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Prostate Cancer (PCa) Risk Variants and Risk of Fatal PCa in the National Cancer Institute Breast and Prostate Cancer Cohort Consortium

Irene M. Shui[a,*], **Sara Lindström**[a], **Adam S. Kibel**[b], **Sonja I. Berndt**[c], **Daniele Campa**[d], **Travis Gerke**[a], **Kathryn L. Penney**[a,e], **Demetrius Albanes**[c], **Christine Berg**[f], **H. Bas Bueno-de-Mesquita**[g,h,bb], **Stephen Chanock**[c,i], **E. David Crawford**[j], **W. Ryan Diver**[k], **Susan M. Gapstur**[k], **J. Michael Gaziano**[a,l,m], **Graham G. Giles**[n,o], **Brian Henderson**[p], **Robert Hoover**[c], **Mattias Johansson**[q,r], **Loic Le Marchand**[s], **Jing Ma**[a,e], **Carmen Navarro**[t,u], **Kim Overvad**[v], **Fredrick R. Schumacher**[p], **Gianluca Severi**[n,w], **Afshan Siddiq**[x], **Meir Stampfer**[a,e], **Victoria L. Stevens**[k], **Ruth C. Travis**[y], **Dimitrios Trichopoulos**[a,z,aa], **Paolo Vineis**[w,bb], **Lorelei A. Mucci**[a], **Meredith Yeager**[c,i], **Edward Giovannucci**[a], and **Peter Kraft**[a]

[a]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA [b]Department of Surgery, Division of Urology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA [c]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA [d]Genomic Epidemiology Group, German Cancer Research Center (Deutsches Krebsforschungszentrum), Heidelberg, Germany [e]Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA [f]Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins Medicine, Baltimore, MD, USA [g]National Institute for Public Health and the Environment, Bilthoven, The Netherlands [h]Department of Gastroenterology and Hepatology, University Medical Centre,

[*]Corresponding author. Harvard School of Public Health, Department of Epidemiology, 677 Huntington Ave, Boston, MA 02115 USA. Tel.: +1 617 432 2916; Fax: +1 617 566 7805. ishui@hsph.harvard.edu (I. Shui).

Author contributions: Irene M. Shui had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Shui, Lindström, Kraft.
Acquisition of data: Shui, Lindström, Giles, Henderson, Le Marchand, Schumacher, Severi, Berndt, Campa, Albanes, Berg, Bueno-de-Mesquita, Chanock, Crawford, Diver, Gapstur, Gaziano, Hoover, Johansson, Ma, Navarro, Overvad, Siddiq, Stampfer, Stevens, Travis, Trichopoulos, Vineis, Yeager, Kraft.
Analysis and interpretation of data: Shui, Lindström, Berndt, Campa, Gerke, Penney, Kibel, Mucci, Giovannucci, Kraft.
Drafting of the manuscript: Shui, Lindström, Berndt, Campa, Gerke, Kibel, Penney, Giovannucci, Kraft.
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Utrecht, The Netherlands [i]Cancer Genomics Research Laboratory, Frederick National Laboratory for Cancer Research, Gaithersburg, MD, USA [j]Urologic Oncology, University of Colorado, Denver, CO, USA [k]Epidemiology Research Program, American Cancer Society, Atlanta, GA, USA [l]Department of Medicine, Harvard Medical School, Boston, MA, USA [m]Division of Aging, Brigham and Women's Hospital, Boston, MA, USA [n]Cancer Epidemiology Centre, Cancer Council Victoria, Melbourne, Australia [o]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Australia [p]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA [q]International Agency for Research on Cancer, Lyon, France [r]Department of Biobank Research, Umeå University, Umeå, Sweden [s]Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI, USA [t]Department of Epidemiology, Murcia Regional Health Authority, Murcia, Spain [u]Department of Health and Social Sciences, Universidad de Murcia, Murcia, Spain [v]Department of Public Health, Aarhus University, Aarhus, Denmark [w]HuGeF Foundation, Torino, Italy [x]Department of Genomics of Common Disease, Imperial College London, London, United Kingdom [y]Cancer Epidemiology Unit, University of Oxford, Oxford, United Kingdom [z]Bureau of Epidemiologic Research, Academy of Athens, Athens, Greece [aa]Hellenic Health Foundation, Athens, Greece [bb]School of Public Health, Imperial College London, London, United Kingdom

Abstract

Background—Screening and diagnosis of prostate cancer (PCa) is hampered by an inability to predict who has the potential to develop fatal disease and who has indolent cancer. Studies have identified multiple genetic risk loci for PCa incidence, but it is unknown whether they could be used as biomarkers for PCa-specific mortality (PCSM).

