Multiple Novel Prostate Cancer Predisposition Loci Confirmed by an International Study:

The PRACTICAL Consortium


Section of Cancer Genetics, The Institute of Cancer Research, Sutton, Surrey, United Kingdom; Cancer Research UK Genetic Epidemiology Unit, Strangeways Laboratory; Surgical Oncology, Cambridge Research Institute, Cambridge, United Kingdom; Division of Public Health Sciences, Fred Hutchinson Cancer Research Center; Departments of Epidemiology and Biostatistics, School of Public Health and Community Medicine, University of Washington, Seattle, Washington; National Human Genome Research Institute, NIH, Bethesda, Maryland; Institute of Medical Technology, University of Tampere and Tampere University Hospital; Department of Urology, Tampere University Hospital, University of Tampere, Tampere, Finland; Department of Preventive Medicine, University of Southern California Keck School of Medicine, Los Angeles, California; Mayo Clinic, Rochester, Minnesota; Department of Cytogenetics and Obstetrics, Gynaecology Research Unit, and Department of Radiation Oncology, Hannover Medical School, Hannover, Germany; Institute for Cancer Studies, University of Sheffield Medical School, Sheffield, United Kingdom; Institut für Humangenetik; Cancer Epidemiology Centre, Unit, Strangeways Laboratory; Surgical Oncology, Cambridge Research Institute, Cambridge, United Kingdom; 4 Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA; 11 Mayo Clinic, Rochester, Minnesota; 12 Department of Radiation Oncology, Queensland University of Technology; 21 Molecular Cancer Epidemiology Laboratory, Queensland Institute of Medical Research; 22 Viertel Centre for Research in Cancer Control, The Cancer Council Queensland; 23 University of Queensland, Department of Surgery, Royal Brisbane and Women’s Hospital; School of Population Health, University of Queensland, Brisbane, Australia; 24 Northern California Cancer Center, Fremont, California, and Stanford University School of Medicine, Stanford, California; 25 Cancer Epidemiology Centre, The Cancer Council Victoria; 26 Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, The University of Melbourne, Carlton, Australia; 27 Genetic Epidemiology Laboratory, Department of Pathology, The University of Melbourne, Parkville, Australia; 28 Division of Medical Genetics, Institut Central des Hôpitaux Valaisains, Sion, Switzerland; and 29 ProMPT and CAP (Comparison Arm for ProtecT) studies are supported by the U.S. National Cancer Institute (R01CA99660). The study in Melbourne was supported by grants CA56678, CA92579, and CA91786 from the National Cancer Institute, NIH, with additional support from the Fred Hutchinson Cancer Research Center. Ongoing work in Montreal has been funded in part by the U.S. Department of Defense (U.S. Army Grant DAMD17-01-1-0033, Principal Investigator: W.D. Foulkes), the Canadian Cancer Diseases Network, and the NIH. The study in Switzerland was supported by the U.S. Army Research Grant DAMD17-00-1-0033 (Principal Investigator: W.D. Foulkes) and a grant from the Institut National des Hôpitaux Valaisains, Sion, Switzerland. The Mayo group was supported by the U.S. National Cancer Institute (R01CA72818). The University of Southern California study was supported by the U.S. National Cancer Institute (R01CA85497) and by the California Cancer Research Program (99-00524V-10258). The San Francisco study was supported by the California Cancer Research Fund (99-00527V-10182). The Tampere (Finland) study was supported by the Academy of Finland grant 118413, The Finnish Cancer Organisation, Sigrid Juselius Foundation, Reino Lahikitari Foundation, and The Medical Research Fund of Tampere University Hospital. The Hannover Prostate Cancer Study was supported by an intramural Hanselohre-Münke stipend to A. Meyer. The Fred Hutchinson Cancer Research Center, Mayo, Melbourne Collaborative Cohort Study, Montreal, Tampere, U.K. Genetic Prostate Cancer Study, and Ulm groups are part of the International Consortium for Prostate Cancer Genetics supported by NIH grant U01 CA99660-04.

Received 4/8/08; revised 5/27/08; accepted 6/5/08.

Grant support: Cancer Research UK grant CS047/A3354. We would also like to thank the following for funding support: The Institute of Cancer Research and The Ewingman Campaign, The Prostate Cancer Research Foundation, Prostate Research Campaign UK, The National Cancer Research Network UK, The National Cancer Research Institute UK, grants from the National Health and Medical Research Council, Australia (209057, 251553, 400104, 390130), VicHealth, The Cancer Council Victoria, The Cancer Council Queensland, The Whitton Foundation, and Tattersall’s. E.A. Ostrander, D.M. Karyadi, and B. Johansson acknowledge the intramural Program of the National Human Genome Research Institute for their support. The ProTeCt study is ongoing and is funded by the Health Technology Assessment Programme (projects 96/20/06 and 96/20/99). The ProTeCt trial and its linked ProMPY and CAL (Comparison Arm for ProTeCt) studies are supported by Department of Health, England, Cancer Research UK grant G0500966, ID 75486 and The National Cancer Research Institute, UK. DNA extraction in ProTeCt was supported by U.S. Department of Defense award WB1XH04-01-0280. The Fred Hutchinson Cancer Research Center work was supported by grants CA56678, CA92579, and CA91786 from the National Cancer Institute, NIH, with additional support from the Fred Hutchinson Cancer Research Center. Ongoing work in Montreal has been funded in part by the U.S. Department of Defense (U.S. Army Grant DAMD17-01-1-0033, Principal Investigator: W.D. Foulkes), the Canadian Cancer Diseases Network, and the NIH. The study in Switzerland was supported by the U.S. Army Research Grant DAMD17-00-1-0033 (Principal Investigator: W.D. Foulkes) and a grant from the Institut Central des Hôpitaux Valaisains, Sion, Switzerland. The Mayo group was supported by the U.S. National Cancer Institute (R01CA72818). The University of Southern California study was supported by the U.S. National Cancer Institute (R01CA85497) and by the California Cancer Research Program (99-00524V-10258). The San Francisco study was supported by the California Cancer Research Fund (99-00527V-10182). The Tampere (Finland) study was supported by the Academy of Finland grant 118413, The Finnish Cancer Organisation, Sigrid Juselius Foundation, Reino Lahikitari Foundation, and The Medical Research Fund of Tampere University Hospital. The Hannover Prostate Cancer Study was supported by an intramural Hanselohre-Münke stipend to A. Meyer. The Fred Hutchinson Cancer Research Center, Mayo, Melbourne Collaborative Cohort Study, Montreal, Tampere, U.K. Genetic Prostate Cancer Study, and Ulm groups are part of the International Consortium for Prostate Cancer Genetics supported by NIH grant U01 CA99660-04.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

D.F. Easton is a Principal Research Fellow of Cancer Research UK. J. Hopper is an Australia Fellow of the National Health and Medical Research Council. A. Spurdle was supported by a National Health and Medical Research Council Career Development Award.


