Null Results in Brief

No Association of Type 2 Diabetes Risk Variants and Prostate Cancer Risk: the Multiethnic Cohort and PAGE

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Abstract

Background: Epidemiologic studies have found evidence of an inverse association between diabetes status and prostate cancer risk. We explored the hypothesis that common genetic variation may explain, in part, the inverse association between diabetes and prostate cancer.

Methods: We tested 17 diabetes risk variants for association with prostate cancer risk in a prostate cancer case-control study of 2,746 cases and 3,317 controls from five racial/ethnic groups in the Multiethnic Cohort (MEC) study.

Results: After adjustment for multiple testing, none of the alleles were statistically significantly associated with prostate cancer risk. Aggregate scores that sum the risk alleles were also not significantly associated with risk.

Conclusions: We did not find evidence of association of this set of diabetes risk alleles with prostate cancer.

Impact: Resequencing and fine-mapping of the loci for diabetes and prostate cancer that were identified by genome-wide association studies are necessary to understand any genetic contribution for the inverse association between these common diseases. Cancer Epidemiol Biomarkers Prev; ©2011 AACR.

Introduction

Epidemiologic studies provide support for type 2 diabetes (T2D) being protective for prostate cancer (1). Recently, 3 loci (HNF1B, JAZF1, and THADA) have been associated with the risk of both diseases, suggesting a genetic link (2).

Support for this hypothesis was recently provided in a prostate cancer study of 18 established T2D genetic risk variants, which reported a summary T2D genetic risk score (both with and without the HNF1B allele) to be associated with decreased prostate cancer risk in men of European ancestry (OR = 0.96; 95% CI = 0.92–0.99; P = 0.02; without HNF1B; ref. 3).

As part of the Population Architecture using Genomics and Epidemiology (PAGE) initiative, we tested established T2D risk alleles in a study of 2,746 incident prostate cancer cases and 3,317 controls among 5 populations from the Multiethnic Cohort (MEC) study.

Methods

Study population

The MEC is a prospective cohort of 215,251 subjects, previously described in detail (4). Incident cancer cases are identified annually through cohort linkage to population-based cancer Surveillance, Epidemiology, and End Results (SEER) registries in Hawaii and Los Angeles County and to the California State cancer registry. The MEC prostate cancer case-control study includes 2,746 invasive cases and 2,288 controls, frequency matched by age (5-year groups) and race (5). We included 1,029 additional male controls with no prostate cancer history from a colorectal cancer MEC case-control study (6). Altogether, this study included 2,746 cases and 3,317 controls [European Americans (472/558), African American (721/954), Latino (668/704), Japanese American (753/936), and Native Hawaiian 132/165]. The Institutional Review Boards at the University of Southern California and University of Hawaii approved the study protocol.

Genotyping

Genotyping of 17 T2D risk variants (Table 1) was done using TaqMan. The variant in SLC30A8 (rs13266634) failed genotyping due to an adjacent single-nucleotide polymorphism (SNP; rs16889462). The genotype completion rate for each SNP was more than 96.0% among both cases and controls in each racial/ethnic group. Of 90 Hardy–Weinberg equilibrium (HWE) tests for each SNP in each racial/ethnic group, 2 were statistically significant (P < 0.05, 4.5 expected).
Table 1. The association of known T2D risk alleles with prostate cancer risk by race/ethnicity*  