Objective—To examine the association of 47 established PCa risk single-nucleotide polymorphisms (SNPs) with PCSM.

Design, setting, and participants—We included 10 487 men who had PCa and 11 024 controls, with a median follow-up of 8.3 yr, during which 1053 PCa deaths occurred.

Outcome measurements and statistical analysis—The main outcome was PCSM. The *risk allele* was defined as the allele associated with an increased risk for PCa in the literature. We used Cox proportional hazards regression to calculate the hazard ratios of each SNP with time to progression to PCSM after diagnosis. We also used logistic regression to calculate odds ratios for each risk SNP, comparing fatal PCa cases to controls.

Results and limitations—Among the cases, we found that 8 of the 47 SNPs were significantly associated ($p < 0.05$) with time to PCSM. The risk allele of rs11672691 (intergenic) was associated with an increased risk for PCSM, while 7 SNPs had risk alleles inversely associated (rs13385191 [*C2orf43*], rs17021918 [*PDLIM5*], rs10486567 [*JAZF1*], rs6465657 [*LMTK2*], rs7127900 (intergenic), rs2735839 [*KLK3*], rs10993994 [*MSMB*], rs13385191 [*C2orf43*]). In the case-control analysis, 22 SNPs were associated ($p < 0.05$) with the risk of fatal PCa, but most did not differentiate between fatal and nonfatal PCa. Rs11672691 and rs10993994 were associated with both fatal and nonfatal PCa, while rs6465657, rs7127900, rs2735839, and rs13385191 were associated with nonfatal PCa only.

Conclusions—Eight established risk loci were associated with progression to PCSM after diagnosis. Twenty-two SNPs were associated with fatal PCa incidence, but most did not differentiate between fatal and nonfatal PCa. The relatively small magnitudes of the associations do not translate well into risk prediction, but these findings merit further follow-up, because they may yield important clues about the complex biology of fatal PCa. Patient summary: In this report, we assessed whether established PCa risk variants could predict PCSM. We found eight risk variants associated with PCSM: One predicted an increased risk of PCSM, while seven were associated with decreased risk. Larger studies that focus on fatal PCa are needed to identify more markers that could aid prediction.

Keywords

Prostate cancer; Risk single nucleotide polymorphisms; Prostate cancer mortality; Genetic epidemiology

1. Introduction

Prostate cancer (PCa) is one of the most heritable cancers, yet even though multiple studies have identified genetic markers for PCa incidence [1], few have investigated the association of genetic susceptibility with death from PCa. These data are urgently needed, because a large proportion of men diagnosed with PCa have an indolent form of disease and will die of causes other than PCa [2]. Determining biomarkers, such as single-nucleotide polymorphisms (SNPs), that can predict relevant clinical outcomes in men who have PCa—the most important being PCa-specific mortality (PCSM)—would provide potentially actionable information.

Only four studies have been conducted to date that specifically evaluated the association between established PCa risk loci and PCSM. Penney et al [3] investigated eight risk loci in the 8q24 and 17q regions among 6460 US PCa cases (693 PCa deaths) and found no significant associations. A Swedish study conducted by Wiklund et al [4] of 2875 PCa cases (440 PCa deaths), evaluated 16 risk loci, and found no significant associations. Gallagher et al [5] evaluated 29 risk loci in a study of 798 PCa cases (91 PCa deaths) of men with Ashkenazi Jewish ancestry and found that the risk allele of rs2735839 (*KLK3*) was inversely associated with PCSM. Pomerantz et al [6] assessed 35 risk loci in 3945 US PCa cases (580 PCa deaths). They observed an inverse association between PCSM and the risk allele of rs2735839 and an increased risk of PCSM with the risk allele of rs7676973, which was associated with an increased risk for PCSM. In the current study, we extend this work and assess whether a set of 47 risk variants were associated with the risk of fatal PCa and progression to PCSM in a large PCa cohort consortium.

2. Methods

2.1. Study population

The Breast and Prostate Cancer Cohort Consortium, a collaboration of eight cohort studies from Europe, the United States, and Australia, has been described in detail previously [7]. In each cohort, men who had incident PCa were identified through population-based cancer

registries or self-reports confirmed by medical records, including pathology reports. Data on disease stage and grade at the time of diagnosis were collected from each cohort. Cases were followed for overall mortality and PCSM using a combination of death certificates, medical record review, and population registries. We restricted the current study to men who self-reported as being of European descent.