Requests for reprints: Rosalind A. Eeles, Translational Cancer Genetics Team, The Institute of Cancer Research, 15 Cotswold Road, Sutton, Surrey SM2 5NG, United Kingdom. Phone: 44-20-8661-3642; Fax: 44-20-8770-1489. E-mail: Rosalind.Eeles@icr.ac.uk

Copyright © 2008 American Association for Cancer Research.

doi:10.1188/1055-9965.EPI08-03017
Abstract

A recent genome-wide association study found that genetic variants on chromosomes 3, 6, 7, 10, 11, 19 and X were associated with prostate cancer risk. We evaluated the most significant single-nucleotide polymorphisms (SNP) in these loci using a worldwide consortium of 13 groups (PRACTICAL). Blood DNA from 7,370 prostate cancer cases and 5,742 male controls was analyzed by genotyping assays. Odds ratios (OR) associated with each genotype were estimated using unconditional logistic regression. Six of the seven SNPs showed clear evidence of association with prostate cancer (P = 0.0007–P = 10 \(-17\)). For each of these six SNPs, the estimated per-allele OR was similar to those previously reported and ranged from 1.12 to 1.29. One SNP on 3p12 (rs2660753) showed a weaker association than previously reported [per-allele OR, 1.08 (95% confidence interval, 1.00–1.16; P = 0.06) versus 1.18 (95% confidence interval, 1.06–1.31)]. The combined risks associated with each pair of SNPs were consistent with a multiplicative risk model. Under this model, and in combination with previously reported SNPs on 8q and 17q, these loci explain 16% of the familial risk of the disease, and men in the top 10% of the risk distribution have a 2.1-fold increased risk relative to general population rates. This study provides strong confirmation of these susceptibility loci in multiple populations and shows that they make an important contribution to prostate cancer risk prediction. (Cancer Epidemiol Biomarkers Prev 2008;17(8):2052–61)

Introduction

Prostate cancer is now the most common cancer in men in the Western world (Cancer Research UK Factsheets 2008). However, its etiology remains poorly understood. Incidence rates vary substantially worldwide, and have done so for many decades, indicating that lifestyle risk factors, perhaps in combination with genetic background, are important. To date, however, no lifestyle risk factors have been definitely identified.

Aside from demographic factors, the only well-established risk factors for prostate cancer are family history and racial/ethnic background. The risk of the disease in first-degree relatives of cases is approximately twice that in the general population (1, 2) and the disease is more common in men of African descent (3). High-penetrance susceptibility loci, identified following genome-wide scans of high-risk families, have been reported by several research groups. However, the relative failure of linkage studies to replicate findings of prostate cancer loci (4) suggests that the disease is genetically complex, with substantial locus heterogeneity. If variant alleles confer a small or moderate risk for prostate cancer, even large-scale family-based, linkage studies including hundreds of families will lack sufficient power to detect deleterious variants.

Genome-wide association studies have emerged as a powerful approach to identify common genetic variants associated with disease risk (5-8). Eeles et al. (9) recently conducted such a study based on 1,854 prostate cancer cases with clinically significant disease who were diagnosed at age ≤ 60 years or with a positive family history. The 1,894 controls were aged ≥50 years and had a low prostate-specific antigen (PSA; <0.5 ng/mL), which predicts a low lifetime prostate cancer risk. DNA samples were evaluated for 541,129 single-nucleotide polymorphisms (SNP) using the Illumina Infinium platform. Associations were replicated in a second stage that included 3,245 cases and 3,329 controls from studies conducted in the United Kingdom and Australia. By this process, we identified SNPs associated with prostate cancer risk at “genome-wide” levels of significance (P\(_{\text{adjusted}} < 10\(-8\)) in seven novel regions: 3p, 6q, 7q, 10q, 11q, 19q, and Xp (9). In each region, a single SNP was sufficient to explain the association with all other tested SNPs (although none is necessarily causally associated with disease risk and the associations may reflect the effects of other as yet untested variants). The associations in three regions on 8q and two on 17q were also confirmed.

To provide accurate estimates of the risks associated with genetic variants and to evaluate the combined associations of these variants, it is necessary to evaluate the variants in a large series of cases and controls. To this end, we have established a new international consortium, PRACTICAL (Prostate cancer association group to investigate cancer associated alterations in the genome). This consortium currently includes studies from 13 centers. Here we report the first results from PRACTICAL for the seven SNPs reported in the U.K./Australian study.

Materials and Methods

Subjects were included from 13 studies comprising prostate cancer cases and controls: 6 from Europe, 5 from North America, and 2 from Australia. These comprised 7,623 prostate cancer cases and 5,913 male controls. Three of the studies used a hospital-based ascertainment of prostate cancer cases, whereas the remainder were population-based studies. The Mayo Clinic study oversampled cases from multiple case families. For two of the studies (San Francisco and University of Southern California), a substantial fraction of subjects were of African American ancestry (19% and 29%, respectively). The University of Southern California study also included a substantial fraction of Hispanic men (26%). The remaining studies were predominantly of men of European ancestry. The Montreal study ascertained men of Ashkenazi Jewish ancestry. All studies have the relevant Institutional Review Board approval in each country in accordance with the principles embodied in the Declaration of Helsinki. Details of each study set are given below, and a summary of the studies is given in Table 1.