<table>
<thead>
<tr>
<th>SNP/allele tested</th>
<th>Chr./nearest gene</th>
<th>European Americans (472 cases, 558 controls)</th>
<th>African Americans (721 cases, 954 controls)</th>
<th>Latinos (660 cases, 704 controls)</th>
<th>Japanese Americans (753 cases, 936 controls)</th>
<th>Native Hawaiians (132 cases, 165 controls)</th>
<th>Pooled (2,746 cases, 3,317 controls)</th>
<th>Pooled P&lt;sub&gt;\text{het}&lt;/sub&gt;</th>
<th>P&lt;sub&gt;\text{het}&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs10929331/T</td>
<td>1/NOTCH2</td>
<td>0.89 (0.67–1.18)</td>
<td>0.91 (0.78–1.05)</td>
<td>1.02 (0.79–1.31)</td>
<td>1.05 (0.65–1.68)</td>
<td>1.02 (0.49–2.13)</td>
<td>0.93 (0.84–1.04)</td>
<td>0.22 (0.09)</td>
<td>0.90 (0.90)</td>
</tr>
<tr>
<td>rs7578597/T</td>
<td>2/THADA</td>
<td>0.97 (0.73–1.29)</td>
<td>1.04 (0.88–1.21)</td>
<td>1.31 (0.97–1.77)</td>
<td>3.47 (1.48–8.18)</td>
<td>0.99 (0.47–2.08)</td>
<td>1.11 (0.98–1.25)</td>
<td>0.092 (0.017)</td>
<td>0.90 (0.90)</td>
</tr>
<tr>
<td>rs1801282/C</td>
<td>3/PPARG</td>
<td>1.09 (0.81–1.46)</td>
<td>1.04 (0.69–1.59)</td>
<td>1.02 (0.78–1.33)</td>
<td>0.98 (0.68–1.42)</td>
<td>1.53 (0.76–3.10)</td>
<td>1.05 (0.90–1.23)</td>
<td>0.51 (0.90)</td>
<td>0.94 (0.94)</td>
</tr>
<tr>
<td>rs4607103/C</td>
<td>3/ADAMTS9</td>
<td>0.96 (0.79–1.17)</td>
<td>1.06 (0.91–1.23)</td>
<td>0.95 (0.81–1.12)</td>
<td>1.02 (0.88–1.17)</td>
<td>1.17 (0.80–1.72)</td>
<td>1.01 (0.93–1.09)</td>
<td>0.89 (0.78)</td>
<td>0.78 (0.78)</td>
</tr>
<tr>
<td>rs4402960/T</td>
<td>3/GF2BP2</td>
<td>1.26 (1.05–1.52)</td>
<td>0.97 (0.85–1.11)</td>
<td>0.99 (0.84–1.18)</td>
<td>1.09 (0.94–1.26)</td>
<td>0.81 (0.55–1.18)</td>
<td>1.05 (0.97–1.13)</td>
<td>0.26 (0.097)</td>
<td>0.69 (0.69)</td>
</tr>
<tr>
<td>rs10010131/G</td>
<td>4/WFS1</td>
<td>1.02 (0.85–1.22)</td>
<td>1.08 (0.93–1.25)</td>
<td>1.11 (0.93–1.31)</td>
<td>0.79 (0.46–1.35)</td>
<td>1.46 (0.93–2.31)</td>
<td>1.07 (0.98–1.17)</td>
<td>0.13 (0.56)</td>
<td>0.76 (0.76)</td>
</tr>
<tr>
<td>rs7754840/C</td>
<td>6/CDKAL1</td>
<td>1.02 (0.85–1.23)</td>
<td>1.14 (1.00–1.32)</td>
<td>0.98 (0.83–1.14)</td>
<td>0.99 (0.86–1.13)</td>
<td>1.05 (0.74–1.48)</td>
<td>1.04 (0.96–1.12)</td>
<td>0.36 (0.58)</td>
<td>0.58 (0.58)</td>
</tr>
<tr>
<td>rs847475/T</td>
<td>7/JAZF1</td>
<td>0.90 (0.75–1.08)</td>
<td>0.96 (0.83–1.12)</td>
<td>0.93 (0.79–1.08)</td>
<td>1.16 (0.98–1.38)</td>
<td>0.85 (0.58–1.25)</td>
<td>0.98 (0.90–1.06)</td>
<td>0.54 (0.25)</td>
<td>0.68 (0.68)</td>
</tr>
<tr>
<td>rs233208/A</td>
<td>9/CDKN2B</td>
<td>0.95 (0.75–1.20)</td>
<td>1.06 (0.88–1.27)</td>
<td>0.93 (0.76–1.14)</td>
<td>1.00 (0.87–1.15)</td>
<td>0.95 (0.63–1.42)</td>
<td>0.99 (0.91–1.08)</td>
<td>0.85 (0.91)</td>
<td>0.75 (0.75)</td>
</tr>
<tr>
<td>rs1111875/C</td>
<td>10/HHEX</td>
<td>1.11 (0.92–1.32)</td>
<td>1.10 (0.94–1.30)</td>
<td>1.03 (0.89–1.20)</td>
<td>0.99 (0.85–1.15)</td>
<td>1.03 (0.72–1.48)</td>
<td>1.05 (0.97–1.14)</td>
<td>0.22 (0.86)</td>
<td>0.68 (0.68)</td>
</tr>
<tr>
<td>rs7903146/T</td>
<td>10/TCF7L2</td>
<td>0.98 (0.81–1.18)</td>
<td>0.97 (0.84–1.13)</td>
<td>1.06 (0.88–1.26)</td>
<td>0.92 (0.66–1.30)</td>
<td>1.02 (0.64–1.64)</td>
<td>1.00 (0.91–1.09)</td>
<td>0.91 (0.93)</td>
<td>0.32 (0.32)</td>
</tr>
<tr>
<td>rs12779790/G</td>
<td>10/CDC123</td>
<td>1.30 (1.03–1.64)</td>
<td>1.04 (0.86–1.26)</td>
<td>0.91 (0.75–1.11)</td>
<td>1.00 (0.83–1.20)</td>
<td>0.92 (0.61–1.38)</td>
<td>1.03 (0.94–1.14)</td>
<td>0.53 (0.23)</td>
<td>0.16 (0.16)</td>
</tr>
<tr>
<td>rs2237895/A/C</td>
<td>11/KCNQ1</td>
<td>0.94 (0.78–1.13)</td>
<td>0.96 (0.81–1.14)</td>
<td>0.92 (0.77–1.09)</td>
<td>1.08 (0.91–1.28)</td>
<td>0.86 (0.59–1.27)</td>
<td>0.98 (0.90–1.06)</td>
<td>0.55 (0.32)</td>
<td>0.35 (0.35)</td>
</tr>
<tr>
<td>rs2237897/A/C</td>
<td>11/KCNQ1</td>
<td>1.03 (0.70–1.50)</td>
<td>0.92 (0.72–1.18)</td>
<td>0.95 (0.78–1.15)</td>
<td>1.05 (0.88–1.24)</td>
<td>1.25 (0.79–1.97)</td>
<td>1.02 (0.92–1.13)</td>
<td>0.76 (0.45)</td>
<td>0.34 (0.34)</td>
</tr>
<tr>
<td>rs5219/T</td>
<td>11/KCNJ11</td>
<td>1.11 (0.92–1.33)</td>
<td>0.97 (0.77–1.22)</td>
<td>0.95 (0.82–1.11)</td>
<td>0.97 (0.84–1.11)</td>
<td>1.22 (0.87–1.72)</td>
<td>1.00 (0.93–1.09)</td>
<td>0.93 (0.57)</td>
<td>0.80 (0.80)</td>
</tr>
<tr>
<td>rs7961581/C</td>
<td>12/TSPAN8</td>
<td>0.99 (0.82–1.19)</td>
<td>0.92 (0.78–1.08)</td>
<td>0.89 (0.74–1.06)</td>
<td>0.87 (0.73–1.03)</td>
<td>0.80 (0.56–1.15)</td>
<td>0.90 (0.83–0.99)</td>
<td>0.021 (0.79)</td>
<td>0.29 (0.17)</td>
</tr>
<tr>
<td>rs8050136/A</td>
<td>16/FTO</td>
<td>1.05 (0.88–1.25)</td>
<td>0.93 (0.81–1.08)</td>
<td>1.07 (0.90–1.26)</td>
<td>0.88 (0.74–1.04)</td>
<td>0.81 (0.55–1.20)</td>
<td>0.97 (0.89–1.05)</td>
<td>0.38 (0.32)</td>
<td>0.32 (0.32)</td>
</tr>
</tbody>
</table>