2.2. Single-nucleotide polymorphism selection and genotyping

We identified 55 confirmed PCa risk loci from the literature for which we had genotyping information. After excluding 8 SNPs in linkage disequilibrium (pairwise $r^2 > 0.2$), 47 SNPs remained (Supplemental Table 1). Each risk SNP had been previously genotyped using the TaqMan assay (Applied Biosystems, Carlsbad, CA, USA) [8]. Blinded, duplicated samples indicated high-quality genotyping (>98.5% concordance). One autosomal SNP (rs1983891) did not meet Hardy-Weinberg equilibrium in the controls ($p < 0.001$).

2.3. Imputation

We imputed missing genotypes by sampling from the observed frequency distribution in men who had nonmissing genotype data in the same age category, stratified by case-control status (*single conditional draw imputation*) [9]. Genotypes from the Finnish site (ATBC) were imputed separately. Subjects from one site (MCCS) were excluded from the imputation because genotyping data for several of the risk SNPs were unavailable, and we also excluded subjects with >20% missing genotypes across the 47 SNPs. On average, <10% of the SNPs were imputed in this subset, and risk allele frequencies before and after imputations were similar; they are displayed in Supplemental Table 2.

2.4. Statistical methods

Fatal PCa was defined as men who had died of PCa. The *risk allele* for each SNP was defined as the allele associated with an increased risk of PCa in the literature. Among cases, we used Cox proportional hazards regression to calculate the per-risk allele hazard ratio (HR) and 95% confidence interval (CI) of each SNP with time to progression to PCSM after diagnosis. In this analysis, person-time to event began at the time of PCa diagnosis and ended at the date of PCSM; otherwise, men were censored if they died from other causes or the end of follow-up. The primary model adjusted for age at diagnosis and cohort, and a secondary model further adjusted for Gleason grade (2–7, 8–10) and clinical stage (A/B, C/D). The proportional hazards assumption was assessed using martingale residuals [10].

We also compared the distribution of the risk alleles in fatal PCa with nonfatal PCa using logistic regression. To determine whether the risk SNPs were associated with the incidence of fatal PCa, we used logistic regression to calculate the per-risk allele odds ratio (OR) and 95% CI for each risk SNP, comparing fatal PCa cases to controls. We then used polytomous logistic regression to assess whether the ORs for fatal PCa compared with controls differed from the ORs for nonfatal PCa compared with controls. For these analyses, we implemented a complete-case analysis to use all available data.

The cumulative association of the 47 PCa risk SNPs with progression to PCSM was assessed in two ways. We created an additive genetic score by summing the number of risk

alleles (0, 1, 2) across the 47 SNPs for each individual. The median number of risk alleles carried was 42 (range: 27–59) in the cases. We calculated the HR for progression to PCSM by quintile of risk score, with the lowest quintile as the reference. To assess the joint multimarker association across the 47 SNPs, we used a kernel machine model with a linear kernel function [11,12]. In contrast to the risk allele score method, the kernel machine method does not require *a priori* assignment of directionality (eg, that SNPs associated with an increased risk of PCa incidence will also be associated with an increased risk of PCSM). Because these analyses could not accommodate missing data, we used the imputed SNP data. We report nominal two-sided *p* values without adjusting for multiple testing. All tests for significance were two-sided, and analyses were conducted in SAS v.9.3 software (SAS Institute, Cary, NC, USA) and R.

3. Results

Characteristics of the study population are described in Table 1. A total of 10 487 cases of PCa and 11 024 controls were included in the analysis. Among cases, the mean age at diagnosis was 68.6 yr of age. The majority of cases were localized stage (A/B) or low grade (2–7). Cases were followed for a median of 8.3 yr after cancer diagnosis; during this time, 1053 men died from PCa.