Fred Hutchinson Cancer Research Center, Seattle, Washington. The study population consists of participants from two population-based case-control studies in Caucasian and African American residents of King County, Washington (Study I and Study II), which have previously been described. Incident cases with histologically confirmed prostate cancer were ascertained from the Seattle-Puget Sound Surveillance,
Table 1. The PRACTICAL Group and sample sets

<table>
<thead>
<tr>
<th>Location</th>
<th>Total no.</th>
<th>Used no.</th>
<th>Type of study</th>
<th>Age range of cases (y)</th>
<th>Case identification</th>
<th>Male controls identification</th>
<th>Matching and ascertainment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>Cases</td>
<td>Controls</td>
<td>Cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FHCRC (Seattle, WA)</td>
<td>1,335 1,409</td>
<td>1,252 1,254</td>
<td>Population based</td>
<td>35-74</td>
<td>Cancer registry based</td>
<td>Age, telephone dialing</td>
<td></td>
</tr>
<tr>
<td>HaPCS (Hannover, Germany)</td>
<td>504 499</td>
<td>501 499</td>
<td>Hospital based</td>
<td>42-82</td>
<td>Hospital based</td>
<td>Ethnic origin, blood donors</td>
<td></td>
</tr>
<tr>
<td>Mayo (Minnesota)</td>
<td>492 859</td>
<td>484 851</td>
<td>Hospital-based cases</td>
<td>40-86</td>
<td>Hospital-based</td>
<td>Geographically, population via epidemiology study</td>
<td></td>
</tr>
<tr>
<td>MCCS (Melbourne, Australia)</td>
<td>280 322</td>
<td>278 320</td>
<td>Population based</td>
<td>49-81</td>
<td>Cancer registry based</td>
<td>Age, electoral roll</td>
<td></td>
</tr>
<tr>
<td>Montreal (Canada)</td>
<td>146 147</td>
<td>146 147</td>
<td>Hospital based</td>
<td>49-84</td>
<td>Hospital based</td>
<td>Ethnic origin, population volunteers</td>
<td></td>
</tr>
<tr>
<td>ProtecT (United Kingdom)</td>
<td>449 465</td>
<td>408 448</td>
<td>Population based</td>
<td>46-71</td>
<td>PSA screen detected disease</td>
<td>Ethnic origin, age</td>
<td></td>
</tr>
<tr>
<td>Queensland (Australia; incorporating the ProsCan Study and the Retrospective Queensland Study)</td>
<td>177 527</td>
<td>171 516</td>
<td>Population based</td>
<td>43-87</td>
<td>Identified through clinicians in public hospitals and private clinics</td>
<td>Sex only, blood donors</td>
<td></td>
</tr>
<tr>
<td>San Francisco (California)</td>
<td>256 391</td>
<td>247 367</td>
<td>Population based</td>
<td>44-79</td>
<td>Cancer registry based</td>
<td>Age, race/ethnicity origin, random digit dialing</td>
<td></td>
</tr>
<tr>
<td>Tampere (Finland)</td>
<td>919 801</td>
<td>913 799</td>
<td>Population based</td>
<td>43-77</td>
<td>Hospital based</td>
<td>Sex only, blood donors</td>
<td></td>
</tr>
<tr>
<td>UKGPCS (United Kingdom; incorporating The Prostate Cancer Research Foundation Study)</td>
<td>375 343</td>
<td>368 327</td>
<td>Population and hospital based</td>
<td>36-84</td>
<td>Hospital based</td>
<td>Ethnic origin and age, GP practices</td>
<td></td>
</tr>
<tr>
<td>ULM (Germany)</td>
<td>214 517</td>
<td>212 516</td>
<td>Population and hospital based</td>
<td>40-84</td>
<td>Hospital based</td>
<td>Geographically, age ± 5 y</td>
<td></td>
</tr>
<tr>
<td>USC (California)</td>
<td>545 1,173</td>
<td>541 1,156</td>
<td>Population based</td>
<td>42-94</td>
<td>Cancer registry based</td>
<td>Age, geographically, neighborhood block walking</td>
<td></td>
</tr>
<tr>
<td>Valais (Switzerland)</td>
<td>221 170</td>
<td>221 170</td>
<td>Population based</td>
<td>49-84</td>
<td>Population based</td>
<td>Age, geographically, blood donors, patients in private clinics</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5,913 7,623</td>
<td>5,742 7,370</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FHCRC, Fred Hutchinson Cancer Research Center; MCCS, Melbourne Collaborative Cohort Study; UKGPCS, U.K. Genetic Prostate Cancer Study; USC, University of Southern California.
Table 2. Combined ORs (95% CI) for tested SNPs

