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Imaging, Diagnosis, Prognosis

Clinical Cancer Research

Susceptibility Loci Associated with Prostate Cancer Progression and Mortality

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Abstract

Purpose: Prostate cancer is a heterogenous disease with a variable natural history that is not accurately predicted by currently used prognostic tools.

Experimental Design: We genotyped 798 prostate cancer cases of Ashkenazi Jewish ancestry treated for localized prostate cancer between June 1988 and December 2007. Blood samples were prospectively collected and de-identified before being genotyped and matched to clinical data. The survival analysis was adjusted for Gleason score and prostate-specific antigen. We investigated associations between 29 single nucleotide polymorphisms (SNP) and biochemical recurrence, castration-resistant metastasis, and prostate cancer–specific survival. Subsequently, we did an independent analysis using a high-resolution panel of 13 SNPs.

Results: On univariate analysis, two SNPs were associated ($P < 0.05$) with biochemical recurrence, three SNPs were associated with clinical metastases, and one SNP was associated with prostate cancer–specific mortality. Applying a Bonferroni correction ($P < 0.0017$), one association with biochemical recurrence ($P = 0.0007$) was significant. Three SNPs showed associations on multivariable analysis, although not after correcting for multiple testing. The secondary analysis identified an additional association with prostate cancer–specific mortality in *KLK3* ($P < 0.0005$ by both univariate and multivariable analysis).

Conclusions: We identified associations between prostate cancer susceptibility SNPs and clinical end points. The rs61752561 in *KLK3* and rs2735839 in the *KLK2-KLK3* intergenic region were strongly associated with prostate cancer–specific survival, and rs10486567 in the *7JAZF1* gene were associated with biochemical recurrence. A larger study will be required to independently validate these findings and determine the role of these SNPs in prognostic models. *Clin Cancer Res; 16(10); 2819–32. ©2010 AACR.*

Prostate cancer is a heterogenous disease with a variable natural history, and thus, the optimal therapeutic approach may vary. Widespread use of prostate-specific antigen (PSA) testing has resulted in an increased rate of diagnosis of prostate cancer, so that a man's risk over a lifetime now approaches 16%, whereas the lifetime risk of dying of the disease remains close to 3% to 4% (1). PSA is a powerful prognostic biomarker (2, 3), but its limited predictive value is well documented. Germ line genetic variation has the potential to identify predisposition to aggressive disease and to provide insight into biological pathways of initiation and progression of prostate cancer.

A variety of prediction tools are used in clinical practice to define the presentation of prostate cancer and tailor the treatment strategy. Nomograms incorporating PSA have been developed to predict the risk of prostate cancer at the time of biopsy, biochemical recurrence after radical prostatectomy, and after radiation therapy, metastatic progression, and overall survival (4). Despite reasonable discriminatory power and promising external validation studies, even the best clinical nomograms are limited in their prognostic capabilities. The widespread use of clinical multivariable prediction tools, and studies suggesting their superiority over clinical experience, supports their utility (5), however, they have not been prospectively studied and may be improved by the incorporation of other factors including genetic markers.

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Nomograms incorporating clinical variables are commonly used to guide the management of early stage prostate cancer, but their prognostic capability is limited. Prostate cancer–specific mortality is the most robust prostate cancer end point but is particularly difficult to predict using clinical variables alone, and novel biomarkers are urgently needed. Common variants in germ line DNA have been associated with increased prostate cancer risk but efforts to identify germ line predictors of outcome have been disappointing. We investigated germ line predictors of progression through the prostate cancer clinical states model in a homogenous group of patients with early stage prostate cancer, and report associations between susceptibility single nucleotide polymorphisms and certain clinical outcomes.

A number of genetic variants have been associated with risk for prostate cancer, most notably, *BRCA2* mutations and single nucleotide polymorphisms (SNP) at 8q24 and at least 20 additional SNPs at 10 different chromosomal loci (6–17). This genetic variation may produce clinically useful biomarkers and reveal unappreciated disease biology. *BRCA2* mutations have been associated with prostate cancer aggressiveness in a number of small studies (18–20), but few of the susceptibility loci discovered by genome scans have been associated with clinical outcome (21–23). In the current study, we investigated an association between 29 SNPs that have been associated with risk of prostate cancer, correlating these SNPs with clinical outcomes of 798 men with prostate cancer.

Materials and Methods

Blood samples were collected from 798 men treated for localized prostate cancer at Memorial Sloan-Kettering Cancer Center between June 1988 and December 2007. All cases identified themselves as being of Ashkenazi Jewish ancestry. Their medical records were collected as part of an institutional prostate cancer research database using standardized questionnaires and chart abstraction forms, created and maintained by the prostate cancer disease management team at Memorial Sloan-Kettering Cancer Center. Analysis for this study was based on data on clinical stage, Gleason score (from needle biopsy), PSA levels, and age at diagnosis of the primary prostate cancer as well as dates of biochemical recurrence, development of castration-resistant metastasis, death due to prostate cancer, and overall survival. All patient records were reviewed by one physician to confirm the clinical end points being tested. Biochemical recurrence refers to the detection of increasing PSA after local therapy, and was defined as a single measure of PSA ≥ 0.2 ng/mL after radical prostatectomy, and a value of "nadir +2" after other therapy (Table 1; refs. 24, 25). Castration-resistant metastases refers to time of progression of disease following initiation of antiandrogen therapy. Cause of death was determined from review of the death certificate and the medical record. In accordance with an Institutional Research Board–approved protocol, patient identifiers were removed at the time of genetic analysis.

