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Established Prostate Cancer Susceptibility Variants are not Associated with Disease Outcome

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Abstract

Recent genome-wide association studies have been successful in identifying common sequence variants associated with prostate cancer risk; however, their importance in prostate cancer prognosis remains unknown. To assess confirmed prostate cancer susceptibility variants with prostate cancer prognosis, we genotyped 16 established susceptibility variants in a Swedish cohort of 2,875 prostate cancer cases, ascertained between 2001 and 2003, with complete follow-up regarding vital status through January 2008. Cox regression models, adjusted for age, clinical stage, pathologic grade, nodal or distant metastases, and diagnostic serum levels of prostate-specific antigen level, were used to assess association between risk variants and prostate cancer–specific survival. During follow-up, 626 men died, and of those, 440 had prostate cancer classified as their underlying cause of death. We found no association between any of the explored sequence variants and prostate cancer–specific mortality, either in exploring individual variants or in assessing the cumulative effect of all variants. We conclude that hitherto established prostate cancer susceptibility variants are not associated with the lethal potential of prostate cancer.

Introduction

Recently, several single nucleotide polymorphisms (SNP) consistently replicated in multiple study populations (1–10) have been implicated in prostate cancer etiology by genome-wide association studies (11–19). In contrast, explorations of these variants with respect to clinicopathologic features of the malignant phenotype have been inconsistent. Genetic variants showed a moderate trend of increasing frequency across increasing degrees of disease aggressiveness in some (1–5, 11, 13, 15) but not in other studies (6, 7, 12, 14). We recently did a systematic evaluation of 15 confirmed risk variants in a cohort of 1,563 cases who underwent radical prostatectomy for the treatment of prostate cancer revealing no association with pathologic stage or grade (20).

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Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

To this end, the importance of these risk variants in prostate cancer prognosis remains unknown. We therefore explored all confirmed prostate cancer risk variants reported to date with respect to cancer-specific mortality in a Swedish population–based case-control study of prostate cancer etiology.

Materials and Methods

Study Cohort

Cancer Prostate in Sweden is a population-based case-control study of prostate cancer etiology. The study design has been described in detail elsewhere (10). Briefly, cases were all men between 35 and 79 years of age with a histologically or cytologically verified adenocarcinoma of the prostate (ICD-10: C61) between 2001 and 2003. Clinical characteristics for all patients were retrieved through linkage to the National Prostate Cancer registry (21). Study participants donated blood on average 4.9 mo (range, 0.7–23.7 mo) after the date of diagnosis and serum was stored at −70°C until analysis. For the present study, DNA samples from blood were available for 2,875 case patients. All participants gave written informed consent and the Research Ethics Committees at Karolinska Institutet and Umeå University approved this investigation.

Follow-up Assessment

With the use of each study participant's unique national registration number, complete follow-up regarding vital status was assessed from date of blood draw up until January 15, 2008 through record linkage to the Swedish Population Registry. Determination of cause of death was obtained through linkage with the Cause of Death Registry up to December 31, 2005. Review of death certificates, done by an oncologist, established cause of death for individuals deceased after December 31, 2005.

SNP Selection and Genotyping

We selected 16 SNPs implicated in four genome-wide association studies and replicated in at least one independent study in the original reports (11–19). They included five SNPs at 8q and 17q (three separate subregions at 8q24, and one region each at 17q12 and 17q24.3) and one SNP each from 2q15, 3p12, 6q25, 7p15, 7q21, 9q33, 10q11, 10q26, 11q13, 19q13, and Xp11. These 16 SNPs were genotyped among all patients using a MassARRAY QGE iPLEX system (Sequenom, Inc.). The average genotype call rate was 98.3% and the average concordance rate among duplicated control samples was 99.8%. Each of the SNPs in the autosomal chromosomes was in Hardy-Weinberg equilibrium ($P \geq 0.05$).

Statistical Methods

To test the association between these 16 risk variants and fatal prostate cancer, we did time-to-event analyses using death from prostate cancer as outcome. Survival time was censored at the time of death for patients dying from causes other than prostate cancer. Association between genotypes and prostate cancer death was assessed in Cox regression models adjusted for age, clinical stage, pathologic grade, nodal or distant metastases, and diagnostic prostate-specific antigen level. For each risk variant, an additive genetic model was assumed. All *P* values reported were based on two-sided hypotheses.

Results

The clinical characteristics of the study population are presented in Table 1. More than 40% of the patients were diagnosed with an advanced cancer (defined by meeting at least one of the following criteria: T_3/T_4, N+, M+, Gleason score of 8 to 10 or prostate-specific antigen level of ≥50 ng/mL). Overall, 626 (21%) of the 2,875 patients died during follow-up, and of

those, 440 (15%) had prostate cancer classified as their underlying cause of death. The average follow-up time among nondeceased patients was 4.9 years (range, 3.7–6.8 years).