<table>
<thead>
<tr>
<th>Marker</th>
<th>Chrom</th>
<th>Alleles</th>
<th>MAF (W/B)</th>
<th>Per-allele OR (95% CI)</th>
<th>Het OR (95% CI)</th>
<th>Hom OR (95% CI)</th>
<th>P_trend</th>
<th>Homogeneity P</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs5660753</td>
<td>3p12</td>
<td>C/T</td>
<td>0.11/0.50</td>
<td>1.08 (1.00-1.16)</td>
<td>1.11 (1.01-1.21)</td>
<td>1.06 (0.84-1.34)</td>
<td>0.06</td>
<td>0.90</td>
</tr>
<tr>
<td>rs9364554</td>
<td>6q25</td>
<td>C/T</td>
<td>0.28/0.06</td>
<td>1.14 (1.08-1.21)</td>
<td>1.20 (1.11-1.29)</td>
<td>1.22 (1.06-1.39)</td>
<td>3 × 10^-6</td>
<td>0.40</td>
</tr>
<tr>
<td>rs6465657</td>
<td>7q21</td>
<td>T/C</td>
<td>0.47/0.87</td>
<td>1.12 (1.07-1.18)</td>
<td>1.10 (1.01-1.20)</td>
<td>1.27 (1.14-1.40)</td>
<td>7 × 10^-6</td>
<td>0.23</td>
</tr>
<tr>
<td>rs10993994</td>
<td>10q11</td>
<td>C/T</td>
<td>0.39/0.68</td>
<td>0.89 (0.83-0.95)</td>
<td>0.86 (0.79-0.94)</td>
<td>0.90 (0.71-1.15)</td>
<td>3 × 10^-11</td>
<td>0.71</td>
</tr>
<tr>
<td>rs7931342</td>
<td>11q13</td>
<td>G/T</td>
<td>0.50/0.24</td>
<td>0.86 (0.80-0.89)</td>
<td>0.87 (0.80-0.94)</td>
<td>0.71 (0.65-0.79)</td>
<td>3 × 10^-11</td>
<td>0.71</td>
</tr>
<tr>
<td>rs2735839</td>
<td>19q13</td>
<td>G/A</td>
<td>0.15/0.30</td>
<td>1.29 (1.20-1.39)</td>
<td>1.29 (1.20-1.39)</td>
<td>1.29 (1.20-1.39)</td>
<td>10^-11</td>
<td>0.29</td>
</tr>
<tr>
<td>rs10993994</td>
<td>10q11</td>
<td>C/T</td>
<td>0.39/0.68</td>
<td>0.89 (0.83-0.95)</td>
<td>0.86 (0.79-0.94)</td>
<td>0.90 (0.71-1.15)</td>
<td>3 × 10^-11</td>
<td>0.71</td>
</tr>
<tr>
<td>rs7931342</td>
<td>11q13</td>
<td>G/T</td>
<td>0.50/0.24</td>
<td>0.86 (0.80-0.89)</td>
<td>0.87 (0.80-0.94)</td>
<td>0.71 (0.65-0.79)</td>
<td>3 × 10^-11</td>
<td>0.71</td>
</tr>
<tr>
<td>rs2735839</td>
<td>19q13</td>
<td>G/A</td>
<td>0.15/0.30</td>
<td>1.29 (1.20-1.39)</td>
<td>1.29 (1.20-1.39)</td>
<td>1.29 (1.20-1.39)</td>
<td>10^-11</td>
<td>0.29</td>
</tr>
<tr>
<td>rs10993994</td>
<td>10q11</td>
<td>C/T</td>
<td>0.39/0.68</td>
<td>0.89 (0.83-0.95)</td>
<td>0.86 (0.79-0.94)</td>
<td>0.90 (0.71-1.15)</td>
<td>3 × 10^-11</td>
<td>0.71</td>
</tr>
<tr>
<td>rs7931342</td>
<td>11q13</td>
<td>G/T</td>
<td>0.50/0.24</td>
<td>0.86 (0.80-0.89)</td>
<td>0.87 (0.80-0.94)</td>
<td>0.71 (0.65-0.79)</td>
<td>3 × 10^-11</td>
<td>0.71</td>
</tr>
<tr>
<td>rs2735839</td>
<td>19q13</td>
<td>G/A</td>
<td>0.15/0.30</td>
<td>1.29 (1.20-1.39)</td>
<td>1.29 (1.20-1.39)</td>
<td>1.29 (1.20-1.39)</td>
<td>10^-11</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Abbreviations: W, Whites; B, Blacks.

Epidemiology, and End Results cancer registry. In Study I, cases were diagnosed between January 1, 1993, and December 31, 1996 and were 40 to 64 y of age at diagnosis. In Study II, cases were diagnosed between January 1, 2002, and December 31, 2005 and were 35 to 74 y of age at diagnosis. Overall, 2,244 eligible prostate cancer patients were identified and 1,754 (78%) were interviewed. Blood samples yielding sufficient DNA for genotyping were drawn from 1,457 (83%) cases who completed the study interview.

A comparison group of controls without a self-reported history of prostate cancer, residing in King County, Washington, was identified for each study using random digit telephone dialing. Controls were frequency matched to cases by 5-y age groups and recruited evenly throughout each ascertainment period for cases. A total of 2,448 men were identified who met the eligibility criteria and 1,754 (72%) were interviewed. Blood samples were drawn and DNA prepared from 1,358 (77%) interviewed controls.

Hannover Prostate Cancer Study, Hannover, Germany. A hospital-based series of 499 unselected Caucasian patients with prostate cancer, who were treated with brachytherapy between October 2000 and September 2007 at Hannover Medical School, were enrolled for this study. All patients had biopsy-proven adenocarcinoma of the prostate. Indication for permanent brachytherapy was clinically localized low-risk early prostate cancer (cT2a or less with a PSA serum level <3 ng/mL) and a Gleason score <7) following an early prostate cancer (cT2a or less with a PSA serum level <3 ng/mL) and a Gleason score <7) following a median at diagnosis was 67 y in this patient series (range, 42-82 y). For comparison, a series of 504 genomic DNA samples was established from ethnically matched adult male blood donors at Hannover Medical School in the period from 2006 to 2007.

Mayo Clinic, Rochester, Minnesota. The Mayo Clinic study (10) consisted of hospital-based cases, including 432 affected men from 177 families with prostate cancer, 489 men with sporadic prostate cancer, 193 with aggressive (Gleason score >7) prostate cancer, and 492 population-based controls. The controls (all males) were randomly selected from a sampling frame of Olmsted County, Minnesota, provided by the Rochester Epidemiology Project. The methods used to ascertain familial and sporadic prostate cancer patients, as well as controls, have previously been described (10). All individuals from the Mayo Clinic study included in this report were of self-reported European descent.

Melbourne Collaborative Cohort Study, Melbourne, Australia. This is a prospective cohort of 17,154 men of ages 40 to 69 y at recruitment in 1990 to 1994 (Melbourne Collaborative Cohort Study; n = 190). Cases (n = 322) were participants diagnosed with prostate cancer during follow-up in early 2005 and were ascertained through linkage with the Victorian Cancer Registry and the National Cancer Statistics Clearing House that includes diagnoses from other states in Australia. Controls (n = 280) were a random sample of the Melbourne Collaborative Cohort Study participants that were not diagnosed with prostate cancer during follow-up. All study subjects were of Caucasian origin.

Montreal Canada. Prostate cancer cases were identified using a hospital-based tumor registry. They included self-reported Ashkenazi Jewish men with prevalent prostate cancer diagnosed between 1991 and 2002 and diagnosed or treated in one of three large McGill University affiliated hospitals in metropolitan Montreal. Patients were considered to be Ashkenazi Jewish if both parents were reported as Ashkenazi Jewish, with no Sephardic heritage. The diagnosis of invasive prostate carcinoma was confirmed by examining the pathology reports present in the medical charts of all eligible participants.

The control group is derived from Ashkenazi Jewish donors who contributed a DNA sample to the National Laboratory for the Genetics of Israeli Populations. All participants are adult Israeli citizens (>18 y old). Available information on these controls is limited to gender and ethnic origin.

ProtecT, United Kingdom. ProtecT (11) is a national study of community-based PSA testing and a randomized trial of subsequent prostate cancer treatment. Approximately 200,000 men between the ages of 50 and 69 y, ascertained through general practices in nine regions in the United Kingdom, are being recruited. Men known to be non-White were excluded. For this study, 449 cases identified by PSA screening within the ProtecT study were analyzed. Controls with normal PSA levels (<3 ng/mL) were selected from the same GP register and 5-y age band as the cases.

