



# Editor's choice: Association of Type 2 Diabetes Susceptibility Variants with Advanced Prostate Cancer Risk in the Breast and Prostate Cancer Cohort Consortium

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## Original Contribution

# Association of Type 2 Diabetes Susceptibility Variants With Advanced Prostate Cancer Risk in the Breast and Prostate Cancer Cohort Consortium

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Observational studies have found an inverse association between type 2 diabetes (T2D) and prostate cancer (PCa), and genome-wide association studies have found common variants near 3 loci associated with both diseases. The authors examined whether a genetic background that favors T2D is associated with risk of advanced PCa. Data from the National Cancer Institute's Breast and Prostate Cancer Cohort Consortium, a genome-wide association study of 2,782 advanced PCa cases and 4,458 controls, were used to evaluate whether individual single nucleotide polymorphisms or aggregations of these 36 T2D susceptibility loci are associated with PCa. Ten T2D markers near 9 loci (*NOTCH2*, *ADCY5*, *JAZF1*, *CDKN2A/B*, *TCF7L2*, *KCNQ1*, *MTNR1B*, *FTO*, and *HNF1B*) were nominally associated with PCa ( $P < 0.05$ ); the association for single nucleotide polymorphism rs757210 at the *HNF1B* locus was significant when multiple comparisons were accounted for (adjusted  $P = 0.001$ ). Genetic risk scores weighted by the T2D log odds ratio and multilocus kernel tests also indicated a significant relation between T2D variants and PCa risk. A mediation analysis of 9,065 PCa cases and 9,526 controls failed to produce evidence that diabetes mediates the association of the *HNF1B* locus with PCa risk. These data suggest a shared genetic component between T2D and PCa and add to the evidence for an interrelation between these diseases.

carcinoma; diabetes mellitus, type 2; genetic predisposition to disease; genetics; genome-wide association study; humans; polymorphism, single nucleotide; prostatic neoplasms

Abbreviations: BPC3, Breast and Prostate Cancer Cohort Consortium; CI, confidence interval; GRS, genetic risk score; OR, odds ratio; PCa, prostate cancer; SNP, single nucleotide polymorphism; T2D, type 2 diabetes.

Prostate cancer (PCa) and type 2 diabetes (T2D) are two of the most common chronic diseases afflicting the US aging male population (1, 2). Observational studies have consistently shown an apparent inverse association between T2D and risk of PCa, with meta-analysis risk ratios ranging from 0.84 to 0.91 (3, 4). The reduction in PCa risk has been reported to increase with years since T2D diagnosis, with men who have had T2D for more than 15 years being at a 22% reduced hazard of PCa (5). The association is

poorly understood, with one hypothesis suggesting that the metabolic status of men with T2D could move gradually from hyperinsulinemia to endogenous insulin deficiency, which could mitigate the oncogenic action of insulin in the prostate (6, 7).

Recently, 3 shared genomic regions for T2D and PCa have been highlighted. The first region, located on chromosome 17, is in intron 2 of *HNF1B*, formerly known as *TCF2*. The major allele A of rs4430796 is positively

associated with PCa risk (odds ratio (OR) = 1.22) and inversely associated with risk of T2D (OR = 0.91) (8–10). The second region is located on chromosome 7 near the *JAZF1* locus, where the major allele G of rs10486567 is inversely associated with risk of PCa (aggressive PCa: OR = 0.89; nonaggressive PCa: OR = 0.74) (11), whereas the minor allele G of rs864745 is positively associated with T2D (OR = 1.10) (12). *THADA* is the third region, located on chromosome 2, with the minor allele A of rs1465618 being associated with PCa (OR = 1.08) (13) and the major allele T of rs7578597 associated with T2D (OR = 1.15) (12). However, the single nucleotide polymorphisms (SNPs) for T2D and PCa in the *JAZF1* and *THADA* regions are weakly linked, with  $R^2$  values of 0.03 and 0.02, respectively. It is not clear that these associations are driven by the same haplotype (14, 15).

Stevens et al. (16) investigated the T2D-PCa relation further and concluded that diabetic status did not mediate the observed relation between the *HNF1B* and *JAZF1* gene variants and PCa risk. In the Atherosclerosis Risk in Communities cohort, Meyer et al. (17) examined the relation of T2D-associated variants with risk of PCa and found that 4 of 13 T2D SNPs were nominally associated with PCa, which provides additional evidence that some of the T2D-PCa association could be driven by shared genetic factors. Another study by Pierce et al. (18) evaluated the ability of risk scores, consisting of 18 replicated T2D risk variants, to predict PCa risk and concluded that persons with increased genetic susceptibility to T2D have a reduced risk of PCa. However, in a recent study of 5 racial/ethnic groups in the Multiethnic Cohort and PAGE (Population Architecture using Genomics and Epidemiology), Waters et al. (19) found no association between T2D risk variants, either individually or in risk scores, and PCa risk.