All blood samples were genotyped for 29 prostate cancer risk SNPs using a Mass ARRAY QGE iPLEX system (Sequenom, Inc.; Fig. 1). The selected SNPs were previously associated with prostate cancer diagnosis in published genome-wide association studies or were SNPs of particular interest to our group. The primers were ordered from Sequenom, Inc. Overall genotyping rate for the 29 SNPs was 96% and each of the SNPs was in Hardy-Weinberg equilibrium. The minor allele frequency ranged from 3% to 48%. We did a second, independent analysis at RSKC at the Wallenberg Research Laboratories, University Hospital in Malmö, Sweden, using a high-resolution SNP panel with primers ordered from Sequenom and genotyped individuals from the original cohort with sufficient DNA remaining (672 of 798 patients; 84%) for 13 SNPs using a new aliquot of DNA for each case. Two of these 13 SNPs were included in the analysis of 29 SNPs, and therefore serve as quality control of the genotyping. These 13 SNPs are located in regions encoding four secretory products of the prostate: *KLK2*, *KLK3*, *KLK4*, and *MSMB* (26).

Table 1. Patient characteristics

Characteristic	Median (interquartile range) or frequency (%)
Age at diagnosis (y)	68 (62-73)
Pretreatment PSA (ng/mL)	7.70 (4.85-15.6)
Clinical stage	
T_1	307 (38%)
T_2	243 (30%)
T_3/T_4	119 (15%)
Unknown	129 (16%)
Biopsy Gleason grade	
≤6	296 (37%)
7	302 (38%)
≥8	177 (22%)
Unknown	23 (3%)
Type of treatment	
Radical prostatectomy	241 (30%)
Radiotherapy alone	271 (34%)
Radiotherapy + hormones	216 (27%)
Hormones alone	35 (4%)
Watchful waiting	34 (4%)
Chemotherapy alone	1 (0.1%)
Year of diagnosis	
1987-1990	28 (4%)
1991-1995	222 (28%)
1996-2000	261 (33%)
2001-2006	287 (36%)

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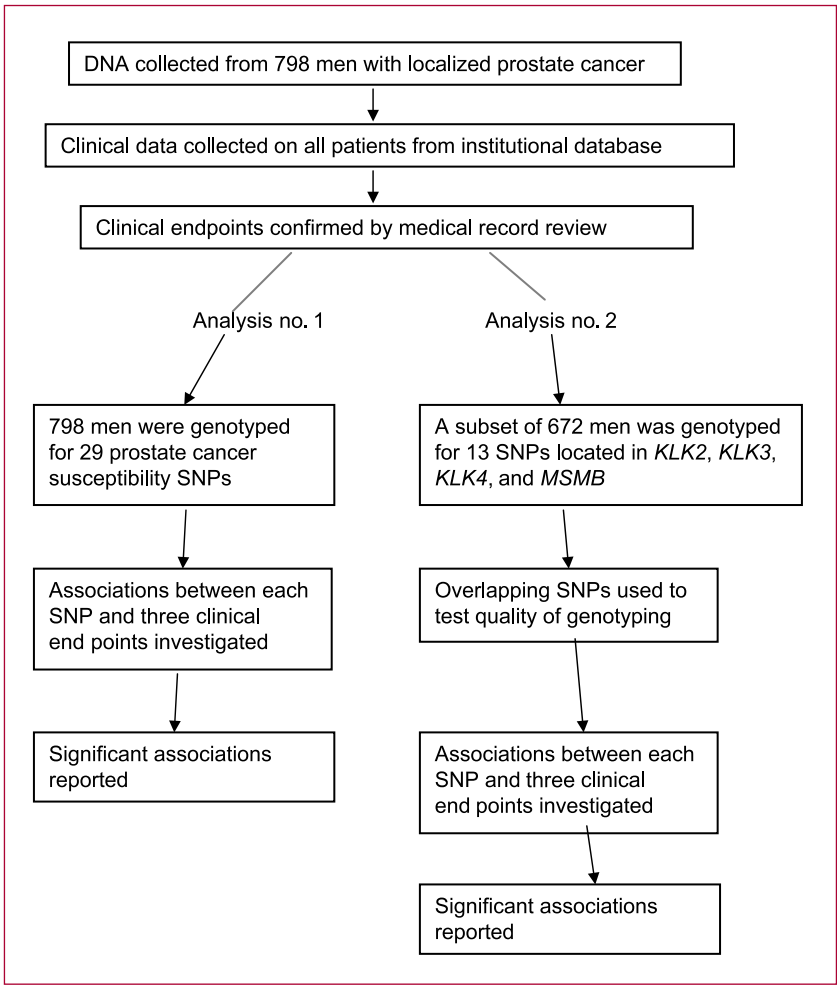

Fig. 1. Study schema.