3.1. Prostate cancer case–only analyses

Eight of the 47 risk loci were significantly ($p < 0.05$) associated with time to PCSM following diagnosis (Table 2; Supplemental Table 3). The risk allele for one SNP (rs11672691; Chr 19 intergenic) was associated with an increased rate of progression to PCSM (HR: 1.18; 95% CI, 1.05–1.34; $p = 0.007$). The other seven significantly associated SNPs (rs13385191, rs17021918, rs10486567, rs6465657, rs7127900, rs2735839, and rs10993994) had risk alleles that were inversely associated with PCSM (HRs ranging from 0.85 to 0.90). Adjusting for Gleason grade and clinical stage at diagnosis did not result in large changes in magnitude for most of the effect estimates, except for rs13385191, which was attenuated towards the null (Supplemental Table 3). Men categorized in the highest quintile of the additive risk score (eg, carrying the greatest number of risk alleles) showed a reduced risk of progression compared with those in the lowest quintile (HR: 0.77; 95% CI, 0.61–0.98), but the overall test for trend ($p = 0.13$) was not significant (Table 3). The global test for a combined effect across all risk loci showed a suggestive association with progression to PCSM ($p = 0.05$). Supplemental Table 4 shows the per-risk allele ORs and 95% CIs for each of the 47 SNPs in fatal compared with nonfatal cancers; the results are similar to those of the survival analysis.

3.2. Comparison of prostate cancer cases and controls

Supplemental Table 5 presents the ORs and 95% CIs for the association of each risk loci with fatal PCa compared with controls and nonfatal PCa compared with controls as well as the *p* value for heterogeneity (*p* contrast) for each of the 47 SNPs. We found that 22 of the risk SNPs were significantly associated with the risk of fatal PCa ($p < 0.05$) and that the magnitude and direction of the majority of the ORs for fatal PCa compared with controls were similar to those of nonfatal PCa compared with controls. Only one SNP (rs11672691)

had a risk allele associated with a significantly larger risk of fatal PCa compared with controls (OR: 1.26; 95% CI, 1.11–1.43; $p = 0.0005$) than nonfatal PCa compared with controls (OR: 1.10; 95% CI, 1.05–1.16; $p = 0.0003$), with a p value for the contrast test <0.05. This was the same SNP whose risk allele was associated with an increased risk for progression to PCSM. When we compared the ORs for the other seven SNPs whose risk alleles were associated with a decreased risk of progression, we found that six of them (rs13385191, rs17021918, rs10486567, rs6465657, rs7127900, and rs2735839) were associated with nonfatal PCa only compared with controls (Table 4). Rs10993994 was significantly associated with fatal PCa compared with controls (OR: 1.11; 95% CI, 1.01–1.22; $p = 0.03$), but the association with nonfatal PCa compared with controls was stronger (OR: 1.24; 95% CI, 1.19–1.29; $p < 0.0001$; p contrast = 0.02).

4. Discussion

Few prior genetic risk studies have examined the most relevant end point of fatal PCa. With >10 000 men and 1053 PCa deaths, our study is the largest and most comprehensive to date to assess whether 47 established PCa risk variants are associated with PCSM. In our survival analysis, we found that eight SNPs predicted time to PCSM following diagnosis. We observed one SNP (rs11672691) whose risk allele was associated with both worse progression to PCSM following diagnosis and an increased risk of fatal PCa compared with controls. This SNP was also recently confirmed to be associated with aggressive PCa in a meta-analysis of several large genome-wide association studies (GWASs) [13]. Rs11672691 lies in the intergenic region on chromosome 19 between the genes *ATP5SL* and *CEACAM21* and within LOC100505495, a hypothetical locus for a noncoding RNA [13]. The *ATP5SL* gene has been associated with height [14], but its function is unknown. *CECAM21* belongs to the immunoglobulin superfamily of genes; genes in this family may have a role in cell adhesion and metastasis [15]. Additional examination of this region may yield further insight into the mechanisms behind PCa progression.

Interestingly, in our survival analysis, the risk alleles of seven SNPs were associated with a decreased risk of progression to PCSM following diagnosis. When we further investigated the association of these SNPs in cases and controls, we found that for the majority of these SNPs, this relationship was driven by the SNPs being associated with nonfatal PCa only. A potential explanation is that these SNPs could be markers of a factor that leads to earlier diagnosis or diagnosis of indolent disease. For example, the risk allele (G) of rs2735839 was inversely associated with time to PCSM, not associated with fatal PCa incidence compared with controls, and strongly associated with nonfatal PCa. The inverse association with time to PCSM has been observed in some [5,6] but not all other studies [4,16]. The G allele of rs2735839 has been associated with a decreased risk of high–Gleason grade cancers [17,18]. Rs2735839 is on chromosome 19 downstream from the *KLK3* gene. *KLK3* encodes prostate-specific antigen (PSA), and rs2735839-G has been associated with increased PSA levels in some studies [19–21]. One hypothesis is that the protective effect of the risk allele (G) is mediated by a lead-time or ascertainment bias because of PSA screening. In a screened population, men carrying the risk allele who have higher PSA levels could have an increased biopsy rate, leading to more and earlier cancer diagnoses, while those without the risk allele would be less likely to be diagnosed with indolent cancer because of their lower PSA levels