With a large sample size and an expanded set of recently published T2D susceptibility loci, we aimed to investigate whether and to what extent individual T2D risk variants and aggregations of T2D replicated risk variants are associated with PCa risk. We used novel approaches to test both whether these risk variants are inversely associated with PCa risk in accordance with the inverse relation observed between T2D and PCa in observational studies and, more generally, whether these T2D loci are associated with PCa risk without regard to directionality of association. Additionally, using causal inference methods, our study attempted to more definitively investigate the potential for mediation of the effect of *HNF1B* on PCa risk through T2D phenotype.

## MATERIALS AND METHODS

Genotyping data for PCa cases and controls came from the National Cancer Institute's Breast and Prostate Cancer Cohort Consortium (BPC3). The BPC3 is a consortium of prospective cohort studies, with contributors including the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (20), the American Cancer Society Cancer Prevention Study II Nutrition Cohort (21), the European Prospective Investigation into Cancer and Nutrition (22), the Health Professionals Follow-up Study, the Melbourne Collaborative Cohort Study (23), the Multiethnic Cohort Study (24),

the Physicians' Health Study, and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (25). In total, 9,065 PCa cases and 9,526 controls comprised the PCa nested case-control study. Diabetes phenotype was self-reported at study baseline, with data available for 96.7% of BPC3 participants. A genome-wide association scan was conducted on a subset of 2,782 European cases with advanced disease and 4,458 controls with European ancestry. Advanced PCa was defined as PCa cases that had either a high histologic grade (Gleason score  $\geq 8$ ) or extraprostatic extension (stage C/D). All controls were free of PCa at the time of selection and were sampled from the same cohort as the cases. Controls were age-matched to cases, and study indicator variables were used to adjust for sampling differences between studies. Informed consent was received from all study participants, and all study protocols were reviewed by the institutional review boards of the National Cancer Institute and each participating study center.

A literature search was conducted to find robustly replicated disease susceptibility loci that are associated with T2D at genome-wide significance levels ( $P < 5 \times 10^{-8}$ ). In total, 36 independent autosomal loci associated with T2D were identified, and published T2D risk alleles and odds ratios were extracted (9, 10, 12, 26–36).

Individual association tests were carried out for each T2D SNP with PCa risk in the BPC3 genome-wide association study (37). Quality control filters were used to remove samples with heterozygosity, underperforming samples or markers, markers with genotype frequencies that significantly departed from Hardy-Weinberg equilibrium, and subjects with significant evidence of non-European ancestry or sample structure. Of the 36 T2D SNPs, 19 were not directly genotyped on the Illumina HumanHap610 Quad Arrays (Illumina, San Diego, California) and were therefore imputed with MACH (<http://www.sph.umich.edu/csg/abecasis/MaCH/>) (38). MACH references the HapMap (<http://hapmap.ncbi.nlm.nih.gov/>) CEU population (Utah residents with Northern and Western European ancestry from the Centre d'Etude du Polymorphisme Humain (CEPH) collection) to infer expected genotype counts for each marker locus. MACH quality scores and  $R^2$  values were more than 0.85 and 0.75, respectively, for all imputed SNPs. Logistic regression models were used to test for T2D SNP associations with PCa risk. The number of T2D risk alleles was used as the exposure, and adjustment was made for cohort (indicator variables). A nominal association  $P$  value of 0.05 was used to assess whether T2D markers exhibited more significant associations with PCa than would be expected by chance. Additional binomial and permutation tests (39) (10,000 permutations) were carried out to test for a relation in risk allele directionality and significant departures of the PCa association statistics from the null distribution, respectively.

The T2D SNPs were combined to form a genetic risk score (GRS) using the `--score` command in PLINK (40). The GRS was calculated in two ways. The first method, referred to here as the count method, involved summing the number of T2D risk alleles at each locus (0, 1, or 2) and then summing across all T2D loci. This count method is an additive model that weights each locus equally and assumes no gene-gene interactions. The second method, referred to

here as the weighted method, uses the log odds ratio of the published T2D loci to weight the sum of T2D risk alleles at each locus and then sums across all T2D loci. The weighted method is an additive model that weights each locus in accordance with the T2D literature and assumes no gene-gene interactions. The rationale for weighting is to create a score that is the best GRS for T2D and therefore can be used as an instrument for testing an association with PCa. For each GRS method, we included the GRS as a predictor in a logistic regression model with PCa case-control status as the outcome, and we adjusted for cohort with an indicator variable. Cohort-specific associations were also calculated.