Univariate Cox proportional hazards regression was used to investigate the association between each SNP and biochemical recurrence, castration-resistant metastases, and prostate cancer–specific mortality. Each SNP was analyzed under a codominant model, with the association determined from a global test for differences in outcome between the three genotypes (common homozygote, heterozygote, and rare homozygote), commonly referred to as a "2 *df* test." For illustrative purposes, we have also shown results from analyses in which each SNP was analyzed under a log-additive (linear trend) model. The probability of freedom from the various events was estimated using Kaplan-Meier methods. Time at risk was calculated from the date of diagnosis to the date of event or date of last contact, and patients without the event were censored at their last follow-up date. For SNPs significant at $P < 0.05$ under the codominant model, multivariable analyses were conducted controlling for PSA (entered as a log-transformed continuous variable), clinical stage (categorized as T_1, T_2, and $T_{3/4}$), and biopsy Gleason score (categorized as ≤6, 7, and ≥7). Because patients received different forms of treatment which could possibly affect the results, we did additional analyses according to primary treatment received (surgery or radiation therapy). Collection of blood samples for genetic testing began in 2000, and therefore, some cases diagnosed before 2000, and who died before 2000 (or who did not participate in blood sampling), were not included in this cohort. This scenario is referred to statistically as "left truncation", and as a sensitivity analysis, we repeated all analyses by calculating time at risk from date of blood draw for genetic testing. Because it was possible for patients to die from other causes, we repeated all analyses using a methodology which considers death from other causes as a competing risk (27). *P* values were not corrected for multiple testing, as it was the intent of these results to be hypothesis generating. To address issues of multiple testing, by examining 29 SNPs and applying a Bonferroni correction, statistical significance was defined as $P < 0.0017$. However, because the intent of this study was to be hypothesis generating, we also report all associations of potential interest for future validation. All statistical analyses were conducted using Stata 10.0 (StataCorp LP).

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Table 2. Univariate associations between SNPs and prostate cancer outcomes under a codominant model

SNP	Chromosomal region	No. of patients	MAF	Published allele frequency	Genotype (% of patients)	Biochemical recurrence			Clinical metastases			Prostate cancer–specific death		
						n = 351			*n* = 146			*n* = 91		
						HR	95% CI	*P**	HR	95% CI	*P**	HR	95% CI	*P**
rs10090154	8q24	759	0.08	NR	C/C (85)	Reference			Reference			Reference		
					C/T (14)	0.97	0.71-1.32		0.75	0.45-1.25		0.86	0.47-1.58	
					T/T (1)	0.6	0.08-4.26	0.9	†	†	0.5	†	†	0.9
					Per allele	0.95	0.71-1.27	0.7	0.72	0.44-1.19	0.2	0.83	0.46-1.51	0.5
rs1016343	8q24	749	0.23	NR	C/C (60)	Reference			Reference			Reference		
					T/C (36)	0.96	0.76-1.21		1.01	0.71-1.45		0.88	0.55-1.40	
					T/T (5)	1.18	0.72-1.94	0.7	1	0.44-2.29	1	1.58	0.68-3.68	0.4
					Per allele	1.01	0.84-1.22	0.9	1.01	0.75-1.35	1	1.05	0.73-1.51	0.8
rs10486567	7	762	0.25	0.2	G/G (51)	Reference			Reference			Reference		
					A/G (42)	1.37	1.09-1.72		1.36	0.95-1.95		1.06	0.67-1.66	
					A/A (8)	1.89	1.31-2.74	0.0007	2.11	1.26-3.55	0.014	1.56	0.80-3.04	0.4
					Per allele	1.37	1.17-1.62	<0.0005	1.43	1.12-1.83	0.005	1.18	0.86-1.62	0.3
rs13254738	8	761	0.45	0.33	A/A (29)	Reference			Reference			Reference		
					C/A (52)	0.97	0.75-1.24		0.78	0.54-1.14		1.06	0.64-1.73	
					C/C (19)	0.89	0.64-1.22	0.7	0.75	0.45-1.24	0.4	0.94	0.48-1.83	0.9
					Per allele	0.94	0.81-1.10	0.5	0.85	0.66-1.09	0.2	0.98	0.71-1.35	0.9
rs16901979	8q24	792	0.04	0.07	C/C (93)	Reference			Reference			Reference		
					C/A (7)	1.14	0.77-1.69		1.6	0.95-2.69		1.06	0.51-2.18	
					A/A (0.1)	5.08	0.71-36.30	0.2	†	†	0.2	†	†	1
					Per allele	1.2	0.83-1.76	0.3	1.48	0.89-2.44	0.13	1.01	0.50-2.07	1
rs1859962	17q24	765	0.44	0.49	G/G (33)	Reference			Reference			Reference		
					G/T (47)	1.07	0.84-1.36		1.15	0.79-1.68		1.06	0.66-1.69	
					T/T (20)	0.95	0.70-1.30	0.7	1.03	0.63-1.70	0.7	0.84	0.44-1.62	0.8
					Per allele	0.99	0.85-1.15	0.9	1.04	0.82-1.31	0.8	0.94	0.70-1.28	0.7
rs2659056	19	731	0.27	0.25	A/A (55)	Reference			Reference			Reference		
					A/G (37)	0.97	0.77-1.23		0.98	0.68-1.41		1.05	0.67-1.66	
					G/G (8)	0.95	0.61-1.46	1	0.91	0.45-1.81	1	1.03	0.44-2.43	1
					Per allele	0.97	0.82-1.16	0.8	0.97	0.73-1.27	0.8	1.03	0.74-1.45	0.8
rs2660753	3p12	755	0.24	0.13	C/C (57)	Reference			Reference			Reference		
					T/C (36)	0.98	0.78-1.23		0.75	0.52-1.07		0.73	0.46-1.16	
					T/T (6)	0.88	0.56-1.38	0.8	0.59	0.27-1.28	0.16	0.81	0.35-1.90	0.4
					Per allele	0.96	0.80-1.14	0.6	0.76	0.57-1.01	0.055	0.82	0.57-1.16	0.3

