

## 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; ref. 5).

## 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  $P < 5E-08$  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

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**Note:** Full list of participants of The PRACTICAL Consortium is provided in the Supplementary Notes.

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

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**Table 1.** Patient characteristics of included study populations

Study	N	Number of prostate cancer deaths	Total person-years	Person-years at risk median (min-max)	Number of SNPs with imputation quality $\geq 0.75$
<b>PRACTICAL</b>					
CAPS	412	49	3,476.6	9.3 (0.4–11.8)	5,752,274 <sup>a</sup>
CAPS1	492	214	3,120.2	7.1 (0.1–11.8)	8,933,855 <sup>b</sup>
CAPS2	1,493	331	11,644.6	9.1 (0–11.8)	8,715,366 <sup>b</sup>
CPCS	925	97	1,772.1	1.3 (0.1–18.1)	5,550,954 <sup>a</sup>
EPIC	404	35	467.4	0 (0–13.2)	5,503,395 <sup>a</sup>
ESTHER	300	22	2,179.9	7.7 (0.1–9.8)	5,495,692 <sup>a</sup>
FHCRC	760	46	7,716.6	8.1 (0.2–18.1)	5,532,283 <sup>a</sup>
MAYO	737	40	4,612.8	6.8 (0.1–13.9)	5,555,791 <sup>a</sup>
MCCS_PCFS	1,663	139	41,656.4	22.6 (0–71.2)	5,425,082 <sup>a</sup>
MEC	581	15	3,531.5	5.8 (0.1–13.1)	5,462,203 <sup>a</sup>
PCMUS	57	7	68.9	1.1 (0.1–4.0)	5,359,978 <sup>a</sup>
SEARCH	1,369	70	4,966.3	3.7 (0.1–4.5)	5,510,831 <sup>a</sup>
STHM1	2,199	71	8,247.2	3.9 (0–4.3)	5,724,947 <sup>a</sup>
TAMPERE	2,463	248	21,037.6	7.8 (0.8–20.9)	6,455,082 <sup>a</sup>
UKGPCS	4,344	826	22,906.2	4.3 (0–27.3)	5,485,041 <sup>a</sup>
UKGPCS1	1,783	457	13,689.0	7.0 (0.1–30.0)	9,536,409 <sup>c</sup>
UKGPCS2	772	189	6,961.8	9.1 (0–24.9)	1,235,003 <sup>d</sup>
ULM	365	32	3,151.9	9.0 (0.6–22.0)	5,457,321 <sup>a</sup>
UTAH	122	27	603.7	4.0 (0.1–26.9)	5,641,408 <sup>a</sup>
<b>BPC3</b>					
ATBC	245	133	1,426.2	5.8 (0–19.9)	8,232,459 <sup>e</sup>
CPSII	636	79	5,859.4	9.2 (0.3–16.3)	7,448,367 <sup>e</sup>
EPIC	431	159	2,197.3	5.2 (0–14.3)	7,612,553 <sup>e</sup>
HPFS	214	37	1,616.6	7.6 (0.1–14.4)	7,539,277 <sup>e</sup>
MEC	244	23	1,868.3	7.7 (0.9–15.4)	7,571,269 <sup>e</sup>
PHS	298	97	2,811.8	9.4 (0–24.7)	7,569,352 <sup>e</sup>
PLCO	714	70	4,664.5	6.7 (0.1–12.9)	7,526,690 <sup>e</sup>
Total	24,023	3,513	182,254.8		
CONOR	1,496	791	8,741.4	5.0 (0.08–20.8)	

<sup>a</sup>Genotyped on a custom Illumina SNP Infinium chip (iCOGS) with 211,155 SNPs, enriched in regions associated with incidence of prostate, breast, and ovarian cancer.

<sup>b</sup>Genotyped on Affymetrix GeneChip 5.0K or 500K.

<sup>c</sup>Genotyped on Illumina Infinium HumanHap 550 Array.

<sup>d</sup>Genotyped on Illumina iSELECT in 43,671 SNPs.