No significant association between disease outcome and single risk variants were observed; only one SNP (rs6465657) on chromosome 7q21 showed nominal association with prostate cancer–specific survival with the reported risk allele (C) associated with decreased prostate cancer–specific survival (hazard ratio, 0.87; 95% confidence interval, 0.75–1.00; $P = 0.05$; Table 2). However, this association was not significant after applying a Bonferroni correction to adjust for 16 independent tests ($P = 0.003$ required to reach a 5% study-wide significance level). Exploring genotype-specific association with disease outcome did not reveal any significant association with prostate cancer outcome (data not shown). Only heterozygous carrier of the rs6465657 SNP showed nominal association with prostate cancer–specific survival (hazard ratio, 0.73; 95% confidence interval, 0.58–0.92, $P = 0.007$); however, this finding was not study-wide significant.

Finally, we explored the cumulative effect of these 16 variants on prostate cancer mortality. The average number of risk alleles carried in the study cohort was 13 (note that each subject could carry a maximum of 31 risk alleles). Using this as a reference group, we observed no study-wide significant association with prostate cancer–specific mortality either among men carrying fewer than 13 risk alleles or among men carrying more than 13 risk alleles (Table 3). A trend test for increasing number of risk alleles carried revealed no significant association with prostate cancer mortality (hazard ratio, 0.94; 95% confidence interval, 0.91–0.98; $P = 0.07$).

Discussion

In this prospectively followed cohort of patients with incident prostate cancer, we observed no evidence in support of the hypothesis that prostate cancer risk variants discovered to date from genome-wide association studies are associated with the lethal potential of prostate cancer. Consistent with previous attempts to explore the association between reported prostate cancer susceptibility variants and clinicopathologic features, our findings indicate that these SNPs are only informative for the initiation of prostate cancer, as opposed to the prognosis of this disease.

Considering the adverse effects associated with radical therapy (22), and that most men affected with prostate cancer will die with—rather than from—this disease (23), there is an urgent need for improved tools to distinguish lethal from indolent disease at diagnosis. Identification of genetic markers associated with lethal prostate cancer hold promise to advance the understanding of the biological aspects behind the metastatic potential of prostate cancer.

It is important to note that failure to detect the association between established prostate cancer susceptibility variants and disease outcome does not imply a lack of such genetic variants in the genome. Recent epidemiologic findings support a genetic component in cancer prognosis (24, 25), and it is probable that hitherto performed efforts to discover prostate cancer susceptibility variants—using case-control designs—are suboptimal in identifying genetic variants associated with the prognosis of this disease. Genome-wide efforts exploring disease progression and fatal outcome in cohorts of patients affected by prostate cancer, as compared with prostate cancer case-control studies, should be more efficient to identify genetic markers associated with the prognosis of prostate cancer.

In conclusion, we observed no association between established prostate cancer susceptibility variants and cancer-specific mortality. Future efforts prospectively assessing disease

outcome in prostate cancer cohorts should be more efficient to identify genetic variants associated with the prognosis and cancer-specific mortality of prostate cancer.

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Table 1

Clinical and pathologic characteristics at recruitment of 2,875 men diagnosed with prostate cancer according to survival status during follow-up

Characteristic	Alive (*n* = 2,249)	Deceased from other events (*n* = 186)	Deceased from prostate cancer (*n* = 440)
Age at diagnosis (y)			
≤65	1,246 (55.4)	49 (26.3)	172 (39.1)
>65	1,003 (44.6)	137 (73.7)	268 (60.9)
Clinical stage			
T_1	982 (43.7)	58 (31.2)	42 (9.5)
T_2	760 (33.8)	56 (30.1)	81 (18.4)
T_3	420 (18.7)	64 (34.4)	236 (53.6)
T_4	34 (1.5)	2 (1.1)	67 (15.2)
T_x	53 (2.4)	6 (3.2)	14 (3.2)
Nodal metastases			
N_0/N_x	2,197 (97.7)	180 (96.8)	403 (91.6)
N_1	52 (2.3)	6 (3.2)	37 (8.4)
Distal metastases			
M_0/M_x	2,178 (96.8)	175 (94.1)	249 (56.6)
M_1	71 (3.2)	11 (5.9)	191 (43.4)
Biopsy Gleason sum			
2–6	1,295 (57.6)	88 (47.3)	44 (10.0)
7	657 (29.2)	63 (33.9)	154 (35.0)
8–10	243 (10.8)	35 (18.8)	224 (50.9)
Missing	54 (2.4)	0	18 (4.1)
PSA level (ng/mL)			
<10	1,124 (51.4)	60 (33.3)	40 (9.3)
10–19	514 (23.5)	46 (25.6)	49 (11.4)
20–49	305 (13.9)	36 (20.0)	84 (19.6)
≥50	245 (11.2)	38 (21.1)	255 (59.6)
Primary treatment			
Expectancy	350 (15.6)	41 (22.0)	17 (3.9)
Curative *	1,068 (47.5)	47 (25.3)	28 (6.4)
Palliative	788 (35.0)	98 (52.7)	387 (88.0)
Unspecified	43 (1.9)	0	8 (1.8)

