Genome-Wide Association Study of Prostate Cancer-Specific Survival


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Abstract

Background: Unnecessary intervention and overtreatment of indolent disease are common challenges in clinical management of prostate cancer. Improved tools to distinguish lethal from indolent disease are critical.

Methods: We performed a genome-wide survival analysis of cause-specific death in 24,023 prostate cancer patients (3,513 disease-specific deaths) from the PRACTICAL and BPC3 consortia. Top findings were assessed for replication in a Norwegian cohort (CONOR).

Results: We observed no significant association between genetic variants and prostate cancer survival.

Conclusions: Common genetic variants with large impact on prostate cancer survival were not observed in this study.

Impact: Future studies should be designed for identification of rare variants with large effect sizes or common variants with small effect sizes. Cancer Epidemiol Biomarkers Prev; 24(11): 1796–800. ©2015 AACR.

Introduction

Prostate cancer is the second leading cause of cancer death among men in the developed world. Randomized trials have shown that PSA-based screening can reduce prostate cancer mortality up to 40%, though at the cost of considerable overdiagnosis and overtreatment of indolent disease (1). Thus, improved tools to distinguish lethal from indolent disease to guide clinicians in treatment decisions are critical. Epidemiologic studies support the existence of a genetic component to prostate cancer prognosis (2). The purpose of this study was to identify SNPs associated with prostate cancer-specific survival. We performed a genome-wide search among individuals from two large prostate cancer genetics consortia (PRACTICAL; ref. 3) and BPC3 (4) with replication of top findings in a Norwegian prostate cancer cohort (CONOR).

Materials and Methods

Study populations and genotyping

In total, 24,023 prostate cancer patients with follow-up on cause-specific death from the PRACTICAL (n = 21,241) and BPC3 (n = 2,782) consortia were included in the present study (Table 1). All men from BPC3 have an aggressive disease, defined by a tumor Gleason score of eight or above. Participants had either been genotyped on a custom-designed SNP chip (iCOGS) with 211,155 markers or on standard genome-wide arrays (Table 1). Imputation was performed using a cosmopolitan panel from the 1000 Genomes Project (March 2012) to increase the genetic coverage. Only SNPs that had an imputation quality above 0.75 and minor allele frequency (MAF) above 1% were assessed (1.2–9.5 million SNPs in each separate study, Table 1). Detailed information regarding study populations, genotyping, and imputation is found in (3) and (4).

Statistical analysis

Within each study, SNPs were assessed for association with disease survival, assuming an additive genetic effect, in a Cox regression model allowing for left truncation and right censoring of observational times. Results were combined in fixed-effects meta-analysis. In the discovery stage, we considered an association to be genome-wide significant if the overall meta-analysis achieved P < SE–08 and the test for heterogeneity across studies was nonsignificant (P > 0.05). We also adjusted the most associated SNPs for population structure (principal components), age at diagnosis, diagnostic PSA, and Gleason score, but we did not observe any confounding (data not shown).

Replication

Genome-wide significant SNPs in the discovery stage were directly genotyped in 1,783 individuals from the UKGPCS1 study (Table 1) using TaqMan assays to verify imputation quality, evaluated as the concordance rate between imputed and genotyped data (percentage of individuals correctly classified by imputation). Significant SNPs from the discovery stage with satisfactory imputation qualities were assessed for replication in a Norwegian case–cohort study (CONOR; ref. 5) comprising 1,496 prostate cancer patients.
We performed a genome-wide search for SNPs associated with prostate cancer survival by combining data from the PRACTICAL and BPC3 consortia. Our null finding is in line with previous smaller studies (8) and implicates that the existence of common genetic variants with large effect sizes is unlikely. We would however like to stress that our analysis was based on imputed data and some areas of the genome were not well represented due to a low number of SNPs with good imputation quality.

Despite a reasonably large replication sample, we saw no evidence of association among the four SNPs that were initially found to be genome-wide significant (P < 5E–08). Two of these SNPs were rare, in which spurious associations occur more easily. It is however more surprising that the two common SNPs (MAF, 7%–8%) and eight rare variants (MAF, 1%–2%) were false positives. This underlines the importance of independent replication in genetic association studies.

From this study, we conclude that the search for SNPs that are associated with prostate cancer survival should focus on the identification of rare variants with large effect sizes or common variants with small effect sizes. Large study populations with complete follow-up information regarding survival are warranted to successfully achieve this task.
Table 2. Genome-wide assessment of prostate cancer survival

<table>
<thead>
<tr>
<th>SNP CHR:BP</th>
<th>Alleles</th>
<th>MAF</th>
<th>Total number of PC/deaths</th>
<th>HR (95% CI) P value</th>
<th>Conor HR (95% CI) P value</th>
<th>All studies* HR (95% CI) P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs190087062</td>
<td>G/A</td>
<td>0.02</td>
<td>2,416/704</td>
<td>2.83 (1.99–4.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t15061785</td>
<td>A/G</td>
<td>0.02</td>
<td>20,051/3,729</td>
<td>1.75 (1.44–2.13)</td>
<td>0.88 (0.42–1.85)</td>
<td>1.67 (1.38–2.03)</td>
</tr>
<tr>
<td>rs19997855</td>
<td>G/A</td>
<td>0.02</td>
<td>23,251/3,274</td>
<td>1.29 (1.18–1.41)</td>
<td>1.01 (0.76–1.35)</td>
<td>1.26 (1.16–1.38)</td>
</tr>
<tr>
<td>rs76010824</td>
<td>A/G</td>
<td>0.07</td>
<td>2.86 (0.8–8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs11414857</td>
<td>G/A</td>
<td>1.75</td>
<td>17,146/2,236</td>
<td>1.98 (1.56–2.50)</td>
<td>1.78 (0.8–8)</td>
<td></td>
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<tr>
<td>rs135990166</td>
<td>G/A</td>
<td>0.02</td>
<td>1,730/464</td>
<td>3.54 (2.31–5.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs192864773</td>
<td>G/A</td>
<td>0.01</td>
<td>3,186/1,577</td>
<td>1.93 (1.53–2.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs117643112</td>
<td>C/A</td>
<td>0.01</td>
<td>2.01 (0.93–3.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs1304659849</td>
<td>A/G</td>
<td>0.02</td>
<td>2.702/271</td>
<td>3.00 (2.06–4.36)</td>
<td>0.75 (0.24–2.33)</td>
<td>2.61 (1.83–3.73)</td>
</tr>
<tr>
<td>rs201949337</td>
<td>A/T</td>
<td>0.01</td>
<td>2.975/3,324</td>
<td>1.17 (1.20–1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs126653357</td>
<td>G/T</td>
<td>0.08</td>
<td>1.50–7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BP, base position (Genome build 37); CHR, chromosome; 95% CI, 95% confidence interval.
*Minor allele/major allele. Minor allele used as effect allele (major as reference) in analysis.
**Proxy for rs190977150 (P = 9.5E-09 in PRACTICAL and BPC3).

**Table 2 continued**

**Disclosure of Potential Conflicts of Interest**
R.A. Eeles has received speakers bureau honoraria from Succinct Communications. No potential conflicts of interest were disclosed by the other authors.

**Authors’ Contributions**


Other (attendance at working group meetings): M.C. Southey

Other (provided samples and data to the manuscript): A. Michael

**References**


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