<sup>e</sup>Genotyped on Illumina Human 610 or 610K.

cancer cases of which 791 died due to prostate cancer during follow-up. Genotypes were derived through TaqMan assays and analyzed in a proportional hazards model for case-cohort designs (6) with adjustment for age at diagnosis.

## Results

Among the 24,023 prostate cancer patients included in the discovery stage, we observed 3,513 deaths due to prostate cancer (Table 1). No inflation was observed in the combined meta-analysis ( $\lambda_{1000} = 1.02$ ; ref. 7). Ten SNPs reached genome-wide significance, two common variants (MAF, 7%–8%) and eight rare variants (MAF, 1%–2%; Table 2). Six of these SNPs failed genotyping in the UKGPCS1 sample (either because of unsuccessful assay design, failed clustering, or monomorphism), whereas the remaining four SNPs (rs114997855 on chromosome 2, rs76010824 on chromosome 3, rs140659849 and rs723557 on chromosome X) had an excellent concordance rate (98%–99%) between genotyped and imputed data. These four SNPs were put forward for replication in the Norwegian CONOR cohort. None of the four SNPs showed any evidence of association in the Norwegian cohort ( $P > 0.05$ ), and inclusion of these results in the meta-analysis resulted in non-genome-wide significance levels for each SNP (Table 2).

## Discussion

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%) 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

SNP CHR:BP	Alleles <sup>b</sup> MAF	Practical and BPC3		Conor	All studies <sup>a</sup>
		Total number of PC/deaths	HR (95% CI) P value	HR (95% CI) P value	HR (95% CI) P value
rs190087062	G/A	2,416/704	2.83 (1.99-4.02)		
1:115063785	0.02		6.5E-09		
rs114997855	A/G	20,051/2,729	1.75 (1.44-2.13)	0.88 (0.42-1.85)	1.67 (1.38-2.03)
2:30622824	0.02		2.6E-08	0.73	1.20E-07
rs76010824	A/G	23,251/3,324	1.29 (1.18-1.41)	1.01 (0.76-1.35)	1.26 (1.16-1.38)
3:67442642	0.07		2.8E-08	0.94	1.10E-07
rs184342703	T/C	6,812/832	2.36 (1.73-3.20)		
4:135989066	0.02		4.2E-08		
rs192864713	G/A	1,738/464	3.54 (2.31-5.43)		
5:27429220	0.01		7.3E-09		
rs111414857	G/A	17,146/2,236	1.98 (1.56-2.50)		
7:126639415	0.01		1.7E-08		
rs149470135	A/T	4,725/599	3.09 (2.09-4.59)		
8:86472701	0.01		2.0E-08		
rs117643112	C/A	6,306/1,577	1.93 (1.53-2.43)		
12:81746712	0.02		3.1E-08		
rs140659849 <sup>c</sup>	A/G	2,702/271	3.00 (2.06-4.36)	0.75 (0.24-2.33)	2.61 (1.83-3.73)
X:50194937	0.01		9.6E-09	0.62	1.20E-07
rs723557 <sup>d</sup>	G/T	23,251/3,324	1.17 (1.10-1.24)	1.00 (0.84-1.19)	1.15 (1.09-1.22)
X:126653357	0.08		1.5E-07	0.98	6.10E-07

Abbreviations: BP, base position (Genome build 37); CHR, chromosome; 95% CI, 95% confidence interval.

<sup>a</sup>Meta-analysis between PRACTICAL, BPC3, and CONOR.

<sup>b</sup>Minor allele/major allele. Minor allele used as effect allele (major as reference) in analysis.

<sup>c</sup>Proxy for rs190977150 ( $P = 9.5E-09$  in PRACTICAL and BPC3).

<sup>d</sup>Proxy for rs13440791 ( $P = 2.7E-08$  in PRACTICAL and BPC3).

**Disclosure of Potential Conflicts of Interest**

R.A. Eeles has received speakers bureau honoraria from Succinct Communication. No potential conflicts of interest were disclosed by the other authors.

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