An assessment of the shared allelic architecture between type 2 diabetes and prostate cancer.

Oriana Hoi Yun Yu1,2, William D. Foulkes3,4,8, Zari Dastani2, Richard M. Martin5; Rosalind Eeles for the PRACTICAL Consortium and the CRUK GWAS Investigators6,7; and J. Brent Richards1,2,8

1Department of Medicine, Division of Endocrinology, Jewish General Hospital, McGill University, Montreal, Québec, Canada
2Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Québec, Canada
3Department of Oncology, Jewish General Hospital, McGill University, Montreal, Québec, Canada
4Department of Medical Genetics, Jewish General Hospital, McGill University, Montreal, Québec, Canada
5School of Social and Community Medicine, University of Bristol, Bristol, UK
6The Institute of Cancer Research, 15 Cotswold Road, Sutton, Surrey, SM2 5NG, UK
7Royal Marsden NHS Foundation Trust, Fulham and Sutton, London and Surrey, UK
8Department of Human Genetics, McGill University, Montréal, Québec, Canada

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Corresponding author: J.B. Richards
Address: 3755 Cote-Sainte-Catherine Road, Suite H-413
Montreal, QC
Canada
H3T 1E2
Telephone number: 514-340-8222
Fax number: 514-340-7502
Email address: brent.richards@mcgill.ca

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Abstract

Background: To determine whether the alleles that influence type 2 diabetes risk and glycemic traits also influence prostate cancer risk.

Materials and Methods: We used a multiple single nucleotide polymorphisms (SNP) genotypic risk score to assess the average effect of alleles that increase type 2 diabetes risk or worsen glycemic traits on risk of prostate cancer in 19,662 prostate cancer cases and 19,715 controls from the PRACTICAL consortium and 5,504 prostate cancer cases and 5,834 controls from the CRUK prostate cancer study.

Results: Calculating the average additive effect of type 2 diabetes or glycemic trait risk alleles on prostate cancer risk using a logistic model revealed no evidence of a shared allelic architecture between type 2 diabetes, or worsened glycemic status, with prostate cancer risk (odds ratio for type 2 diabetes alleles: 1.00 (P=0.58), fasting glycemia alleles: 1.00 (P=0.67), HbA1c 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 2 diabetes, or glycemic risk, with prostate cancer.

Impact: Our results showed that alleles influencing type 2 diabetes and related glycemic traits were not found to be associated with the risk of prostate cancer.
Introduction

Type 2 diabetes has been shown in observational studies to be associated with a decreased risk of developing prostate cancer (1). Understanding the association between type 2 diabetes and prostate cancer is of considerable interest to determine the role of glucose metabolism in prostate carcinogenesis, since both 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 employed a multiple SNP genotypic risk score to determine whether alleles influencing type 2 diabetes and related glycemic traits were associated with the risk of prostate cancer.

Materials and Methods

SNPs associated with type 2 diabetes at a genome-wide significant level (P < 5x10^-8, N = 14) were obtained from the DIAbetes Genetics Replication and Meta-analysis (DIAGRAM) consortium (2). SNPs that were genome-wide significantly associated with fasting glycemia (N = 290), HbA1c (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, comprised of 5,504 prostate cancer cases and 5,834 controls (6), which had undergone imputation.

A total of 310 SNPs with their derived beta and standard errors 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 beta and standard errors 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 1).

Using a multiple SNP genotypic risk score we have previously described (7), we determined if the allelic architecture of both type 2 diabetes and its related glycemic traits were associated with prostate cancer risk. We stress that this approach does not constitute a Mendelian randomization study since pleiotropic effects cannot be excluded. To create such a genotypic risk score, independent alleles, for each trait were selected using an LD threshold of \( r^2 \leq 0.05 \) in the HapMap 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 2). To summarize, the multiple SNP genotyping risk score uses a logistic regression model that calculates the average additive effect (i.e. beta), of the alleles that increase the risk of type 2 diabetes and glycemic traits, on the risk of prostate cancer. For purposes of presentation, the betas were then transformed to odds ratios (OR). 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 2 diabetes, or glycemic risk alleles on risk of prostate cancer (type 2 diabetes alleles: OR 1.00 (95% CI: 0.99, 1.02), fasting glycemia alleles: OR 1.00 (95% CI: 0.99, 1.02), HbA1c 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 demonstrated no evidence for a shared allelic architecture between type 2 diabetes and glycemic 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 2 diabetes and prostate cancer risk (OR: 0.87 (95% CI: 0.78, 0.97, P=0.015) using thirty-six type 2 diabetes risk variants(8). However, the thirty-six 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 2 diabetes and glycemic trait consortia, our results provide no evidence to support the contention that type 2 diabetes and glycemic traits influence the risk of prostate cancer.
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The PRACTICAL Consortium:

The CRUK GWAS Investigators:
Rosalind Eeles 1,2, Doug Easton 3, Zsofia Kote-Jarai 1, Kenneth Muir 4, Graham Giles 5,6, Gianluca Severi 5,6, David Neal 13, Jenny L. Donovan 31, Freddie C. Hamdy 32

1 The Institute of Cancer Research, 15 Cotswold Road, Sutton, Surrey, SM2 5NG, UK, 2 Royal Marsden NHS Foundation Trust, Fulham and Sutton, London and Surrey, UK, 3 Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Strangeways Laboratory, Worts Causeway, Cambridge, UK, 4 University of Warwick, Coventry, UK, 5 Cancer Epidemiology Centre, The Cancer Council Victoria, 1 Rathdowne street, Carlton Victoria, Australia, 6 Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, The University of Melbourne, Victoria, Australia, 7 Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden, 8 Department of Preventive Medicine, Keck School of Medicine, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, California, USA, 9 Department of Medical Biochemistry and Genetics, University of Turku, Turku, Finland, 10 Institute of Biomedical Technology/BioMediTech, University of Tampere and FinLab Laboratories, Tampere, Finland, 11 Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark, 12 Cancer Epidemiology Unit, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK, 13 Surgical Oncology (Uro-Oncology: S4), University of Cambridge, Box 279, Addenbrooke’s Hospital, Hills Road, Cambridge, UK and Cancer Research UK Cambridge Research Institute, Li Ka Shing Centre, Cambridge, UK, 14 Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Strangeways Laboratory, Worts Causeway, Cambridge, UK, 15 Cambridge Institute of Public Health, University of Cambridge, Forvie Site, Robinson Way, Cambridge CB2 0SR, 16 Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle,
Washington, USA, 17 Department of Epidemiology, School of Public Health, University of Washington, Seattle, Washington, USA, 18 International Epidemiology Institute, 1455 Research Blvd., Suite 550, Rockville, MD 20850, 19 Mayo Clinic, Rochester, Minnesota, USA, 20 Department of Urology, University Hospital Ulm, Germany, 21 Institute of Human Genetics University Hospital Ulm, Germany, 22 Brigham and Women's Hospital/Dana-Farber Cancer Institute, 45 Francis Street- ASB II-3, Boston, MA 02115, 23 Washington University, St Louis, Missouri, 24 International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland, 25 Division of Genetic Epidemiology, Department of Medicine, University of Utah School of Medicine, 26 Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Heidelberg Germany, 27 Division of Cancer Prevention and Control, H. Lee Moffitt Cancer Center, 12902 Magnolia Dr., Tampa, Florida, USA, 28 Molecular Medicine Center and Department of Medical Chemistry and Biochemistry, Medical University - Sofia, 2 Zdrave St, 1431, Sofia, Bulgaria, 29 Australian Prostate Cancer Research Centre-Qld, Institute of Health and Biomedical Innovation and Schools of Life Science and Public Health, Queensland University of Technology, Brisbane, Australia, 30 Department of Genetics, Portuguese Oncology Institute, Porto, Portugal and Biomedical Sciences Institute (ICBAS), Porto University, Porto, Portugal, 31 School of Social and Community Medicine, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol, UK, 32 Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK, Faculty of Medical Science, University of Oxford, John Radcliffe Hospital, Oxford, UK

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References
Table 1: Results of the multiple SNP genotypic risk score, assessing the average effect of type 2 diabetes or glycemic risk alleles on risk of prostate cancer.

<table>
<thead>
<tr>
<th>Trait</th>
<th>Number of SNPs</th>
<th>OR (95% CI)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Type 2 diabetes</td>
<td>14</td>
<td>1.00 (0.99, 1.02)</td>
<td>0.58</td>
</tr>
<tr>
<td>Fasting glycemia</td>
<td>18</td>
<td>1.00 (0.99, 1.02)</td>
<td>0.69</td>
</tr>
<tr>
<td>HbA$_{1c}$</td>
<td>11</td>
<td>1.00 (0.97, 1.04)</td>
<td>0.93</td>
</tr>
<tr>
<td>2 hour OGTT$^a$</td>
<td>3</td>
<td>1.01 (1.00, 1.03)</td>
<td>0.14</td>
</tr>
<tr>
<td>HOMA-B$^b$</td>
<td>4</td>
<td>0.99 (0.94, 1.04)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

$^a$2 hour OGTT = Glucose level 2 hour post 75g oral glucose tolerance test
$^b$HOMA-B = Homeostatic model assessment for beta cell function.
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