)
<i>SLC2A2</i> (rs5400) [†]	0.85 [‡] (0.71-1.01)	0.75 [§] (0.60-0.95)	0.98 (0.76-1.27)
<i>TCF7L2</i> (rs7903146)	0.84 (0.68-1.03)	0.81 (0.63-1.04)	0.90 (0.62-1.30)
<i>UCP2</i> (rs660339) [†]	0.83 [§] (0.72-0.96)	0.82 [§] (0.69-0.98)	0.85 (0.65-1.10)
Age (y)	1.11 (1.09-1.13)	1.12 (1.09-1.15)	1.09 (1.06-1.13)
Black race	1.75 (1.35-2.28)		
Family history of PrCa			
No	Reference	Reference	Reference
Yes	1.94 (1.39-2.72)	1.78 ^{**} (1.20-2.65)	2.53 ^{**} (1.33-4.81)
Unknown	1.32 [†] (1.00-1.76)	1.06 (0.69-1.62)	1.70 (1.13-2.52)
Prevalent diabetes	0.62 [§] (0.43-0.89)	0.63 [‡] (0.38-1.03)	0.64 (0.36-1.12)

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

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

[‡] $P < 0.1$.

[§] $P < 0.05$.

^{||}Under a dominant genetic model (i.e., 0 or ≥ 1 diabetes risk-raising alleles).

^{||} $P < 0.001$.

^{**} $P < 0.01$.

Finnish sample, the *SLC2A2* rs5400 G allele was associated with a 14% increase in risk of T2D (9) compared with a 24% reduction in risk of PrCa in whites from the ARIC study. The *CAPN10* rs3792267 G allele was associated with a 9% increase in the risk of T2D in a summary measure from 20 samples of multiple racial/ethnic origins (7) compared with 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 with 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 shows the strongest allelic association with T2D (OR, 1.37 per T allele; ref. 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 with a 21% reduction in risk of PrCa, and the *IGF2BP2* rs4402960 T allele was associated with a 16% increase in prevalent T2D compared with a 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, and testosterone levels over time in men with diabetes ameliorates the oncogenic effects of

these hormones in the prostate (17). 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 (a) a pathway that proceeds through diabetes and the concomitant "diabetic environment" and/or (b) 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 (18-21), 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 (22). *IGF2BP2* belongs to a family of mRNA-binding proteins that traffic untranslated insulin-like growth

factor II mRNA (23). IGF2 binding proteins have been implicated in cell motility, cell proliferation, and cancer (reviewed in refs. 24, 25). TCF7L2 belongs to a family of transcription factors involved in apoptosis, differentiation, and migration (26). The UCP2 protein is involved in the uncoupling of oxidative phosphorylation and is known to help regulate the oxidative stress response (27, 28). The *SLC2A2* gene codes for GLUT2, a protein involved in monitoring blood glucose concentrations and glucose transport across the plasma membrane (29). 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 (30-32), 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 (33) 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 (34). However, Zmuda et al. (35) found an increased risk of PrCa in carriers of the *PPARG* Ala12 allele in men with a body mass index of >27.2 kg/m². We found no evidence of an interaction between the Pro12Ala SNP and obesity in ARIC (data not shown).

Because we are one of the first to report associations between these T2D SNPs and the risk of PrCa, our findings should be confirmed by others in independent studies. Furthermore, we did multiple tests and had low power for some of our tests, so some of our results may be false positives or false 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 because the T2D-PrCa association has previously been shown to differ by disease stage or grade in some (18, 20, 36-39), but not all studies (21, 40, 41). 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).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The authors thank the staff and participants of the ARIC study for their important contributions.

Grant Support

National Heart, Lung, and Blood Institute contracts (N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received 9/3/09; revised 11/10/09; accepted 11/20/09; published online 2/8/10.

References

- Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2006; 15:2056-62.
- Easton DF, Eeles RA. Genome-wide association studies in cancer. *Hum Mol Genet* 2008;17:R109-15.
- Winckler W, Weedon MN, Graham RR, et al. Evaluation of common variants in the six known maturity-onset diabetes of the young (MODY) genes for association with type 2 diabetes. *Diabetes* 2007; 56:685-93.
- Gudmundsson J, Sulem P, Steinthorsdottir V, et al. Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. *Nat Genet* 2007;39:977-83.
- Frayling T, Colhoun H, Florez J. A genetic link between type 2 diabetes and prostate cancer. *Diabetologia* 2008;51:1757-60.
- Parikh H, Groop L. Candidate genes for type 2 diabetes. *Rev Endocr Metab Disord* 2004;5:151-76.
- Jensen DP, Urhammer SA, Eiberg H, et al. Variation in CAPN10 in relation to type 2 diabetes, obesity and quantitative metabolic traits: studies in 6018 whites. *Mol Genet Metab* 2006;89:360-7.
- Laukkanen O, Lindstrom J, Eriksson J, et al. Polymorphisms in the *SLC2A2* (GLUT2) gene are associated with the conversion from impaired glucose tolerance to type 2 diabetes: the Finnish Diabetes Prevention Study. *Diabetes* 2005;54:2256-60.
- Willer CJ, Bonnycastle LL, Conneely KN, et al. Screening of 134 single nucleotide polymorphisms (SNPs) previously associated with type 2 diabetes replicates association with 12 SNPs in nine genes. *Diabetes* 2007;56:256-64.
- Yu X, Jacobs DR, Jr., Schreiner PJ, et al. The uncoupling protein 2 Ala55Val polymorphism is associated with diabetes mellitus: the CARDIA study. *Clin Chem* 2005;51:1451-6.
- ARIC Coordinating Center. Operations manual no. 10: clinical chemistry determinations, version 1.0. Chapel Hill (NC): 1987.
- Tande AJ, Platz EA, Folsom AR. The metabolic syndrome is associated with reduced risk of prostate cancer. *Am J Epidemiol* 2006;164: 1094-102.
- Balding DJ. A tutorial on statistical methods for population association studies. *Nat Rev Genet* 2006;7:781-91.
- Horvath S, Xu X, Laird NM. The family based association test method: strategies for studying general genotype-phenotype associations. *Eur J Hum Genet* 2001;9:301-6.
- Prokopenko I, McCarthy MI, Lindgren CM. Type 2 diabetes: new genes, new understanding. *Trends Genet* 2008;24:613-21.
- Garant MJ, Kao WL, Brancati F, et al. SNP43 of CAPN10 and the risk of type 2 diabetes in African-Americans. The Atherosclerosis Risk in Communities Study. *Diabetes* 2002;51:231-37.
- Giovannucci E, Michaud D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. *Gastroenterology* 2007;132:2208-25.

18. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Diabetes mellitus and risk of prostate cancer (United States). *Cancer Causes Control* 1998;9:3–9.
19. Rodriguez C, Patel AV, Mondul AM, et al. Diabetes and risk of prostate cancer in a prospective cohort of US men. *Am J Epidemiol* 2005;161:147–52.
20. Darbinian JA, Ferrara AM, Van Den Eeden SK, Quesenberry CP, Jr., Fireman B, Habel LA. Glycemic status and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2008;17:628–35.
21. 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.
22. Carragher NO, Frame MC. Calpain: a role in cell transformation and migration. *Int J Biochem Cell Biol* 2002;34:1539–43.
23. Nielsen J, Christiansen J, Lykke-Andersen J, et al. A family of insulin-like growth factor II mRNA-binding proteins represses translation in late development. *Mol Cell Biol* 1999;19:1262–70.
24. Yaniv K, Yisraeli JK. The involvement of a conserved family of RNA binding proteins in embryonic development and carcinogenesis. *Gene* 2002;287:49–54.
25. Yisraeli JK. VICKZ proteins: a multi-talented family of regulatory RNA-binding proteins. *Biol Cell* 2005;97:87–96.
26. Terry S, Yang X, Chen MW, et al. Multifaceted interaction between the androgen and Wnt signaling pathways and the implication for prostate cancer. *J Cell Biochem* 2006;99:402–10.
27. Chan CB, Harper ME. Uncoupling proteins: role in insulin resistance and insulin insufficiency. *Curr Diabetes Rev* 2006;2:271–83.
28. Mattiasson G, Sullivan PG. The emerging functions of UCP2 in health, disease, and therapeutics. *Antioxid Redox Signal* 2006;8:1–38.
29. Im SS, Kim SY, Kim HI, et al. Transcriptional regulation of glucose sensors in pancreatic β cells and liver. *Curr Diabetes Rev* 2006;2:11–8.
30. Cher ML, Bova GS, Moore DH, et al. Genetic alterations in untreated metastases and androgen-independent prostate cancer detected by comparative genomic hybridization and allelotyping. *Cancer Res* 1996;56:3091–102.
31. Sattler HP, Lensch R, Rohde V, et al. Novel amplification unit at chromosome 3q25-27 in human prostate cancer. *Prostate* 2000;45:207–15.
32. Sattler HP, Rohde V, Bonkhoff H, et al. Comparative genomic hybridization reveals DNA copy number gains to frequently occur in human prostate cancer. *Prostate* 1999;39:79–86.
33. Ilir Agalliu MS, Prokunina-Olsson L, Johanneson B, Collins FS, Stanford JL, Ostrander EA. Evaluation of a variant in the transcription factor 7-like 2 (TCF7L2) gene and prostate cancer risk in a population-based study. *Prostate* 2008;68:740–7.
34. Paltoo D, Woodson K, Taylor P, et al. Pro12Ala polymorphism in the peroxisome proliferator-activated receptor- γ (PPAR- γ) gene and risk of prostate cancer among men in a large cancer prevention study. *Cancer Lett* 2003;191:67–74.
35. Zmuda JM, Modugno F, Weissfeld JL, et al. Peroxisome proliferator-activated receptor- γ polymorphism, body mass and prostate cancer risk: evidence for gene-environment interaction. *Oncology* 2006;70:185–9.
36. Rosenberg DJ, Neugut AI, Ahsan H, Shea S. Diabetes mellitus and the risk of prostate cancer. *Cancer Invest* 2002;20:157–65.
37. Zhu K, Lee IM, Sesso HD, et al. History of diabetes mellitus and risk of prostate cancer in physicians. *Am J Epidemiol* 2004;159:978–82.
38. Gong Z, Neuhauser ML, Goodman PJ, et al. Obesity, diabetes, and risk of prostate cancer: results from the Prostate Cancer Prevention Trial. *Cancer Epidemiol Biomarkers Prev* 2006;15:1977–83.
39. Leitzmann MF, Ahn J, Albanes D, et al. Diabetes mellitus and prostate cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Cancer Causes Control* 2008;19:1267–76.
40. 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.
41. Calton BA, Chang S-C, Wright ME, 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.