*Among the 1,143 patients treated with curative intent, 537 underwent radical prostatectomy and 585 received radiotherapy.

Table 2

Association between 16 reported prostate cancer susceptibility SNPs with prostate cancer–specific survival

Marker SNP	Chromosome	Position*	Alleles†		Frequency of risk allele	HR (95% CI)	P‡
			Reference	Risk allele			
rs721048	2p15	63043382	G	A	0.20	1.10 (0.93–1.30)	0.25
rs2660753	3p12	87193364	C	T	0.10	1.15 (0.92–1.44)	0.21
rs9364554	6q25	16075365	C	T	0.33	0.97 (0.84–1.12)	0.63
rs10486567	7p15	27943088	T	C	0.78	0.96 (0.82–1.13)	0.64
rs6465657	7q21	97654263	T	C	0.51	0.87 (0.75–1.00)	0.05
rs16901979	8q24 (2)	128194098	C	A	0.06	0.89 (0.67–1.18)	0.41
rs6983267	8q24 (3)	128482487	T	G	0.56	1.04 (0.91–1.19)	0.58
rs1447295	8q24 (1)	128554220	C	A	0.17	0.95 (0.79–1.15)	0.62
rs1571801	9q33	121506927	G	T	0.31	0.88 (0.75–1.03)	0.11
rs10993994	10q11	51219502	C	T	0.43	0.94 (0.82–1.08)	0.39
rs4962416	10q26	126686862	A	G	0.24	0.96 (0.82–1.13)	0.65
rs10896449	11q13	68751243	A	G	0.49	0.99 (0.86–1.13)	0.83
rs4430796	17q12	33172153	C	T	0.61	0.91 (0.79–1.05)	0.20
rs1859962	17q24	66620348	T	G	0.54	1.03 (0.89–1.18)	0.69
rs2735839	19q13	56056435	A	G	0.88	0.94 (0.77–1.15)	0.54
rs5945619	Xp11	51258412	A	G	0.42	0.88 (0.72–1.07)	0.20

NOTE: Association between genotypes and prostate cancer – specific survival was assessed in a Cox regression model assuming an additive genetic effect. In each regression model, covariates representing age, clinical stage, biopsy Gleason sum, diagnostic serum PSA level, and nodal and distal metastases were included.

Abbreviations: HR, hazard ratio; CI, confidence interval; PSA, prostate-specific antigen.

*Based on build 35.

†Risk alleles are based on previously published studies.

‡*P* value from a score test in Cox regression analysis.

Table 3

Cumulative effect of 16 reported prostate cancer susceptibility SNPs on prostate cancer–specific survival

No. of risk alleles	Frequency in all patients	HR (95% CI)	*P*
≤8	0.03	1.43 (0.76–2.68)	0.26
9	0.05	1.78 (1.12–2.83)	0.01
10	0.09	1.25 (0.84–1.85)	0.27
11	0.13	1.53 (1.06–2.21)	0.02
12	0.14	1.23 (0.84–1.78)	0.29
13	0.16	1.00 (Referent)	
14	0.14	1.30 (0.88–1.91)	0.19
15	0.11	0.88 (0.55–1.39)	0.58
16	0.07	1.50 (0.93–2.41)	0.09
17	0.04	0.73 (0.38–1.40)	0.34
≥18	0.04	1.60 (0.93–2.77)	0.09
P trend *	0.07		

NOTE: Association between number of risk alleles carried and prostate cancer – specific survival was assessed in a Cox regression model using carriers of 13 risk variants as reference group. Covariates representing age, clinical stage, biopsy Gleason sum, diagnostic serum PSA level, and nodal and distal metastases were included.

Abbreviations: HR, hazard ratio; CI, confidence interval; PSA, prostate-specific antigen.

* *P* value from a score test of a continuos variable representing number of risk alleles carried in a Cox regression analysis.