not reaching the threshold for biopsy. However, other studies have not seen an association with rs2735839 and PSA [6] or have found an association with the SNP and PCa risk even in cohorts whose cases were primarily not identified through PSA screening [17,20], consistent with a mechanism that is independent of PSA screening ascertainment bias.

Rs10993994 is located upstream from the gene *MSMB* on chromosome 10, which encodes a protein that is secreted by epithelial cells in the prostate. The risk allele of rs10993994 has been associated with higher PSA levels [4,19]. Thus, it is possible that PSA detection bias could also mediate some of the association with PCa. Independent of its influence on PSA, rs10993994 has been associated with RNA expression of the *MSMB* and *NCOA4* genes, which may mediate prostate carcinogenesis through transforming prostate cells to become anchorage independent [22]. We found that rs10993994 was associated with fatal PCa compared with controls, but the association was stronger for nonfatal PCa. Also, the risk allele was more common in nonfatal PCa compared with fatal PCa and was associated with a decreased rate of progression to PCSM. Ahn et al [23] also observed that the risk allele was associated with an increased risk for metastatic PCa compared with controls but was not associated with time to recurrence in PCa cases following diagnosis. A study comparing aggressive and nonaggressive cases of PCa found the risk allele to be more frequent in men who had less aggressive disease [18]. Three case-only studies did not find an association with rs10993994 and time to PCSM [4–6].

Rs10486567, which lies in an intron of the *JAZF1* gene on chromosome 7, had the strongest association with time to PCSM (HR: 0.85; 95% CI, 0.76–0.94; $p = 0.001$). The risk allele of this SNP was also associated with a significantly decreased risk of biochemical recurrence and clinical metastases as well as a nonsignificantly decreased risk of PCSM in one study [5]. However, two other case-only studies found no association with PCSM [4,6]. The biological function of this SNP is unclear and merits further investigation.

The other nominally significant SNPs that were associated with time to PCSM following diagnosis were rs13385191, rs17021918, rs6465657, and rs7127900. Both rs17021918 (intronic in *PDLIM5;* Chr 4) and rs7127900 (intergenic; Chr 11) were assessed in the Pomerantz et al study [6], and there was no significant association for either SNP with PCSM; these SNPs were not assessed in other studies [4,5]. The Swedish case-only study [4] also observed a nominally significant inverse association with the risk allele of rs6465657 (intronic in *LMTK2;* Chr 7) and PCSM, but another United States–based study did not find an association [6]. To our knowledge, Rs13385191 (intronic in *C2orf43;* Chr 2) has not been investigated for an association with PCSM in other studies.

The development of prognostic tools to determine progression to PCSM is a much-needed and active area of research. A few promising models exist [24,25] that incorporate factors such as stage, Gleason grade, and PSA, but they are in need of external validation. Our study sample was limited because we did not have consistent access to more granular information on stage, grade, and PSA at diagnosis as well as other clinicopathologic information (eg, tumor volume) and treatment information that would be useful for testing prediction. Even so, we did not observe a change in C-statistic when we compared a Cox proportional hazards model predicting time to PCSM that included age at diagnosis, Gleason grade, and

stage (c = 0.777) against a model with those variables and the additional eight SNPs that were predictive of time to PCSM (c = 0.781), indicating that the modest associations of this subset of risk SNPs do not translate well into clinical prediction.

Finally, our case-control results showed that most of the 47 established risk alleles were associated with both fatal and nonfatal PCa in a similar manner; 22 of the 47 SNPs were significantly associated with fatal PCa, but the majority of the SNPs did not differentiate between fatal and nonfatal disease. It is likely that many of these SNPs are necessary for the initiation of cancer, and other markers or exposures determine progression. The one exception was rs11672691, which was more strongly associated with fatal disease and also predicted PCSM following diagnosis.

