Null Results in Brief

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

Oriana Hoi Yun Yu1,4, William D. Foulkes2,3,5, Zari Dastani4, Richard M. Martin6, Rosalind Eeles, for the PRACTICAL Consortium and the CRUK GWAS Investigators7,8, and J. Brent Richards1,4,5

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 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), 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 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. Cancer Epidemiol Biomarkers Prev; 22(8); 1473–5. ©2013 AACR.

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 × 10−8, 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, 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 glycemic 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 $r^2 \leq 0.05$ 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 through the GWAMA software package version 2.1 (Supplementary Table S1).

Results of the analysis did not provide any evidence for association of type II diabetes or glycemic risk alleles on risk of prostate cancer (type II 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 1.00 (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 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 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 glycemic trait consortia, our results provide no evidence to support the contention that type II diabetes and glycemic traits influence the risk of prostate cancer.

Disclosure of Potential Conflicts of Interest

R. Eeles received an educational support grant from Janssen Pharmaceuticals, Vista Diagnostics, Genprobe, and Illumina. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Conception and design: O.H.Y. Yu, J.B. Richards

Development of methodology: Z. Dastani, J.B. Richards

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R. Eeles

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): O.H.Y. Yu, Z. Dastani, J.B. Richards

Writing, review, and/or revision of the manuscript: O.H.Y. Yu, W.D. Foulkes, R.M. Martin, R. Eeles

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): O.H.Y. Yu, W.D. Foulkes, R. Eeles, J.B. Richards

Study supervision: J.B. Richards

The PRACTICAL Consortium


The CRUK GWAS Investigators

Rosalind Eeles1,2, Doug Easton1, Zsofia Kote-Jarai1, Kenneth Muir4, Graham Giles3,6, Gandluca Severi29,30, David Neal13, Jenny L. Donovan1, Freddie C. Handyside2

1. The Institute of Cancer Research, 15 Cotswold Road, Sutton, Surrey, SM2 5NG, UK, 2Royal Marsden NHS Foundation Trust, Fulham and London and Surrey, UK, 3Centre for Cancer Genetic

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

<table>
<thead>
<tr>
<th>Trait</th>
<th>Number of SNPs</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type II 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>HbA1c</td>
<td>11</td>
<td>1.00 (0.97–1.04)</td>
<td>0.93</td>
</tr>
<tr>
<td>2 hour OGTT</td>
<td>3</td>
<td>1.01 (1.00–1.03)</td>
<td>0.14</td>
</tr>
<tr>
<td>HOMA-B2</td>
<td>4</td>
<td>0.99 (0.94–1.04)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

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

*bHOMA-B = Homeostatic model assessment for β cell function.
Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Conference Laboratory, Worts Causeway, Cambridge, UK, University of Warwick, Coventry, UK, Cancer Epidemiology Centre, The Cancer Council Victoria, 1 Rathdowne Street, Carlton, Victoria, Australia, Centre for Molecular, Environmental, Genetic and Analytical Epidemiology, The University of Melbourne, Victoria, Australia, Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden, Department of Preventive Medicine, Keck School of Medicine, University of Southern California/ Norris Comprehensive Cancer Center, Los Angeles, California, USA, Department of Medical Epidemiology and Genetics, University of Turku, Turku, Finland, Institute of Biomedical Technology/Biometry, University of Tampere and FimLab Laboratories, Tampere, Finland, Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark, Cancer Epidemiology Unit, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK, Surgical Oncology (Uro-Oncology: 54), 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, Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Conference Laboratory, Worts Causeway, Cambridge, UK, Cambridge Institute of Public Health, University of Cambridge, Forvie Site, Robinson Way, Cambridge CB2 0SR, Division of Public Health, University Health, School of Public Health, Washington, USA, Department of Epidemiology, School of Public Health, University of Washington, Seattle, Washington, USA, International Epidemiology Institute, 1455 Research Blvd., Suite 550, Rockville, MD 20850, Mayo Clinic, Rochester, Minnesota, USA, Department of Urology, University Hospital Ulm, Germany, Institute of Human Genetics, University Hospital Ulm, Germany, Brigham and Women’s Hospital/Dana-Farber Cancer Institute, 45 Francis Street, Boston, MA 02115, Washington University, St Louis, Missouri, International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland, Division of Genetic Epidemiology, Department of Medicine, University of British Columbia, Vancouver, Canada, Division of Clinical Epidemiology, Department of Epidemiology, Research and Aging Research, German Cancer Research Center, Heidelberg, Germany, Division of Cancer Prevention and Control, H. Lee Moffitt Cancer Center, 12902 Magnolia Dr., Tampa, Florida, USA, Molecular Medicine Center and Department of Medical Chemistry and Biochemistry, Medical University - Sofia, 2 Zdrave St, 1431, Sofia, Bulgaria, 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, Department of Genetics, Portuguese Oncology Institute, Porto, Portugal and Biomedical Sciences Institute (ICBAS), Porto University, Porto, Portugal, School of Social and Community Medicine, University of Bristol, Cannyge Hall, 39 Whately Road, Bristol, UK, 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

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