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Table 2. Univariate associations between SNPs and prostate cancer outcomes under a codominant model (Cont'd)

SNP	Chromosomal region	No. of patients	MAF	Published allele frequency	Genotype (% of patients)	Biochemical recurrence			Clinical metastases			Prostate cancer–specific death		
						n = 351			*n* = 146			*n* = 91		
						HR	95% CI	*P**	HR	95% CI	*P**	HR	95% CI	*P**
rs266849	19	764	0.24	0.19	A/A (59)	Reference			Reference			Reference		
					A/G (34)	1.09	0.87-1.37		1.31	0.93-1.86		1.34	0.86-2.09	
					G/G (7)	0.88	0.56-1.40	0.6	1.14	0.57-2.27	0.3	1.8	0.85-3.83	0.2
					Per allele	1.01	0.85-1.20	0.9	1.17	0.90-1.52	0.2	1.34	0.97-1.85	0.075
rs4242382	8q24	759	0.8	0.14	G/G (85)	Reference			Reference			Reference		
					A/G (14)	1.05	0.78-1.41		0.77	0.47-1.27		1	0.57-1.78	
					A/A (1)	1.13	0.36-3.52	0.9	†	†	0.6	†	†	1
					Per allele	1.05	0.80-1.37	0.7	0.71	0.44-1.14	0.16	0.91	0.53-1.57	0.7
rs4430796	17q12	751	0.47	0.56	G/G (29)	Reference			Reference			Reference		
					A/G (49)	0.82	0.64-1.05		0.88	0.60-1.29		1.22	0.73-2.03	
					A/A (22)	0.87	0.64-1.18	0.3	0.87	0.54-1.40	0.8	1.28	0.70-2.33	0.7
					Per allele	0.92	0.79-1.07	0.3	0.93	0.73-1.17	0.5	1.13	0.85-1.52	0.4
rs4962416	10q26	756	0.33	0.28	T/T (46)	Reference			Reference			Reference		
					T/C (42)	0.94	0.75-1.18		0.71	0.50-1.01		0.8	0.51-1.26	
					C/C (12)	0.74	0.51-1.08	0.3	0.47	0.23-0.93	0.031	0.64	0.29-1.42	0.4
					Per allele	0.89	0.76-1.04	0.15	0.69	0.53-0.91	0.008	0.8	0.58-1.11	0.19
rs5945572	Xp11	766	0.3	0.35	G/G (71)	Reference			Reference			Reference		
					A/G (0.3)	1.23	0.17-8.80		†	†		†	†	
					A/A (29)	0.89	0.69-1.13	0.6	1.42	1.00-2.03	0.15	1.17	0.73-1.85	0.8
					Per allele	0.94	0.83-1.06	0.3	1.19	1.00-1.42	0.051	1.08	0.86-1.36	0.5
rs721048	2p15	772	0.15	0.19	G/G (71)	Reference			Reference				Reference	
					A/G (26)	1.12	0.88-1.42		1.02	0.70-1.49		1.07	0.67-1.73	
					A/A (3)	1.31	0.73-2.33	0.5	0.99	0.37-2.71	1	2.28	0.91-5.72	0.2
					Per allele	1.13	0.93-1.37	0.2	1.01	0.74-1.39	0.9	1.26	0.86-1.83	0.2
rs7501939	17q12	759	0.41	0.62	C/C (35)	Reference			Reference			Reference		
					C/T (48)	0.94	0.74-1.19		1.12	0.77-1.63		0.87	0.55-1.38	
					T/T (17)	0.97	0.71-1.32	0.9	1.14	0.68-1.90	0.8	0.84	0.43-1.63	0.8
					Per allele	0.98	0.84-1.14	0.8	1.08	0.84-1.38	0.5	0.91	0.66-1.24	0.5
rs7920517	10	758	0.43	0.53	G/G (34)	Reference			Reference			Reference		
					A/G (47)	1.26	0.98-1.61		0.94	0.64-1.38		0.92	0.57-1.48	
					A/A (19)	1.42	1.05-1.92	0.056	1.01	0.64-1.61	0.9	0.83	0.45-1.53	0.8
					Per allele	1.2	1.03-1.39	0.017	1	0.79-1.26	1	0.91	0.68-1.23	0.5