Queensland, Australia. The Queensland (12) cases were ascertained from two studies: (a) a series of men recruited within 2 y of their diagnosis of prostate cancer

23 http://www.tau.ac.il/medicine/NLGIP/nlgip.htm
Figure 1. Forrest plots for the tested SNPs shown individually by study center for each SNP: rs2660753 (3p12), rs9364554 (6q25), rs6465657 (7q21), rs10993994 (10q11), rs7931342 (11q13), rs2735839 (19q13), and rs5945619 (Xp11).
Table 3. Per-allele ORs (95% CI) associated with a family history of prostate cancer among cases compared with men without a family history

<table>
<thead>
<tr>
<th>Marker</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2660753 (3p12)</td>
<td>0.92 (0.80-1.07)</td>
</tr>
<tr>
<td>rs9364554 (6q25)</td>
<td>1.06 (0.94-1.20)</td>
</tr>
<tr>
<td>rs6465657 (7q21)</td>
<td>0.96 (0.86-1.07)</td>
</tr>
<tr>
<td>rs10993994 (10q11)</td>
<td>1.08 (0.98-1.21)</td>
</tr>
<tr>
<td>rs7931342 (11q13)</td>
<td>0.89 (0.79-0.99)</td>
</tr>
<tr>
<td>rs2735839 (19q13)</td>
<td>1.02 (0.88-1.18)</td>
</tr>
<tr>
<td>rs5945619 (Xp11)</td>
<td>0.90 (0.63-1.29)</td>
</tr>
</tbody>
</table>

Table 4. ORs (95% CI) by age (at diagnosis for cases and age at interview for controls)

<table>
<thead>
<tr>
<th>Marker</th>
<th>&lt;55</th>
<th>55-59</th>
<th>60-64</th>
<th>65-69</th>
<th>70+</th>
<th>P_trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2660753 (3p12)</td>
<td>0.96 (0.77-1.18)</td>
<td>1.01 (0.83-1.23)</td>
<td>1.06 (0.86-1.28)</td>
<td>1.25 (1.01-1.54)</td>
<td>1.33 (1.06-1.66)</td>
<td>0.07</td>
</tr>
<tr>
<td>rs9364554 (6q25)</td>
<td>1.14 (0.97-1.34)</td>
<td>1.06 (0.91-1.22)</td>
<td>1.28 (1.11-1.47)</td>
<td>1.03 (0.88-1.22)</td>
<td>1.19 (1.00-1.42)</td>
<td>0.82</td>
</tr>
<tr>
<td>rs6465657 (7q21)</td>
<td>1.20 (1.03-1.38)</td>
<td>1.20 (1.04-1.37)</td>
<td>1.02 (0.90-1.17)</td>
<td>1.16 (1.00-1.34)</td>
<td>1.06 (0.90-1.25)</td>
<td>0.17</td>
</tr>
<tr>
<td>rs10993994 (10q11)</td>
<td>1.32 (1.14-1.53)</td>
<td>1.35 (1.18-1.54)</td>
<td>1.13 (1.00-1.29)</td>
<td>1.26 (1.08-1.46)</td>
<td>1.45 (1.24-1.70)</td>
<td>0.64</td>
</tr>
<tr>
<td>rs7931342 (11q13)</td>
<td>0.87 (0.75-1.01)</td>
<td>0.81 (0.71-0.93)</td>
<td>0.78 (0.69-0.89)</td>
<td>0.83 (0.72-0.96)</td>
<td>0.90 (0.77-1.05)</td>
<td>0.66</td>
</tr>
<tr>
<td>rs2735839 (19q13)</td>
<td>0.82 (0.67-1.00)</td>
<td>0.73 (0.61-0.88)</td>
<td>0.95 (0.71-1.33)</td>
<td>0.85 (0.69-1.04)</td>
<td>1.02 (0.83-1.25)</td>
<td>0.18</td>
</tr>
<tr>
<td>rs5945619 (Xp11)</td>
<td>1.34 (1.07-1.68)</td>
<td>1.25 (1.02-1.52)</td>
<td>1.48 (1.22-1.79)</td>
<td>1.21 (0.97-1.50)</td>
<td>1.27 (1.01-1.60)</td>
<td>0.91</td>
</tr>
</tbody>
</table>
University of Southern California, Los Angeles, Southern California. Subjects were participants in a population-based case-control study of aggressive prostate cancer conducted in Los Angeles County. Cases were identified through the Los Angeles County Cancer Surveillance Program rapid case ascertainment system. Large hospitals are screened at least weekly, and other sites at least monthly. Eligible cases included African American, Hispanic, and non-Hispanic White men diagnosed with a first primary prostate cancer between January 1, 1999 and December 31, 2003. Eligible cases also had (a) prostatectomy with documented tumor extension outside the prostate, (b) metastatic prostate cancer in sites other than prostate, (c) needle biopsy of the prostate with Gleason grade ≥ 8, or (d) needle biopsy with Gleason grade 7 and tumor in more than two thirds of the biopsy cores.

Eligible controls were men never diagnosed with prostate cancer, living in the same neighborhood as a case, and were frequency matched to cases on age (± 5 y) and race/ethnicity. Controls were identified by a neighborhood walk algorithm, which proceeds through an obligatory sequence of adjacent houses or residential units beginning at a specific residence that has a specific geographic relationship to the residence where the case lived at diagnosis.

Valais, Switzerland. Between December 1, 2002 and January 31, 2007, all urologists in a relatively isolated alpine region of Switzerland (canton du Valais) invited their patients diagnosed with invasive prostate cancer (all stages) to participate to a research project on genetic factors involved in prostate cancer. Both parents were required to originate from the canton du Valais. A detailed family history on at least three generations was collected by a trained research nurse, as well as a blood sampling. A series of healthy men, without a self-reported family history of prostate cancer, originating from the same region, participated as controls (blood donors and elderly patients seen in private practice). Most of these men had regular PSA screening.