Additionally, multilocus linear kernel tests were used to assess the joint relation between the 36 T2D variants and PCa risk. These linear models allow associations of multiple genetic loci to be tested simultaneously with one test statistic (41) and have been generalized for dichotomous outcomes (42). Unlike the GRS methods, these tests require no prespecification of risk allele directionality (i.e., that the risk allele is associated with increased risk of T2D and decreased risk of PCa).

The *HNF1B* locus was the only T2D locus significantly associated with PCa risk after adjustment for multiple comparisons, so it was carried forward for mediation analysis to evaluate whether T2D phenotype is a potential mediator of the relation between *HNF1B* and PCa. We used an expanded set of data on 9,065 PCa cases (including nonaggressive cases) and 9,526 controls from the BPC3 (43) with self-reported information on diabetes phenotype. Data on rs7501939 at *HNF1B* were generated as part of a previous project characterizing known PCa loci; this SNP is in high linkage disequilibrium with rs757210 ( $R^2 = 0.81$ ). This was the only T2D risk marker typed in the larger BPC3 data set. To assess mediation, we used the mediation framework proposed by Baron and Kenny (44), extended into the counterfactual framework by VanderWeele and Vansteelandt (45) as direct and indirect effects, and further generalized for use with dichotomous intermediate and outcome. This framework for mediation analysis is flexible to an interaction between exposure and an intermediate factor, has a causal interpretation, and can assess mediation on both the multiplicative and additive scales. Assessing mediation in this manner involved fitting both an outcome model and a mediator model. The outcome model was a logistic regression model that modeled PCa as the outcome, included parameters for the T2D variant of interest and diabetes phenotype, and adjusted for potential confounders of the exposure-outcome and intermediate-outcome relations, including cohort indicator, age at baseline, and body mass index (weight (kg)/height (m)<sup>2</sup>). The mediator model was a logistic regression model that modeled diabetes phenotype as the outcome, included a parameter for the T2D variant of interest, and controlled for potential confounders, including cohort indicator, age at baseline, and body mass index. In the mediator model, the case-control nature of the BPC3 needed to be accounted for to obtain consistent effect estimates. This was accomplished by fitting the model only in the PCa controls, who represent the study's base population, and assuming a rare outcome. Once both the outcome and mediator models were fitted, parameter estimates were

used to calculate direct and indirect (mediated) effects by which to assess mediation (45).

The PCa study was conducted between May and August of 2011. All statistical analyses were carried out in SAS 9.1 (SAS Institute Inc., Cary, North Carolina) and R 2.11.1 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

Results from the individual association tests showed that 10 of the 36 T2D markers had a *P* value less than 0.05 for association with PCa, significantly more than the 1.8 markers that would be expected by chance ( $P = 7.5 \times 10^{-6}$ ) (Table 1). These markers include the *HNF1B* and *JAZF1* loci, as well as *NOTCH2*, *ADCY5*, *CDKN2A/B*, *TCF7L2*, *MTNR1B*, *FTO*, and 2 independent loci at *KCNQ1* (Table 1). After permutation adjustment for multiple comparisons, only *HNF1B* remained significant (adjusted  $P = 0.001$ ). Small fluctuations in effect estimates of  $\leq 3\%$  were observed when adjustment for diabetes status was made in the models, with overall conclusions remaining the same (results not shown). We observed an inflation in the observed *P* values for these 36 SNPs ( $\lambda_{GC} = 2.0$ ; Figure 1). When the observed  $\lambda_{GC}$  was compared with the distribution of permutation  $\lambda_{GC}$  values, the observed  $\lambda_{GC}$  was significantly elevated ( $P = 0.03$ ), which indicated that the distribution of association *P* values was significantly lower than expected.