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Table 2. Univariate associations between SNPs and prostate cancer outcomes under a codominant model (Cont'd)

SNP	Chromosomal region	No. of patients	MAF	Published allele frequency	Genotype (% of patients)	Biochemical recurrence			Clinical metastases			Prostate cancer–specific death		
						n = 351			*n* = 146			*n* = 91		
						HR	95% CI	*P**	HR	95% CI	*P**	HR	95% CI	*P**
rs7931342	11q13	760	0.29	0.44	G/G (51)	Reference			Reference			Reference		
					G/T (39)	0.96	0.76-1.20		1.55	1.09-2.20		1.41	0.91-2.20	
					T/T (9)	0.95	0.65-1.40	0.9	1.3	0.71-2.37	0.053	1.06	0.47-2.37	0.3
					Per allele	0.97	0.82-1.14	0.7	1.26	0.99-1.61	0.06	1.16	0.85-1.59	0.3
rs902774	12	749	0.14	0.15	G/G (74)	Reference			Reference			Reference		
					A/G (24)	1.05	0.82-1.35		0.84	0.56-1.25		1.01	0.62-1.63	
					A/A (2)	1.09	0.51-2.31	0.9	0.62	0.15-2.50	0.6	1.02	0.25-4.19	1
					Per allele	1.05	0.85-1.30	0.7	0.82	0.58-1.18	0.3	1.01	0.67-1.53	1
rs9364554	6p25	767	0.21	0.32	C/C (62)	Reference			Reference			Reference		
					T/C (34)	1.06	0.84-1.32		1.11	0.78-1.58		1.32	0.85-2.05	
					T/T (4)	0.74	0.39-1.40	0.6	0.73	0.23-2.30	0.7	0.87	0.21-3.57	0.4
					Per allele	0.98	0.81-1.19	0.9	1.03	0.76-1.39	0.9	1.18	0.82-1.72	0.4
rs10896449	11q13	778	0.3	0.45	G/G (50)	Reference			Reference			Reference		
					G/A (40)	0.96	0.76-1.20		1.52	1.07-2.15		1.43	0.93-2.22	
					A/A (10)	0.89	0.61-1.29	0.8	1.33	0.76-2.34	0.062	1.22	0.59-2.52	0.3
					Per allele	0.95	0.81-1.11	0.5	1.26	0.99-1.59	0.058	1.2	0.89-1.62	0.2
rs109939944	10q11	772	0.47	0.44	T/T (29)	Reference			Reference			Reference		
					T/C (48)	1.07	0.82-1.38		1.11	0.75-1.66		1.03	0.64-1.67	
					C/C (23)	1.34	1.00-1.78	0.11	0.93	0.58-1.48	0.7	0.78	0.43-1.41	0.6
					Per allele	1.16	1.00-1.34	0.052	0.97	0.77-1.21	0.8	0.89	0.68-1.19	0.4
rs1447295	8q24	764	0.08	0.16	C/C (86)	Reference			Reference			Reference		
					C/A (13)	0.99	0.72-1.35		0.82	0.50-1.35		0.95	0.53-1.71	
					A/A (1)	1.07	0.27-4.29	1	†	†	0.7	†	†	1
					Per allele	0.99	0.74-1.32	1	0.78	0.48-1.25	0.3	0.9	0.51-1.59	0.7
rs2735839	19q13	774	0.17	0.13	G/G (70)	Reference			Reference			Reference		
					G/A (26)	1	0.79-1.28		1.39	0.97-1.98		1.96	1.28-3.02	
					A/A (4)	0.76	0.40-1.43	0.7	1.11	0.45-2.75	0.2	1.83	0.66-5.07	0.007
					Per allele	0.95	0.78-1.16	0.6	1.24	0.93-1.64	0.14	1.65	1.18-2.30	0.003
rs4242384	8q24	768	0.08	NR	A/A (86)	Reference			Reference			Reference		
					C/A (14)	1.03	0.76-1.39		0.78	0.47-1.27		0.98	0.55-1.74	
					C/C (1)	0.61	0.09-4.33	0.9	†	†	0.6	†	†	1
					Per allele	1	0.75-1.33	1	0.75	0.46-1.22	0.2	0.94	0.54-1.66	0.8

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Table 2. Univariate associations between SNPs and prostate cancer outcomes under a codominant model (Cont'd)