Genotyping. We tested the seven SNPs (one from each genomic region) that were independently associated with prostate cancer in the study by Eeles et al. (Table 2; ref. 9). One SNP (rs5945619) failed for the Queensland study and this study is not therefore included in the analysis of this SNP. For all but two centers, the genotyping was done with the 5’ nuclease assay (TaqMan™) using the ABI Prism 7900HT sequence detection system according to the manufacturer’s instructions. Primers and probes were supplied by Applied Biosystems as Assay-by-Design™. For the genotyping done in Montreal (Valais and Montreal sample sets), the Applied Biosystems 7500 fast Real-time PCR system, using 96-well plates, was used according to the manufacturer’s instructions for TaqMan. The Australian center in Queensland used the iPLEX Sequenom MassArray system. For genotyping of The Fred Hutchinson Cancer Research Center samples (the Fred Hutchinson Cancer Research Center/National Human Genome Research Institute group), National Human Genome Research Institute investigators used the Applied Biosystems SNPioplex Genotyping System and proprietary GeneMapper software for allele assignment. Discrimination of the specific SNP allele was carried out with the ABI 3730xl DNA Analyzer, based on the presence of a unique sequence assigned to the original allele-specific oligonucleotide. Assays at all sites included at least two negative controls and two duplicates (in Queensland there were 140 duplicates). Quality control guidelines were followed by all the participating groups (see Supplementary data). We excluded any subjects that provided genotype data for less than six of the seven SNPs. All markers passed the Hardy-Weinberg threshold of \( P < 0.00001 \) and the call rate threshold of 95%. All centers typed at least 2% of samples as blind duplicates; in all instances, fewer than 2% of duplicate samples were discordant. Before the publication by Eeles et al. (9), the SNP hits were disclosed to the PRACTICAL collaborating groups under confidentiality release agreements. The Mayo Clinic group had, before the establishment of PRACTICAL, independently typed several SNPs in collaboration with deCODE Genetics (16). Although not identical, one of these was in the vicinity of the X-chromosome marker reported in the present PRACTICAL study. Of the total Mayo samples genotyped for this region, 90% are in common between the two studies (16).

Statistical Methods. ORs and 95% confidence intervals (95% CI) associated with each genotype were estimated using unconditional logistic regression, stratified by study and racial/ethnic group. We assessed the association between each SNP and prostate cancer using a stratified 1-degree-of-freedom Cochran-Armitage trend test and a general 2-degree-of-freedom \( \chi^2 \) test. For all studies, except the San Francisco and University of Southern California studies, minority racial/ethnic minority groups were excluded. We also excluded 148 female controls typed by the Montreal study. The Mayo Clinic study included an additional 675 affected individuals from 177 multiple case families. For the test statistics, only one affected individual from each family, selected at random, was included. For the OR estimates,

### Table 5. ORs (95% CI) by tumor grade

<table>
<thead>
<tr>
<th>Marker</th>
<th>Gleason 1-4</th>
<th>Gleason 5-7</th>
<th>Gleason 8+</th>
<th>( P_{\text{trend}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2660753 (3p12)</td>
<td>1.04 (0.74-1.44)</td>
<td>1.14 (1.02-1.28)</td>
<td>0.94 (0.76-1.18)</td>
<td>0.25</td>
</tr>
<tr>
<td>rs9364554 (6q25)</td>
<td>0.94 (0.75-1.20)</td>
<td>1.12 (1.03-1.22)</td>
<td>1.15 (0.99-1.35)</td>
<td>0.06</td>
</tr>
<tr>
<td>rs6465657 (7q21)</td>
<td>0.87 (0.70-1.07)</td>
<td>1.16 (1.07-1.25)</td>
<td>0.98 (0.84-1.13)</td>
<td>0.89</td>
</tr>
<tr>
<td>rs10993994 (10q11)</td>
<td>1.06 (0.86-1.32)</td>
<td>1.27 (1.18-1.37)</td>
<td>1.14 (0.99-1.32)</td>
<td>0.73</td>
</tr>
<tr>
<td>rs931342 (11q13)</td>
<td>0.92 (0.75-1.12)</td>
<td>0.86 (0.80-0.93)</td>
<td>0.84 (0.73-0.97)</td>
<td>0.36</td>
</tr>
<tr>
<td>rs2739839 (13q13)</td>
<td>0.91 (0.67-1.25)</td>
<td>0.91 (0.81-1.01)</td>
<td>0.95 (0.77-1.17)</td>
<td>0.54</td>
</tr>
<tr>
<td>rs5945619 (Xp11)</td>
<td>1.03 (0.76-1.41)</td>
<td>1.34 (1.21-1.50)</td>
<td>1.37 (0.95-1.43)</td>
<td>0.45</td>
</tr>
</tbody>
</table>
cases from these multiple case families were excluded entirely to avoid inflation of the risk estimates due to selection for family history. After these exclusions, 7,370 prostate cancer cases and 5,742 control subjects were included in the analysis.

The combined associations of multiple SNPs were first evaluated by testing for departures from a multiplicative model of interaction. This was done in two ways: first, using a case-only analysis in which the genotypes at one SNP were regressed against the genotypes of another SNP in cases using polynymous regression; second, by a case-control analysis, which included an interaction term in multiple logistic regression. We also assessed the combined effects of the SNPs by deriving a risk score based on the estimated ORs for each SNP (without interactions) and then estimating the OR based on the data available. Modification of the OR by age at diagnosis was tested using a case-only analysis, which assessed the association of age at onset on SNP genotypes in the cases using polynymous regression. The association of family history on the ORs was also assessed by a case-only analysis, treating a positive history as the outcome in a logistic regression. The contribution of each locus to the overall familial risk was estimated by log (OR/1), where k is the predicted relative risk to offspring of affected individuals due to locus k, given the allele frequency and per-allele OR, and k is the observed familial relative risk, assumed to be 2 (1, 2, 17). The combined effect of all loci was computed by summing the individual effects (i.e., assuming a multiplicative model). All analyses were done using Stata version 9.0 (18).

Results and Discussion

Six of the seven SNPs tested in this study showed clear evidence of association with prostate cancer (Table 2; Fig. 1). For each SNP, the estimated per-allele OR was very similar to that estimated by the second stage of the original genome-wide association study (9). For the 3p marker, rs2660753, the estimated OR (OR, 1.08; 95% CI, 1.00-1.16) was lower than found by the original study (OR, 0.91) and of borderline statistical significance, although the confidence intervals still overlapped. None of the SNPs showed significant heterogeneity in the per-allele OR across studies.