We used exact binomial tests to assess whether significantly more T2D risk alleles were inversely associated with PCa risk than would be expected by chance. By chance alone, 1.8 of the 36 markers would be expected to be significant, of which, under the null, 0.9 would be expected to be significantly associated with increased risk of PCa and 0.9 would be expected to be significantly associated with decreased risk of PCa. In our data, we observed 2 T2D loci that were significantly associated with increased PCa risk, which did not differ statistically from the 0.9 loci expected by chance ( $P = 0.23$ ). However, the 8 T2D loci we observed to be significantly associated with reduced risk of PCa were significantly more than the 0.9 that would be expected by chance ( $P = 2.45 \times 10^{-6}$ ), which indicates that more T2D risk alleles than expected are associated with reduced risk of PCa.

Associations for GRS using both the unweighted count and the weighted log odds method are shown in Table 2. The risk score for the unweighted count did not show evidence for an association of these genetic variants with PCa risk. However, a significant association was observed for the weighted log odds method when *HNF1B* was both included in ( $P = 0.002$ ) and excluded from ( $P = 0.015$ ) the GRS. No changes in results were observed when we adjusted for diabetes status in the models (results not shown). Study-specific analyses showed that the log odds-weighted GRS was statistically significant only in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, although the test for heterogeneity indicated no significant departures from homogeneity ( $P = 0.60$ ).

The multilocus kernel test that jointly tested for a PCa association with all 36 T2D loci without specifying weight

**Table 1.** Individual Associations of 36 Independent Type 2 Diabetes Susceptibility Variants With Prostate Cancer Risk in the Breast and Prostate Cancer Cohort Consortium<sup>a</sup>

Chromosome	Reported Gene(s)	Single Nucleotide Polymorphism	Genotyped? <sup>b</sup>	Type 2 Diabetes Risk Allele	Frequency of Risk Allele	Odds Ratio <sup>c</sup>	95% Confidence Interval	P Value	Adjusted P Value
1	<i>NOTCH2</i>	rs10923931	No	T	0.11	0.86 <sup>d</sup>	0.76, 0.96	0.008*	0.255
1	<i>PROX1</i>	rs340874	Yes	C	0.52	1.01	1.08, 0.94	0.845	1.000
2	<i>GCKR</i>	rs780094	Yes	C	0.61	0.98 <sup>d</sup>	1.05, 0.91	0.498	1.000
2	<i>THADA</i>	rs7578597	Yes	T	0.91	1.03	1.16, 0.91	0.644	1.000
2	<i>BCL11A</i>	rs243021	Yes	A	0.47	1.02	0.95, 1.10	0.511	1.000
2	<i>IRS1</i>	rs2943641	Yes	C	0.64	0.95 <sup>d</sup>	1.02, 0.88	0.140	0.995
3	<i>PPARG</i>	rs1801282	No	C	0.86	0.96 <sup>d</sup>	1.07, 0.87	0.465	1.000
3	<i>ADAMTS9</i>	rs4607103	No	C	0.76	0.99 <sup>d</sup>	1.08, 0.91	0.853	1.000
3	<i>ADCY5</i>	rs11708067	No	A	0.78	0.91 <sup>d</sup>	0.99, 0.84	0.028*	0.630
3	<i>IGF2BP2</i>	rs4402960	Yes	T	0.32	1.03	0.95, 1.11	0.456	1.000
4	<i>WFS1</i>	rs10010131	No	G	0.60	1.00	1.07, 0.93	0.924	1.000
5	<i>ZBED3</i>	rs4457053	No	G	0.29	1.02	0.94, 1.10	0.672	1.000
6	<i>CDKAL1</i>	rs7754840	Yes	C	0.32	1.04	0.97, 1.13	0.270	1.000
7	<i>DGKB</i>	rs2191349	No	T	0.52	1.00	1.07, 0.93	0.945	1.000
7	<i>JAZF1</i>	rs864745	No	T	0.50	1.08	1.16, 1.01	0.033*	0.694
7	<i>GCK</i>	rs4607517	Yes	A	0.15	1.06	0.96, 1.16	0.256	1.000
7	<i>KLF14</i>	rs972283	No	G	0.53	1.02	1.09, 0.95	0.627	1.000
8	<i>TP53INP1</i>	rs896854	Yes	T	0.51	1.02	1.09, 0.95	0.668	1.000
8	<i>SLC30A8</i>	rs13266634	Yes	C	0.68	1.00	1.08, 0.93	0.963	1.000
9	<i>CDKN2A/B</i>	rs10811661	No	T	0.82	0.91 <sup>d</sup>	1.00, 0.83	0.045*	0.809
9	<i>TLE4</i>	rs13292136	No	C	0.93	0.93 <sup>d</sup>	1.07, 0.81	0.312	1.000
10	<i>CDC123/CAMK1D</i>	rs12779790	No	G	0.18	1.06	0.97, 1.16	0.206	1.000
10	<i>HHEX/IDE</i>	rs1111875	Yes	C	0.58	1.01	1.09, 0.94	0.713	1.000
10	<i>TCF7L2</i>	rs7903146	Yes	T	0.28	0.90 <sup>d</sup>	0.83, 0.97	0.009*	0.276
11	<i>KCNQ1</i>	rs231362	No	G	0.50	0.92 <sup>d</sup>	0.86, 0.98	0.014*	0.393
11	<i>KCNQ1</i>	rs2237892	Yes	C	0.94	0.85 <sup>d</sup>	0.98, 0.74	0.030*	0.659
11	<i>KCNJ11</i>	rs5215	Yes	T	0.61	0.99 <sup>d</sup>	1.06, 0.92	0.719	1.000
11	<i>CENTD2</i>	rs1552224	Yes	A	0.83	1.00	1.10, 0.91	0.963	1.000
11	<i>MTNR1B</i>	rs10830963	No	G	0.28	1.10	1.01, 1.19	0.023*	0.561
12	<i>HMG2</i>	rs1531343	No	C	0.10	0.98 <sup>d</sup>	0.88, 1.10	0.764	1.000
12	<i>TSPAN8/LGR5</i>	rs7961581	No	C	0.26	1.05	0.97, 1.13	0.259	1.000
12	<i>HNF1A/TCF1</i>	rs7957197	No	T	0.80	0.96 <sup>d</sup>	1.05, 0.88	0.346	1.000
15	<i>ZFAND6</i>	rs11634397	No	G	0.66	1.04	1.12, 0.96	0.346	1.000
15	<i>PRC1</i>	rs8042680	Yes	A	0.32	1.04	0.97, 1.12	0.286	1.000
16	<i>FTO</i>	rs9939609	No	A	0.40	0.93 <sup>d</sup>	0.86, 1.00	0.041*	0.775
17	<i>HNF1B/TCF2</i>	rs757210	Yes	T	0.35	0.85 <sup>d</sup>	0.79, 0.92	3e <sup>-05*</sup>	0.001 <sup>e</sup>