SNP	Chromosomal region	No. of patients	MAF	Published allele frequency	Genotype (% of patients)	Biochemical recurrence			Clinical metastases			Prostate cancer–specific death		
						n = 351			*n* = 146			*n* = 91		
						HR	95% CI	*P**	HR	95% CI	*P**	HR	95% CI	*P**
rs6465657	7q21	766	0.44	0.49	T/T (33)	Reference			Reference			Reference		
					T/C (47)	1.11	0.87-1.42		1.12	0.75-1.67		0.87	0.53-1.43	
					C/C (20)	0.99	0.73-1.35	0.6	1.82	1.17-2.84	0.017	1.61	0.94-2.75	0.052
					Per allele	1.01	0.87-1.17	0.9	1.35	1.07-1.70	0.011	1.26	0.94-1.68	0.12
rs6983267	8q24	773	0.45	0.56	G/G (32)	Reference			Reference			Reference		
					G/T (47)	1.16	0.90-1.48		1.03	0.71-1.51		1.59	0.95-2.64	
					T/T (21)	1.16	0.86-1.57	0.5	1.11	0.70-1.77	0.9	1.66	0.91-3.03	0.15
					Per allele	1.08	0.94-1.25	0.3	1.05	0.84-1.32	0.7	1.29	0.97-1.72	0.077
rs6983561	8q24	769	0.04	NR	A/A (92)	Reference			Reference			Reference		
					C/A (7)	1.16	0.78-1.72		1.62	0.96-2.74		1.07	0.52-2.22	
					C/C (0.1)	5.21	0.73-37.28	0.2	†	†	0.19	†	†	1
					Per allele	1.23	0.84-1.79	0.3	1.5	0.91-2.49	0.11	1.03	0.50-2.10	0.9
rs7000448	8q24	772	0.48	NR	T/T (29)	Reference			Reference			Reference		
					T/C (47)	0.94	0.73-1.20		1.1	0.74-1.65		1.15	0.68-1.93	
					C/C (24)	0.95	0.71-1.27	0.9	1.53	0.99-2.39	0.13	1.78	1.02-3.09	0.087
					Per allele	0.97	0.84-1.13	0.7	1.24	0.99-1.56	0.063	1.34	1.01-1.79	0.042
rs7008482	8q24	742	0.36	NR	T/T (43)	Reference			Reference			Reference		
					G/T (43)	0.78	0.62-0.98		0.96	0.67-1.37		1.15	0.73-1.79	
					G/G (14)	0.68	0.48-0.98	0.036	0.65	0.36-1.19	0.4	0.79	0.38-1.64	0.6
					Per allele	0.81	0.69-0.95	0.012	0.86	0.67-1.10	0.2	0.96	0.71-1.31	0.8
rs11670728	19	506	0.26	0.36	G (56)	Reference			Reference			Reference		
					GA (36)	1.1	0.83-1.47		0.73	0.46-1.16		0.67	0.38-1.21	
					A (8)	1.25	0.77-2.04	0.6	0.42	0.15-1.15	0.13	0.98	0.41-2.34	0.4
					Per allele	1.11	0.90-1.37	0.3	0.69	0.48-0.99	0.042	0.86	0.57-1.29	0.5
1541int	19	499	0.05	NR	G (91)	Reference			Reference			Reference		
					GT (9)	0.69	0.40-1.19		1.31	0.63-2.72		1.21	0.48-3.05	
					T (0.4)	21.26	5.02-90.04	<0.0005	17.35	4.11-73.26	<0.0005	0	†	0.9
					Per allele	0.89	0.55-1.44	0.6	1.87	1.04-3.38	0.037	1.12	0.46-2.70	0.8
rs1654553	19	494	0.45	0.49	G (32)	Reference			Reference			Reference		
					GA (46)	1.13	0.83-1.54		1.25	0.76-2.06		1.19	0.65-2.19	
					A (22)	1.01	0.68-1.49	0.7	1.15	0.62-2.14	0.7	1.1	0.51-2.35	0.9
					Per allele	1.02	0.84-1.23	0.9	1.09	0.81-1.46	0.6	1.06	0.74-1.53	0.8

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Table 2. Univariate associations between SNPs and prostate cancer outcomes under a codominant model (Cont'd)