Three of the six autosomal markers showed a clear allele dosage association, with an intermediate risk for heterozygotes, consistent with the associations reported previously. For two markers, rs6465657 (7q21) and rs10993994 (10q11), the homozygote OR was greater than predicted under a multiplicative model, but not significantly so. For rs9364554 (6q21), we saw no apparent difference in risk between heterozygotes and homozygotes (i.e., a dominant model; P = 0.06 for departure from multiplicativity), consistent with the pattern seen in stage 2 of the genome-wide association study. rs2660753 (3p12) and rs2735839 (19q13) also seemed to be more consistent with a dominant model, but the minor allele for these markers was relatively rare in men of European and Australian and American ancestry (11% and 15%, respectively), and the ORs did not differ significantly from a multiplicative model. This apparent dominant association was also seen in stage 2 of the genome-wide association study for rs2735839 (19q13), but not for rs2660753 (3p12) where the homozygote OR was markedly higher (OR, 2.09; 95% CI, 1.39-3.15) than observed here (OR, 1.06; 95% CI, 0.84-1.34). For six of the seven SNPs, the minor allele in men of European ancestry was associated with an increased prostate cancer risk [for rs7931342 (11q13), the alleles were of approximately equal frequency]. There were, however, substantial differences in allele frequencies between racial/ethnic groups for many of the SNPs. In particular, for rs6465657 (7q21) and rs10993994 (10q11), the risk allele was the major allele in the African American controls. The number of African American samples analyzed here was too small to estimate the ORs separately for this group. However, there was no evidence for a difference in the per-allele OR between this racial/ethnic group and the men of European ancestry for any of the tested SNPs. In particular, for the most strongly associated SNP rs10993994 in MSMB the estimated OR did not differ between European and African American men [OR, 1.24 (95% CI, 0.97-1.59; P = 0.09) in African Americans and 1.25 (95% CI, 1.18-1.31; P = 5 x 10^-17) in men of European/European American ancestry].

The per-allele ORs for each SNP by family history are summarized in Table 3. For rs10993994 (10q11), the frequency of the risk allele was somewhat higher in men with a family history (P = 0.06), as would be expected under a simple polygenic model (Table 3). None of the other markers showed a significantly stronger association for men with a family history. However, only 20% of cases reported a positive family history in any relative, so the confidence limits of the ORs associated with a family history are wide. There was some suggestion of an increase in the OR with age at diagnosis for rs2660753 (3p12; P = 0.07), but there was no evidence for a similar trend in OR for any other SNP (Table 4).

Gleason score was available for 3,125 of the cases used in the analyses; of these, 190 had a score of <5; 2,454 were in the range of 5 to 7; and 481 men had a score of ≥8. We found some evidence that the association with the chromosome 6 marker, rs9364554, was more pronounced for high-grade tumors (P = 0.06; Table 5). There was no clear pattern of association with tumor grade for any of the other SNPs.

We investigated the joint association of each pair of SNPs, using both case-only and case-control analyses, to examine departures from a multiplicative model. None of the 21 pairwise analyses showed significant evidence for interaction on this scale: the strongest evidence found was for rs2735839 (19q13) and rs5945619 (Xp11; P = 0.07 in the case-only analysis), rs9364554 (6q25) and rs10993994 (10q11; P = 0.08 in the case-control analysis), and rs7931342 (11q13) and rs2735839 (19q13; P = 0.08 in the case-control analysis).

### Table 6. ORs (95% CI) by approximate quantiles of the risk score

<table>
<thead>
<tr>
<th>Marker</th>
<th>OR (95% CI)</th>
<th>Predicted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1%</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1-10%</td>
<td>1.36 (0.78-2.40)</td>
<td>1.22</td>
</tr>
<tr>
<td>10-25%</td>
<td>1.86 (1.07-3.22)</td>
<td>1.61</td>
</tr>
<tr>
<td>25-75%</td>
<td>2.35 (1.35-4.08)</td>
<td>2.03</td>
</tr>
<tr>
<td>75-90%</td>
<td>3.06 (1.76-4.08)</td>
<td>2.42</td>
</tr>
<tr>
<td>90-99%</td>
<td>3.50 (2.08-6.12)</td>
<td>2.97</td>
</tr>
<tr>
<td>&gt;99%</td>
<td>3.52 (1.87-6.64)</td>
<td>3.81</td>
</tr>
</tbody>
</table>
Appendix A. The PRACTICAL Group (excluding those named in the author list)

U.K. Genetic Prostate Cancer Study
Cancer Research UK Genetic Epidemiology Group,
Cambridge, United Kingdom
Jonathan Morrison

The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom
Sameer Jhavar
Audrey Ardern-Jones
Amanda Hall
Rosemary Wilkinson
Lynne O’Brien
David P. Dearnaley
Alan Horwich
Robert A. Huddart
Vincent S. Khoo
Christopher C. Parker
Christopher J. Woodhouse
Alan Thompson
Tim Christmas
Chris Ogden
Cyril Fisher
Charles Jamieson
Colin S. Cooper

The U.K. Genetic Prostate Cancer Study Collaborators/British Association of Urological Surgeons’ Section of Oncology
[for list, see Eeles et al. (9)]

The ProtecT Study
Jenny Donovan
Freddie Hamdy
Sarah Lewis
Paul M. Brown
Gemma Marsden
The U.K. ProtecT Study Collaborators (9, 11)

The Melbourne Group
John Pedersen TissuPath, Melbourne, Australia.

The Montreal Study
Kimberley Kotar
Ulma, Germany

Institut für Humangenetik:
Manuel Luedeke
Harald Surowy
Bärbel Weber

Klinikum für Urologie und Kinderurolologie:
Kathleen Herkommer
Thomas Paiss

Finnish Genetic Predisposition to Prostate Cancer Study
Institute of Medical Technology, University of Tampere and Tampere University Hospital, Tampere, Finland
Henna Mattila
Sanna Siltanen
Sanna Pakkanen
Jarkko Isotalo

Department of Urology, Tampere University Hospital and Medical School, University of Tampere, Tampere, Finland
Mika Mattikainen

The Hannover Prostate Cancer Study
Stefan Machtens
Jörn Hagemanns
Peter Hillemanns
Michael Bremer
Johann H. Karstens

Prostate Cancer Study in Valais, Switzerland
Cédric Biedermann, M.D.
Hans-Ulrich Peter, M.D.
Nicolas Defabiani, M.D.
Sabine Bieri, M.D.
Christophe Girardet, M.D.
Isabelle Konzelmann, M.D.
Michele Stalder, M.D.
Marie-Mathilde Meier, R.N.