An important point is that this study focused on known risk variants of PCa incidence and was also limited to the 47 SNPs for which we had genotyping data. Thus, it was not designed to identify novel variants. GWASs specifically designed to assess PCSM are needed to identify further genetic markers that could improve predictive ability, although to date, few studies have been large enough to do so [26]. New risk loci continue to be confirmed that were not included in our study. For example, the most recently published study has identified 23 novel PCa risk loci, including 16 that were associated with aggressive disease; however, these SNPs did not differentiate between aggressive and nonaggressive PCa when compared with controls [1].

Most genetic studies have relied on Gleason grade as a surrogate of PCa aggressiveness, but not all high–Gleason grade cancers will progress to PCSM. In addition, although Gleason grade is strongly associated with progression, the positive predictive value of Gleason score is relatively low (<30% for Gleason ≥7) [27,28], making it a suboptimal proxy. A major strength of our study was that we were able to follow men over time and accrue >1000 deaths from PCa. Still, with longer follow-up, it is possible that some of the nonfatal cases will progress to PCSM; thus, there may be some misclassification of our end point that would reduce our power to detect effects, especially when comparing fatal and nonfatal cases. Likewise, misclassification of PCSM resulting from the use of death registries as primary sources for this information may exist. Several of the contributing sites had dedicated end points committees to determine PCSM based on the death registries combined with information from medical records as well as physician and kin reporting to reduce this misclassification. Despite our relatively large sample size, it is possible that our findings could be the result of chance, but our finding that 8 of the 47 SNPs were associated with time to PCSM was more than the 2.4 loci that would be expected by chance (p = 0.002). Moreover, we observed a borderline significant (p = 0.05) global association across all of the risk loci with time to PCSM, supporting idea that our findings were not the result of chance.

5. Conclusions

Although dozens of common germline genetic risk variants are clearly associated with overall PCa risk, a key question with high clinical utility is whether these markers can improve the prognostication of PCSM following diagnosis. We identified eight SNPs that

were associated with time to PCSM, including rs11672691, whose risk allele was predictive of increased progression to PCSM and increased risk of fatal PCa. The associations observed were of fairly small magnitude and thus do not translate well into improved risk prediction, but these findings merit further follow-up to investigate the biological mechanisms behind the associations. Future GWASs focused on fatal PCa are needed to identify novel markers that can differentiate disease aggressiveness and therefore be integrated into clinical practice and help clarify the biology behind PCa progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Take-home message

Although several germline genetic risk variants have been established for prostate cancer (PCa) incidence, a key question is whether they are also related to survival. We assessed 47 PCa risk loci and found a subset that was related to PCa mortality.

Table 1

Study population characteristics

	ATBC	CPS-II	EPIC	HPFS	MCCS	MEC	PHS	PLCO	All cohorts combined
Cases, no.	1036	2284	1573	1287	1031	665	1381	1230	10 487
%	10	22	15	12	10	6	13	12	
Age at diagnosis, yr									
Mean (SD)	69.6 (5.7)	70.1 (5.7)	65.4 (6.3)	69.6 (7.5)	67.6 (6.9)	69.0 (7.5)	70.3 (7.6)	66.9 (5.5)	68.6 (6.8)
Grade, %									
2–7	64	72	46	76	83	65	83	90	72
8–10	19	14	5	9	14	31	14	10	13
Missing	17	14	49	15	3	4	3	0	15
Stage, %									
A or B	55	79	52	74	88	85	42	80	68
C or D	25	18	16	11	9	13	17	20	16
Missing	20	3	32	15	3	2	41	0	15
Year of diagnosis, %									
≤1992	9	1	0	0	5	0	37	0	6
1993–1997	37	33	11	34	24	30	27	35	29
1998–2002	50	51	59	55	30	46	31	60	49
2003–2007	4	15	30	11	40	24	6	6	16
Deaths									
Total deaths, no.	749	479	393	351	228	154	460	225	3039
Total deaths, %	72	21	25	27	22	23	33	18	29
PCa deaths, no.	289	126	213	82	75	28	176	64	1053
PCa deaths, %	28	6	14	6	7	4	13	5	10
Controls, no.	952	2303	1845	1349	1397	743	1382	1053	11 024
%	9	21	17	12	13	7	13	10	
Age at selection, yr									
Mean (SD)	69.0 (5.7)	70.2 (5.7)	65.4 (6.3)	67.6 (7.6)	54.4 (8.8)	70.4 (7.3)	70.2 (7.6)	69.0 (5.7)	66.8 (8.5)

SD = standard deviation; PCa = prostate cancer.