SNP	Chromosomal region	No. of patients	MAF	Published allele frequency	Genotype (% of patients)	Biochemical recurrence			Clinical metastases			Prostate cancer–specific death		
						n = 351			*n* = 146			*n* = 91		
						HR	95% CI	*P**	HR	95% CI	*P**	HR	95% CI	*P**
rs17526278	19	509	0.1	0.1	G (83)	Reference			Reference			Reference		
					AG (15)	1.34	0.93-1.91		1.56	0.89-2.73		1.31	0.64-2.67	
					A (2)	1.05	0.39-2.82	0.3	3.16	0.76-13.15	0.1	3.19	0.43-23.70	0.4
					Per allele	1.21	0.90-1.61	0.2	1.63	1.03-2.59	0.039	1.42	0.77-2.64	0.3
rs198972	19	495	0.37	0.3	C (42)	Reference			Reference			Reference		
					CT (43)	1.15	0.86-1.53		0.93	0.59-1.49		0.94	0.55-1.62	
					T (15)	0.74	0.47-1.15	0.14	1.07	0.58-1.98	0.9	0.56	0.21-1.46	0.5
					Per allele	0.93	0.77-1.12	0.4	1.01	0.75-1.37	0.9	0.81	0.55-1.20	0.3
rs198977	19	500	0.25	0.26	C (57)	Reference			Reference			Reference		
					CT (37)	1.07	0.81-1.42		1.08	0.69-1.69		0.7	0.39-1.24	
					T (6)	0.71	0.35-1.46	0.5	1.42	0.56-3.57	0.7	1.15	0.35-3.74	0.4
					Per allele	0.97	0.77-1.22	0.8	1.13	0.79-1.62	0.5	0.83	0.52-1.33	0.4
rs198978	19	496	0.35	0.34	G (44)	Reference			Reference			Reference		
					GT (43)	1.05	0.79-1.40		1.12	0.71-1.78		0.87	0.50-1.51	
					T (13)	0.86	0.55-1.34	0.7	0.92	0.45-1.86	0.8	0.51	0.18-1.45	0.4
					Per allele	0.96	0.79-1.17	0.7	1	0.74-1.37	1	0.77	0.51-1.17	0.2
rs2271094	19	455	0.38	0.43	A (40)	Reference			Reference			Reference		
					GA (45)	0.89	0.65-1.21		0.78	0.48-1.27		0.95	0.52-1.74	
					G (15)	1.06	0.69-1.62	0.6	0.7	0.32-1.51	0.5	1.05	0.44-2.49	1
					Per allele	0.99	0.81-1.22	1	0.82	0.58-1.16	0.3	1.01	0.67-1.52	1
rs3760728	19	505	0.25	0.42	C (56)	Reference			Reference			Reference		
					GC (36)	1.14	0.86-1.52		0.79	0.50-1.23		0.73	0.41-1.29	
					G (7)	1.4	0.86-2.28	0.3	0.44	0.16-1.21	0.2	1.03	0.43-2.46	0.5
					Per allele	1.17	0.95-1.44	0.15	0.73	0.51-1.03	0.075	0.89	0.59-1.35	0.6
rs6998	19	488	0.22	0.29	G (63)	Reference			Reference			Reference		
					GA (31)	1.13	0.84-1.52		0.64	0.39-1.02		0.62	0.34-1.13	
					A (6)	1.01	0.57-1.79	0.7	0.35	0.11-1.12	0.051	0.77	0.27-2.15	0.3
					Per allele	1.06	0.85-1.32	0.6	0.62	0.42-0.91	0.014	0.74	0.48-1.16	0.2
rs61752561	19	440	0.03	0.04	G (95)	Reference			Reference			Reference		
					GA (4)	0.71	0.32-1.61		1.85	0.75-4.60		4.49	2.00-10.07	
					A (1)	0.77	0.11-5.52	0.7	5.79	1.41-23.79	0.025	6.49	1.56-27.05	<0.0005
					Per allele	0.77	0.40-1.47	0.4	2.16	1.20-3.90	0.011	3.1	1.84-5.20	<0.0005

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Table 2. Univariate associations between SNPs and prostate cancer outcomes under a codominant model (Cont'd)

SNP	Chromosomal region	No. of patients	MAF	Published allele frequency	Genotype (% of patients)	Biochemical recurrence			Clinical metastases			Prostate cancer–specific death		
						n = 351			*n* = 146			*n* = 91		
						HR	95% CI	*P**	HR	95% CI	*P**	HR	95% CI	*P**
rs10993994swe	19	505	0.48	0.44	T (30)	Reference			Reference			Reference		
					TC (45)	1.1	0.79-1.52		1.16	0.70-1.91		0.97	0.54-1.77	
					C (25)	1.21	0.84-1.74	0.6	0.81	0.44-1.48	0.4	0.62	0.29-1.32	0.4
					Per allele	1.1	0.92-1.32	0.3	0.91	0.69-1.21	0.5	0.81	0.57-1.15	0.2
rs2735839swe	19	490	0.19	0.13	G (68)	Reference			Reference			Reference		
					GA (27)	1.09	0.81-1.48		1.78	1.13-2.82		2.11	1.21-3.67	
					A (5)	0.93	0.47-1.82	0.8	2.21	0.94-5.22	0.02	3.1	1.19-8.09	0.008
					Per allele	1.03	0.81-1.30	0.8	1.61	1.15-2.24	0.005	1.88	1.27-2.79	0.002

NOTE: Values in boldface represent SNPs with associations at $P < 0.05$ by the 2 *df* test.

Abbreviations: SNP, single nucleotide polymorphism; MAF, minor allele frequency; swe, genotyping from second analysis done in Malmö, Sweden; NR, not reported.

*The first *P* value shown for each SNP was determined by a 2 *df* test for a global difference across genotypes; the second *P* value shown was determined by a log-additive (linear trend) model.

†HRs were not estimated due to the low number of events and the low number of patients with genotype frequency.

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Results

Seven hundred and ninety-eight patients were genotyped. Patient characteristics are given in Table 1, and treatment at presentation was based on patient and physician preference. The majority of patients (92%) were treated with curative intent: 241 (30%) had radical prostatectomy and 487 (61%) had radiotherapy with or without androgen deprivation therapy. Most patients (75%) had biopsy Gleason score ≤7, and 46% of patients with available clinical staging information had T_1 disease. At last follow-up, 176 patients had died, with 91 having died from prostate cancer. The median follow-up for survivors was 7.6 years. Biochemical recurrence was documented in 351 patients, and castration-resistant metastasis was found in 146 patients.