Abbreviations: CI, confidence interval; OR, odds ratio; T2D, type 2 diabetes; RA, risk allele; SNP, single nucleotide polymorphism.

\*  $P < 0.05$ .

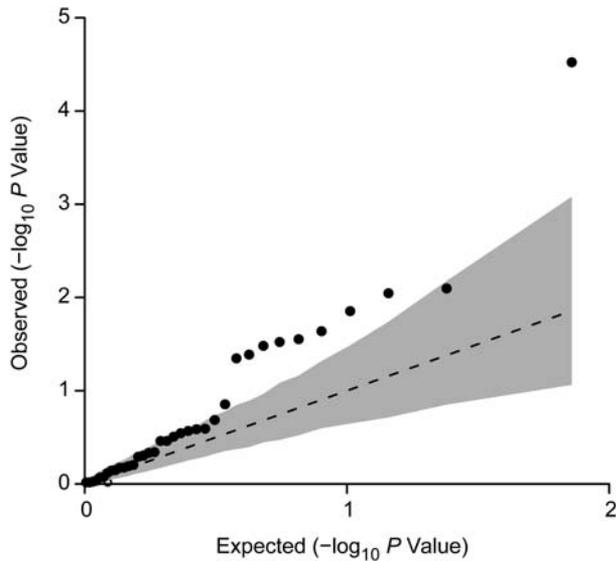
<sup>a</sup> Association tests were carried out in the Breast and Prostate Cancer Cohort Consortium using a log-additive genetic model with adjustment made for cohort indicators.

<sup>b</sup> Indicates whether or not variants were genotyped. Variants that were not directly genotyped were imputed.

<sup>c</sup> Odds ratio for the increase in prostate cancer risk associated with a 1-unit increase in the number of type 2 diabetes risk alleles carried at each locus.

<sup>d</sup> Association for prostate cancer was in the inverse direction.

<sup>e</sup> Significant after permutation correction for multiple testing.