Queensland University of Technology
Kimberly Hinze—School of Public Health, Institute of Health and Biomedical Innovation, Queensland University of Technology
Beth Newman—School of Public Health, Institute of Health and Biomedical Innovation, Queensland University of Technology

Retrospective Queensland Study
John Yaxley—Brisbane Private Clinic
David Nicol—Princess Alexandra Hospital

The ProCesCan Study
Megan Ferguson—The Cancer Council Queensland
David Nicol—Princess Alexandra Hospital

The Northern Section of the Urological Society of Australia and New Zealand
Royal Brisbane and Women’s Hospital
Princess Alexandra Hospital
Mater Adults Hospital
Ipswich Hospital
Greenslopes Private Hospital
Redlands Hospital
Redcliffe Hospital
The Townsville Hospital
Mackay Base Hospital
Mayo Clinic

Liang Wang
Julie Cunningham

We next ranked each man based on his predicted risk, assuming a simple multiplicative model [i.e., the sum of the number of high-risk alleles, weighted by the estimated log (per-allele OR), and computed empirical ORs for categories of risk. As expected, the estimated ORs increased consistently with increasing risk score, the OR being 3.52-fold for men in the top 1% of the distribution compared with men in the lowest 1% (Table 6). These ORs are close to those predicted under a simple multiplicative model.

The primary purpose of this study was to test a large number of prostate cancer cases and controls collected from diverse populations for association with seven loci previously identified by a genome-wide association study. All seven loci showed at least some evidence of association consistent with that found by the original study. Five of the SNPs were significant at $P = 7 \times 10^{-6}$ or better in the replication study, with per-allele ORs close to those found in stage 2 of the genome-wide association study (9), which was based on case-control studies conducted in Australia and the United Kingdom. For the chromosome 19 SNP (rs2735839), which lies between KLK2 and KLK3, the association was more modest ($P = 0.0007$) but the per-allele OR was still close to that observed in the original genome-wide association study, rs2660753, on chromosome 3, showed a somewhat weaker association. This may simply be a chance finding because the OR did not differ significantly from that previously found, but it may reflect, in part, “winner’s curse,” whereby the magnitudes of the most significant associations tend to be exaggerated in the initial study compared with those in the replication studies. Although rs2660753 reached genome-wide levels of significance, this was the weakest of the associations found by the genome-wide association study ($P = 2.7 \times 10^{-8}$) and was therefore the most susceptible to this phenomenon.

Of the autosomal loci, the strongest association was with rs10993994 on 10q11, for which the estimated per-allele OR was 1.25 and the estimated OR for TT
homzygotes, relative to CC homozygotes, was 1.57. This SNP lies only 2 bp upstream of the transcription initiation site of the MSMB gene, a gene that encodes PSTD94, an immunoglobulin binding factor that is secreted into the seminal plasma (19). Thomas et al. (20) independently reported an association with this SNP, with a very similar OR, from their recent genome-wide association study. The same group resequenced across MSMB in 80 individuals and found no other closely correlated SNPs, suggesting that this variant may be causally implicated in the observed association. It is interesting to note that this SNP seems to confer a similar relative risk in African American men to that in men of European ancestry, indicating that this association is independent of racial/ethnic background. Thomas et al. (20) also found strong evidence of association with a marker on chromosome 11q13, rs10896449, which is closely correlated with rs7931342 at 11q13.

The highest per-allele OR for any marker was found on the X chromosome with marker rs5945619; the estimated per-allele OR in the present study (OR, 1.29; 95% CI, 1.20-1.39) was actually slightly higher than that found in the genome-wide association study. This marker lies in a block spanning >2 Mb that includes the X centromere. Gudmundsson et al. (16) reported an association with another SNP in the same region, rs9545572, which is closely correlated with this SNP, further supporting this association.

The combined associations of these loci on prostate cancer risk seem to be consistent with a simple multiplicative model, as judged both by examining pairwise interactions between loci and by estimating the ORs using quantiles of the risk distribution. If this model is assumed to be correct, the estimated risk to men in the top 1% of the risk distribution is ∼3.8-fold greater than the risk to men in the bottom 1%, which translates into an ∼2-fold risk relative to the population average. In addition to the loci considered here, eight additional common prostate cancer susceptibility loci have been reported: three on 8q, two on 17q, and the recent loci on 2q reported by Gudmundsson et al. (16) and on 10q and 7p by Thomas et al. (20). If one assumes that all these loci combine multiplicatively, the combined risk distribution defined by all these SNPs would imply a risk of ∼3.2-fold for the top 1% of the risk distribution, or 2.1-fold for the top 10%, compared with the population average. These risks correspond to absolute lifetime risks of prostate cancer of ∼26% and 18%, respectively, by age 80 y, based on recent reports of incidence rates for England and Wales, compared with the population average of 9% (Cancer Research UK Factsheets).

In total, the 15 reported susceptibility variants explain ∼16% of the familial risk of prostate cancer. Additional variants are likely to be identified through further analysis of genome-wide association studies, and these will improve the predictive power of genetic profiling for prostate cancer risk. Large-scale collaborations such as PRACTICAL will be needed to estimate with confidence and precision the combined prostate cancer risks associated with all variants.

Disclosure of Potential Conflicts of Interest

S. Machtens: Bard, Pfizer, Sanofi-Aventis Speakers Bureau/Honoraria. The other authors disclosed no potential conflicts of interest.

Acknowledgments

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

We thank all the patients and control men who took part in this study. We also thank the staff at Tepnel Life Sciences, Sheila Doyle, Amanda Priest, Alison Barlow, Sarah Howe, and Louise Holliday, for their help with this study; Kimberly Kotar for recruitment of the Montreal cases; and Joëlle Vuignier, Corinne Sierro, Barbara Varone, and Aurélie Ayme for technical and administrative assistance. We thank Linda Enroth for her help with The Tampere Study.

The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Department of Health of England.

References


Cancer Epidemiol Biomarkers Prev 2008;17(8). August 2008

Downloaded from cebp.aacrjournals.org on May 28, 2017. © 2008 American Association for Cancer Research.