*In each cell is the OR (and 95% CI) for allele dosage effects along with the risk allele frequency in controls. ORs adjusted for age (quartiles), BMI (quartiles), T2D (self-report), and ethnicity (in pooled analysis).

bNational Center for Biotechnology Information (NCBI) build 36 (forward strand).

cP value for heterogeneity of allelic effects across ethnic groups (4 df test).

drs2237895 and rs2237897 adjusted for each other.
Statistical analysis

ORs and 95% CIs for log-additive effects were estimated in unconditional logistic regression models adjusted for age, diabetes self-report, and body mass index (BMI; kg/m²). Subjects missing genotype information for more than 5 SNPs were excluded (n = 62). Aggregate T2D risk scores (sum of total risk alleles – assigned on the basis of an OR >1 in published T2D genome-wide association studies) were used to test the hypothesis that overall T2D susceptibility is protective for prostate cancer risk. The risk score per allele ORs assumed independent effects of approximately the same magnitude for each allele. Individuals missing genotypes for a SNP were assigned the average number of risk alleles within each ethnicity.

Results

On average, cases (mean = 69.3 years) were slightly older than controls (68.6). After adjusting for multiple tests, we observed no statistically significant associations with prostate cancer risk. In racial/ethnic pooled analysis, the TSPAN8 variant (rs7961581) was nominally significantly associated with risk prior to adjustment for multiple tests (OR = 0.90; 95% CI = 0.83–0.99; P = 0.021). In racial/ethnic specific analysis, we observed P values <0.05 with variants in IGFBP2, CDC123, and THADA (HWE P value = 2.0 × 10⁻⁴ for rs7578997 in Japanese Americans due to 2 rare homozygotes, 0.4 expected).

In the pooled sample, the mean risk allele count was 17.0 (range 8–25) and the per allele OR of the T2D risk score was 1.00 (95% CI = 0.98–1.03; P = 0.69). The ORs for the risk score ranged from 0.98 in Latinos to 1.03 in European Americans and were not statistically significant in any population (all P values >0.20).

Discussion

In this multiethnic study, we found limited evidence that the known T2D risk variants are associated with prostate cancer risk independently or in combination. Our null findings with the summary risk score is different than that of a previous prostate cancer study of European Americans that found an inverse association (3). Aside from the SLC30A8 allele, the same variants were investigated in both studies (although for many SNPs, highly correlated proxies to the index SNPs were used in the previous study). Discovered in European ancestry populations, many of these markers may not be proxies of the functional alleles in other populations due to differences in linkage disequilibrium and allele frequencies. However, we previously showed that the majority of these alleles in these populations were associated with T2D risk independently and in aggregate (7). We also did not observe significant population heterogeneity in the associations of these variants. In the combined sample, we had more than 77% power (adjusting for 17 tests) to detect an OR of 0.85 for common alleles (minor allele frequency ≥ 0.25). We were underpowered, however, to detect modest associations in any single racial/ethnic group.

In conclusion, we did not find evidence for associations between validated T2D risk variants and prostate cancer risk in multiple populations. Once identified, the functional alleles at these loci, as well as at other novel T2D risk loci, will need to be examined for a role in prostate cancer risk in these populations.

Disclosure of Potential Conflict of Interest

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. No potential conflicts of interest were disclosed.

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