**Figure 1.** Quantile-quantile plot comparing the uniformly distributed  $-\log_{10} P$  values for the 36 type 2 diabetes (T2D) susceptibility markers with  $-\log_{10} P$  values observed in the Breast and Prostate Cancer Cohort Consortium data set when the authors tested for an association with prostate cancer (PCa) risk by means of a Wald test. The dotted line shows the expected  $-\log_{10} P$  value distribution. The black points represent observed  $P$  values for the association of each T2D locus with PCa risk. The gray region is the 95% confidence interval for 10,000 permutations. The inflation index ( $\lambda_{GC}$ ) of 1.95 is significantly elevated ( $P=0.02$ ), which indicates an overall inflation in association  $P$  values but gives no information about the directionality of association between the T2D variants and PCa risk.

or directionality of risk alleles was statistically significant ( $P=0.0001$ ). When *HNF1B* was removed from the list of included markers and the remaining 35 markers were fitted, the  $P$  value was attenuated but remained significant ( $P=0.01$ ), which indicated that a substantial portion of the association was a result of the *HNF1B* locus but that other T2D loci were associated with PCa as well.

We conducted mediation analyses for the *HNF1B* locus to investigate whether the locus had effects that act directly on PCa risk or whether the effects of the locus were mediated through diabetes phenotype (Table 3). The outcome model produced significant evidence for an association between *HNF1B* and PCa risk (OR=0.83, 95% confidence interval (CI): 0.79, 0.86;  $P=6.37 \times 10^{-19}$ ) and an association between diabetes phenotype and PCa risk (OR=0.76, 95% CI: 0.66, 0.87;  $P=8.13 \times 10^{-5}$ ). The mediator model indicated that the minor T allele of rs7501939 was not statistically significantly associated with an increased risk of diabetes among the 9,526 PCa controls (OR=1.10, 95% CI: 0.97, 1.25;  $P=0.14$ ), although the per-allele odds ratio for association with T2D was consistent with previous reports (8–10). When these results were combined together, the estimated direct effect of *HNF1B* on PCa risk was statistically significant (OR=0.83, 95% CI: 0.79, 0.86;  $P=1.02 \times 10^{-18}$ ), but the mediated (indirect) effect through diabetes phenotype was

nonsignificant (OR=1.00, 95% CI: 1.00, 1.00;  $P=0.71$ ). These results are in agreement with the standard mediation analysis, which produced an insignificant 0.5% change in the parameter estimate for the effect of *HNF1B* when diabetes status was included as a covariate.

## DISCUSSION

Our study suggests that genetic variants associated with T2D are also associated with PCa risk. Ten of 36 T2D susceptibility markers were nominally associated with PCa risk at *NOTCH2*, *ADCY5*, *JAZF1*, *CDKN2A/B*, *TCF7L2*, *KCNQ1*, *MTNR1B*, *FTO*, and *HNF1B*, although only the *HNF1B* locus remained significantly associated with PCa risk after adjustment for multiple testing. However, log odds ratio-weighted GRS and kernel machine models also were associated with PCa risk both with and without inclusion of the *HNF1B* locus, which suggests that other genetic variants associated with T2D risk also contribute to PCa risk. Finally, mediation analysis provided insufficient evidence that the association of the *HNF1B* locus with PCa risk is mediated through diabetes phenotype.

Our study adds to the evidence that a genetic background favorable to the development of T2D is associated with PCa risk. The *HNF1B* locus was most strongly associated with PCa risk in this analysis and accounted for some but not all of the association between the T2D variants and PCa risk in the GRS and the kernel regression. The noted inflation in our association  $P$  values for other T2D SNPs is consistent with what others have observed (17, 18) and indicates that more germline variants are held in common between T2D and PCa than would be expected by chance.

Our study's large sample size and recently published T2D susceptibility loci permitted us to detect potentially novel genetic relations between T2D and PCa that have not been reported previously. Seven loci (*NOTCH2*, *ADCY5*, *CDKN2A/B*, *TCF7L2*, *KCNQ1*, *MTNR1B*, and *FTO*) not previously associated with PCa at genome-wide significance levels were seen as nominally associated in our study, one of which (*FTO*) was also reported by Pierce et al. (18). Four of these loci (*CDKN2A/B*, *TCF7L2*, *KCNQ1*, and *MTNR1B*) are associated with altered beta cell dysfunction or impaired insulin release and could result in less insulin production, thus blunting insulin effects in increasing PCa risk (46). Additionally, our second most highly associated locus, the *NOTCH2* locus ( $P=0.008$ ; permutation  $P=0.26$ ), is of interest. *NOTCH2* is a member of the *NOTCH* family of receptors, which modulate cellular differentiation, proliferation, and apoptosis (47). The locus has been reported to be associated with both T2D and breast cancer (48, 49). Evidence from gene expression data indicates that *NOTCH2* is expressed in developing prostate stroma and that *NOTCH* signaling affects stromal survival only in the presence of testosterone (50). Therefore, the regulatory ability of *NOTCH2* and its sensitivity to the presence of testosterone might be important in prostate carcinogenesis, although additional studies are needed to investigate this further.

