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An Assessment of the Shared Allelic Architecture between Type II Diabetes and Prostate Cancer

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Abstract

Background—To determine whether the alleles that influence type II diabetes risk and glycemic traits also influence prostate cancer risk.

Methods—We used a multiple single-nucleotide polymorphisms (SNP) genotypic risk score to assess the average effect of alleles that increase type II diabetes risk or worsen glycemic traits on

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed by the other authors.

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risk of prostate cancer in 19,662 prostate cancer cases and 19,715 controls from the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) consortium and 5,504 prostate cancer cases and 5,834 controls from the Cancer Research UK (CRUK) prostate cancer study.

Results—Calculating the average additive effect of type II diabetes or glycemic trait risk alleles on prostate cancer risk using a logistic model revealed no evidence of a shared allelic architecture between type II diabetes, or worsened glycemic status, with prostate cancer risk [OR for type II diabetes alleles: 1.00 ($P = 0.58$), fasting glycemia alleles: 1.00 ($P = 0.67$), HbA_{1c} alleles: 1.00 ($P = 0.93$), 2-hour OGTT alleles: 1.01 ($P = 0.14$), and HOMA-B alleles: 0.99 ($P = 0.57$)].

Conclusions—Using genetic data from large consortia, we found no evidence for a shared genetic etiology of type II diabetes or glycemic risk with prostate cancer.

Impact—Our results showed that alleles influencing type II diabetes and related glycemic traits were not found to be associated with the risk of prostate cancer.

Introduction

Type II diabetes has been shown in observational studies to be associated with a decreased risk of developing prostate cancer (1). Understanding the association between type II diabetes and prostate cancer is of considerable interest to determine the role of glucose metabolism in prostate carcinogenesis because both the diseases are among the most common major diseases affecting elderly men.

By using datasets from the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) consortium and Cancer Research UK (CRUK) study, which included data from up to 50,715 men, we used a multiple single-nucleotide polymorphism (SNP) genotypic risk score to determine whether alleles influencing type II diabetes and related glycemic traits were associated with the risk of prostate cancer.

Materials and Methods

SNPs associated with type II diabetes at a genome-wide significant level ($P < 5 \times 10^{-8}$, $N = 14$) were obtained from the DIAbetes Genetics Replication and Meta-analysis (DIAGRAM) consortium (2). SNPs that were genomewide significantly associated with fasting glycemia ($N = 290$), HbA_{1c} ($N = 11$), 2 hour OGTT ($N = 5$), and HOMA-B ($N = 119$) from the Meta-Analyses of Glucose and Insulin-related traits consortium (MAGIC) were also obtained for our analysis (3–5). The association of these SNPs with risk of prostate cancer was then sought in the PRACTICAL consortium, which included 30 studies, involving a total of 19,662 cases and 19,715 controls. Only 28 of the requested SNPs were genotyped in the PRACTICAL consortium and the remaining SNPs were not available through imputation. Therefore, to obtain a maximum number of SNPs for our analysis, the remaining SNPs ($N = 287$) were obtained from the CRUK study, composed of 5,504 prostate cancer cases and 5,834 controls (6) which had undergone imputation.

A total of 310 SNPs with their derived β (additive effect) and SEs for their additive effect on prostate cancer risk were obtained. All of the data used from the PRACTICAL consortium excluded individuals from the CRUK study. The β and SEs from CRUK and from PRACTICAL were then meta-analyzed for SNPs that were present in all datasets using an inverse-variance fixed-effects model through the GWAMA software package version 2.1 (Supplementary Table S1).

Using a multiple SNP genotypic risk score we have previously described (7), we determined whether the allelic architecture of both type II diabetes and its related glyceic traits were associated with prostate cancer risk. We stress that this approach does not constitute a Mendelian randomization study because pleiotropic effects cannot be excluded. To create such a genotypic risk score, independent alleles for each trait were selected using a linkage disequilibrium (LD) threshold of $r^2 = 0.05$ in the HapMap Utah residents with ancestry from northern and western Europe (CEU) population to select one genome-wide significant SNP per LD block. When more than one SNP arose from a single LD block, the SNP with the highest variance explained on the phenotypic outcome was selected. A total of 50 independent LD blocks from the 310 SNPs were obtained to calculate the multiple SNP genotyping risk score (Supplementary Table S2). To summarize, the multiple SNP genotyping risk score uses a logistic regression model that calculates the average additive effect (i.e., β), of the alleles that increase the risk of type II diabetes and glyceic traits, on the risk of prostate cancer. For purposes of presentation, the β were then transformed to ORs. The multiple SNP genotypic risk score was calculated using STATA version 10.1.

Results

Results of the analysis did not provide any evidence for association of type II diabetes or glyceic risk alleles on risk of prostate cancer [type II diabetes alleles: OR 1.00 (95% confidence interval, CI, 0.99–1.02), fasting glyceic alleles: OR 1.00 (95% CI, 0.99–1.02), HbA_{1c} alleles: OR 1.00 (95% CI, 0.97–1.04), 2 hour OGTT alleles: OR 1.01 (95% CI, 1.00–1.03), and HOMA-B alleles: OR 0.99 (95% CI, 0.94–1.04); Table 1].

Discussion

Using a multiple SNP genotypic risk score of only genome-wide significant SNPs derived from the largest meta-analyses to date, in a large consortium of prostate cancer studies, we showed no evidence for a shared allelic architecture between type II diabetes and glyceic traits and prostate cancer.

The results from this study are different from that of a recent study using data from the National Cancer Institute's Breast and Prostate Cancer Cohort Consortium, which found an inverse association between type II diabetes and prostate cancer risk [OR: 0.87 (95% CI, 0.78–0.97, $P = 0.015$)] using 36 type II diabetes risk variants (8). However, the 36 diabetes risk variants used in their study included variants that have not been replicated.

In summary, despite the largest prostate cancer sample size to date and using only genome-wide significant SNPs arising from the largest type II diabetes and glyceic trait consortia,

our results provide no evidence to support the contention that type II diabetes and glycemic traits influence the risk of prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

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Table 1

Results of the multiple SNP genotypic risk score, assessing the average effect of type II diabetes or glycemic risk alleles on risk of prostate cancer

Trait	Number of SNPs	OR (95% CI)	P
Type II diabetes	14	1.00 (0.99–1.02)	0.58
Fasting glycemia	18	1.00 (0.99–1.02)	0.69
HbA _{1c}	11	1.00 (0.97–1.04)	0.93
2 hour OGTT ^a	3	1.01 (1.00–1.03)	0.14
HOMA-B ^b	4	0.99 (0.94–1.04)	0.57

^a2 hour OGTT = Glucose level 2 hour post 75 g oral glucose tolerance test.

^bHOMA-B = Homeostatic model assessment for β cell function.