*Percentages may not add up to 100% due to rounding.

Table 2

Per-allele hazard ratios for risk single-nucleotide polymorphisms and time to prostate cancer–specific mortality*

SNP	Gene	Location	Chr	Risk allele	Reference allele	HR (95% CI)	*p* value
rs13385191	*C2orf43*	Intronic	2	G	A	0.88 (0.78–1.00)	0.05
rs17021918	*PDLIM5*	Intronic	4	C	T	0.89 (0.81–0.97)	0.01
rs10486567	*JAZF1*	Intronic	7	G	A	0.85 (0.76–0.94)	0.001
rs6465657	*LMTK2*	Intronic	7	C	T	0.90 (0.82–0.98)	0.02
rs10993994	*MSMB*	Upstream	10	T	C	0.90 (0.83–0.98)	0.02
rs7127900	–	Intergenic	11	A	G	0.86 (0.77–0.97)	0.01
rs11672691	*N/A*	Intergenic	19	G	A	1.18 (1.05–1.34)	0.007
rs2735839	*KLK3*	Downstream	19	G	A	0.82 (0.73–0.93)	0.002

SNP = single-nucleotide polymorphism; Chr = chromosome; HR = hazard ratio; CI = confidence interval; PCa = prostate cancer.

*10 487 men with PCa (1053 PCa-specific deaths); model adjusted for age and cohort.

Only findings with a *p* value <0.05 are presented in this table; for complete results, see Supplemental Table 3.

Table 3

Association of single-nucleotide polymorphism score* (quintiles) with time to prostate cancer–specific mortality

	Model 1^			Model 2^		
	HR	**95% CI**	***p* trend**	**HR**	**95% CI**	***p* trend**
Quintile 1	1.00	Reference		1.00	Reference	
Quintile 2	0.97	(0.76–1.23)		0.91	(0.72–1.16)	
Quintile 3	0.93	(0.74–1.18)	0.13	0.95	(0.75–1.20)	0.3
Quintile 4	1.03	(0.83–1.27)		1.00	(0.81–1.24)	
Quintile 5	0.77	(0.61–0.98)		0.82	(0.65–1.04)	

HR = hazard ratio; CI = confidence interval.

* The score equals the sum of the number of risk alleles over 47 risk SNPs.

^ Model 1 was adjusted for age and cohort; model 2 was additionally adjusted for Gleason grade and clinical stage.

Table 4

Per-risk allele odds ratio for each risk single-nucleotide polymorphism and fatal prostate cancer (PCa) versus controls and nonfatal PCa versus controls*

							Fatal		Nonfatal		
SNP	**Gene**	**Location**	**Chr**	**Position**	**Risk allele**	**Reference allele**	**OR (95% CI)**	**p value**	**OR (95% CI)**	***p* value**	***p* contrast**
rs17021918	*PDLIM5*	Intronic	4	95781900	C	T	0.97 (0.88–1.07)	0.55	1.09 (1.05–1.14)	<0.0001	**0.02**
rs10486567	*JAZF1*	Intronic	7	27943088	G	A	1.04 (0.94–1.16)	0.46	1.22 (1.16–1.28)	<0.0001	**0.004**
rs6465657	*LMTK2*	Intronic	7	97654263	C	T	0.98 (0.90–1.08)	0.73	1.11 (1.07–1.16)	<0.0001	**0.009**
rs10993994	*MSMB*	Upstream	10	51219502	T	C	1.11 (1.01–1.22)	0.03	1.24 (1.19–1.29)	<0.0001	**0.02**
rs7127900	–	Intergenic	11	2190150	A	G	1.01 (0.89–1.13)	0.92	1.16 (1.10–1.22)	<0.0001	**0.02**
rs11672691	*N/A*	Intergenic	19	46677771	G	A	1.26 (1.11–1.43)	0.0005	1.10 (1.05–1.16)	0.0003	**0.05**
rs2735839	*KLK3*	Downstream	19	56056435	G	A	0.96 (0.84–1.09)	0.50	1.19 (1.12–1.26)	<0.0001	**0.001**

SNP = single-nucleotide polymorphism; Chr = chromosome; OR = odds ratio; CI = confidence interval.

*1053 fatal cases, 9434 nonfatal cases, 11 024 controls; model adjusted for age and study cohort. Only results with a *p* contrast <0.05 are shown; see Supplemental Table 5 for complete results.