Our use of GRS and kernel machine models allowed us to investigate the cumulative effect of T2D susceptibility

**Table 2.** Individual Cohort and Combined Results for Unweighted and Log Odds Ratio-Weighted Type 2 Diabetes Genetic Risk Score in the Breast and Prostate Cancer Cohort Consortium<sup>a</sup>

Cohort	No. in Cohort	No. of Cases	Total <sup>b</sup>	Mean <sup>c</sup>		GRS			GRS (- <i>HNF1B</i> ) <sup>d</sup>			
				Cases	Controls	OR	95% CI	P Value	OR	95% CI	P Value	
Unweighted count												
ATBC	1,490	245	72	36.48	36.44	1.00	0.97, 1.04	0.894	1.00	0.97, 1.04	0.841	
CPSII	1,258	636	72	37.48	37.55	1.00	0.97, 1.03	0.740	1.00	0.97, 1.03	0.839	
EPIC	857	431	72	37.47	37.66	0.99	0.95, 1.02	0.460	1.00	0.96, 1.04	0.984	
HPFS	418	214	72	37.70	37.47	1.02	0.97, 1.07	0.539	1.02	0.97, 1.08	0.419	
MEC	503	244	72	37.80	37.89	0.99	0.95, 1.04	0.779	1.00	0.96, 1.05	0.936	
PHS	553	298	72	37.59	37.81	0.99	0.95, 1.03	0.521	1.00	0.95, 1.04	0.800	
PLCO	2,161	714	72	37.36	37.64	0.98	0.96, 1.00	0.111	0.98	0.96, 1.01	0.191	
Combined <sup>e</sup>	7,240	2,782	72	37.42	37.31	0.99	0.98, 1.00	0.168	1.00	0.98, 1.01	0.534	
Weighted log OR												
ATBC	1,490	245	8.16	4.33	4.34	0.93	0.68, 1.29	0.675	0.94	0.68, 1.30	0.718	
CPSII	1,258	636	8.16	4.45	4.47	0.89	0.69, 1.14	0.358	0.90	0.70, 1.16	0.416	
EPIC	857	431	8.16	4.45	4.47	0.90	0.67, 1.20	0.460	1.01	0.75, 1.36	0.961	
HPFS	418	214	8.16	4.49	4.46	1.11	0.73, 1.68	0.635	1.17	0.76, 1.80	0.481	
MEC	503	244	8.16	4.49	4.54	0.78	0.53, 1.15	0.215	0.83	0.56, 1.23	0.352	
PHS	553	298	8.16	4.45	4.52	0.76	0.53, 1.07	0.118	0.80	0.56, 1.15	0.232	
PLCO	2,161	714	8.16	4.43	4.49	0.74	0.61, 0.91	0.004	0.76	0.62, 0.93	0.008	
Combined <sup>e</sup>	7,240	2,782	8.16	4.44	4.45	0.84	0.75, 0.94	0.002	0.87	0.78, 0.97	0.015	

Abbreviations: ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI, confidence interval; CPSII, American Cancer Society Cancer Prevention Study II Nutrition Cohort; EPIC, European Prospective Investigation into Cancer and Nutrition; GRS, genetic risk score; HPFS, Health Professionals Follow-up Study; MEC, Multiethnic Cohort Study; OR, odds ratio; PCa, prostate cancer; PHS, Physicians' Health Study; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; T2D, type 2 diabetes.

<sup>a</sup> Logistic regression models were used to regress GRS on risk of PCa.

<sup>b</sup> Total indicates the maximum bound for the respective GRS, with a value close to this total indicating high genetic predisposition for T2D.

<sup>c</sup> Mean GRS was calculated for PCa cases and PCa controls.

<sup>d</sup> *HNF1B* was excluded from the GRS and included as a separate covariate.

<sup>e</sup> For combined estimates, cohort indicators were added to adjust for cohort effects.

variants on PCa risk. Although another study was successful in showing an association between unweighted T2D

**Table 3.** Mediation Analysis for the Association Between *HNF1B* (rs7501939) and Prostate Cancer With Diabetes Phenotype as a Potential Intermediate in the Breast and Prostate Cancer Cohort Consortium<sup>a</sup>

	Odds Ratio	95% Confidence Interval	P Value
<i>HNF1B</i> -T2D association	1.10	0.97, 1.25	0.14
T2D-prostate cancer association	0.76	0.66, 0.87	$8.13 \times 10^{-05}$
Natural indirect effect	1.00	1.00, 1.00	0.71
Natural direct effect	0.83	0.79, 0.86	$1.02 \times 10^{-18}$
Total effect	0.83	0.79, 0.86	$6.37 \times 10^{-19}$

Abbreviation: T2D, type 2 diabetes.

<sup>a</sup> All analyses were conducted in the Breast and Prostate Cancer Cohort Consortium and were adjusted for cohort indicator, age at baseline (years), and body mass index (weight (kg)/height (m)<sup>2</sup>).

GRS and PCa (18), our study did not find a relation between unweighted T2D risk scores and PCa. A potential explanation for our lack of association is that with the most recent T2D loci added to our risk score, including T2D variants found through meta-analyses with lower-than-average effect sizes, the number of SNPs doubled, and the range of effect estimates for each variant might have widened. Our study did find a significant association between the log odds-weighted T2D risk scores and PCa. This association was significant when the *HNF1B* locus was both included in and excluded from the GRS. Although one of the larger cohorts, the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, seems to have been responsible for most of this association, a test of heterogeneity indicated that there was no significant evidence for heterogeneity. The fact that the log odds ratio-weighted GRS was significant and the unweighted risk score was insignificant indicates that some T2D variants could have a stronger influence on PCa risk than others. The GRS approach makes the assumption that all T2D loci included in the GRS have T2D risk alleles that function in the same direction when PCa risk is considered. This might not be the case, with some T2D-associated loci

possibly having the same rather than the (expected) opposite direction of effect on PCa. Multilocus kernel tests allowed us to assess the cumulative effect of these 36 T2D variants on PCa risk without requiring an assumption about risk allele directionality. Results from the multilocus kernel tests indicated that the 36 T2D variants were significantly associated with PCa risk when *HNF1B* was both included in and excluded from the models, which suggests that common pathways could be involved in both T2D and PCa.

A potential limitation of this study is that information on diabetes phenotype was self-reported (43). However, previous studies have shown that self-reporting of diabetes has up to 97% agreement with medical records (51, 52). Another limitation is that we could not differentiate between cases of type 1 diabetes and T2D, although the median age (62 years; interquartile range, 55–70) and ethnicity of our study population were such that the majority of diabetes cases were likely to be T2D (53). Furthermore, BPC3 data on T2D status were available only at baseline, and although this could have resulted in underestimation of the true prevalence of diabetes in our study population, it did guard against potential reverse causality.

Our study showed a highly significant inverse relation between T2D and PCa. The estimate was adjusted for body mass index, age at baseline, and cohort indicator and is unlikely to be due to chance or uncontrolled bias. To our knowledge, this is the largest case-control study in which this inverse association has been examined, and our estimate (OR = 0.76) is comparable to, albeit slightly stronger than, the point estimates reported in meta-analyses and other studies, including prior reports from 2 cohorts in the BPC3 (i.e., relative risks ranged from 0.84 to 0.91) (3–5, 54).

We further assessed the potential for T2D phenotype to mediate the effect of *HNF1B* with PCa risk. Results indicated a highly significant direct association between *HNF1B* and PCa risk, but there was no significant evidence for an indirect association. Although other investigators have observed a significant relation between *HNF1B* and T2D risk (8, 9), we did not, which indicates that our sample set might have lacked sufficient statistical power to detect this effect. The lack of a mediation role for diabetes phenotype in the *HNF1B*-PCa association has been reported elsewhere in a smaller subset of the BPC3 data (16), although larger studies are needed to more definitively rule out the potential for mediation.

The majority of our analysis, excluding the mediation analysis, was conducted on data from a genome-wide association study of advanced PCa. Although there is concern that results from our study might not be generalizable to other subtypes of PCa, the overwhelming number of similarities between our analysis and others indicates that T2D risk variants have a similar effect on advanced PCa risk and on total PCa risk. This is in agreement with association studies comparing PCa germline variants that show very few examples of different effects by disease aggressiveness.

In conclusion, our data provide additional evidence for a relation between T2D and PCa. Current investigations of a shared genetic background that could underlie this observed

association are still in their infancy but suggest that a genetic predisposition to T2D might also be associated with PCa risk. Future studies should further investigate the potential genetic factors that link these two common chronic diseases.

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