Univariate associations between the 29 SNPs and prostate cancer outcomes are summarized in Table 2. In the first analysis, 2 of 29 SNPs were associated with biochemical recurrence with $P < 0.05$ (rs10486567 and rs7008482). Three SNPs were associated with castration-resistant metastases with $P < 0.05$ (rs4962416, rs10486567, and rs6465657). One SNP was associated with prostate cancer–specific mortality with $P < 0.05$ (rs2735839). For illustrative purposes, the probability of freedom from biochemical recurrence stratified by rs10486567 is given in Fig. 2, and the probability of freedom from prostate cancer–specific mortality stratified by rs2735839 is given in Fig. 3. Of note, only one of these associations (between rs10486567 and biochemical recurrence) would have been significant had a formal Bonferroni correction for multiple testing been applied. There was little overlap between the SNPs associated with each outcome. For example, although rs2735839 was associated with prostate cancer–specific mortality ($P = 0.0017$), there was no significant association with biochemical recurrence ($P = 0.7$) or castrate-resistant metastasis ($P = 0.2$). Hazard ratios (HR) were similar when subgroups defined by primary treatment received were analyzed, and we therefore saw no evidence that treatment affected the results from the cohort when analyzed overall, e.g., rs10486567 and biochemical recurrence: HR for common heterozygote versus common homozygote, 1.79 [95% confidence interval (CI), 1.05-3.06] for the surgery group and HR = 1.90 (95% CI, 1.12-3.20) for the radiation therapy group. Associations between the 29 SNPs and PSA, biopsy Gleason score, and clinical stage are given in the Supplementary Table.

On multivariable analysis, biopsy Gleason score was significantly associated with all three outcomes (all $P < 0.003$), whereas PSA was not significantly associated with any of the three outcomes (all $P > 0.3$) and clinical stage was significantly associated with biochemical recurrence ($P = 0.01$), but not clinical metastases ($P = 0.146$) or prostate cancer–specific death ($P = 0.7$). In relation to patients with biopsy Gleason score ≤ 6, the HR for prostate cancer–specific death for a Gleason score of 7 was 2.4 (95% CI, 1.2-4.7); and for Gleason score of ≥ 8, HR was 3.6 (95% CI, 1.8-7.4). For the SNPs associated with the various outcomes at $P < 0.05$, we did multivariable analyses controlling for age, PSA, clinical stage, and biopsy Gleason score separately for each SNP (Table 3). Trends for association were observed for three SNPs: between rs10486567 and biochemical recurrence ($P = 0.037$) and clinical metastases ($P = 0.013$), between rs6465657 and clinical metastases ($P = 0.050$), and between rs2735839 and prostate cancer–specific death ($P = 0.002$).

Sensitivity analyses were conducted to verify that our results were not affected by left truncation or the competing risk of death from other causes. None of the results from the sensitivity analyses would have led to different conclusions as obtained from the main analyses (data not shown). For example, in both sensitivity analyses, we found rs10486567 to be associated with biochemical recurrence (left truncation analysis, HR = 1.3 for heterozygotes and 1.9 for rare homozygotes versus common homozygotes; $P = 0.001$; competing risk analysis, HR = 1.4 for heterozygotes and 1.9 for rare homozygotes versus common homozygotes; $P = 0.0004$) whereas rs2735839 was found to be associated with prostate cancer–specific survival (left truncation analysis, HR = 2.0 for heterozygotes and 1.6 for rare homozygotes versus common homozygotes; $P = 0.009$; competing risk analysis, HR = 2.0 for heterozygotes and 1.5 for rare homozygotes versus common homozygotes; $P = 0.008$).

The results of the secondary independent analysis were concordant with the primary genotyping study for the two overlapping SNPs. We confirmed the association with rs2735839. Additionally, we identified associations between rs61752561, an Asp-Asn SNP in *KLK3* (28), and prostate cancer–specific mortality on both univariate (HR, 4.82 for having any rare allele versus common homozygote; 95% CI, 2.33-9.98; $P < 0.0005$) and multivariable analyses (HR, 5.1; 95% CI, 2.7-11.8; $P < 0.0005$), and between 1541int and biochemical recurrence ($P < 0.0005$) and castration-resistant metastasis ($P < 0.0005$).

Conclusions

We identified associations between known susceptibility loci for prostate cancer and biochemical recurrence, castration-resistant progression of disease, and prostate cancer–specific death. Five of the 29 SNPs examined in the initial analysis showed evidence of an association with biochemical recurrence, clinical metastases, or prostate cancer–specific death, and three additional associations were identified in the high-resolution SNP panel. Due to the small size of this study, we did not formerly correct for multiple testing and our results are therefore intended to be hypothesis-generating; however, even after accounting for multiple testing in the primary analysis, one of the SNPs, rs10486567 located in the *7JAZF1* gene, was significantly associated with biochemical recurrence.

Prostate cancer incidence continues to increase, but the death rate remains close to 3% to 4% (1), suggesting that indolent disease is being increasingly diagnosed and treated. Biomarkers that compliment the clinical

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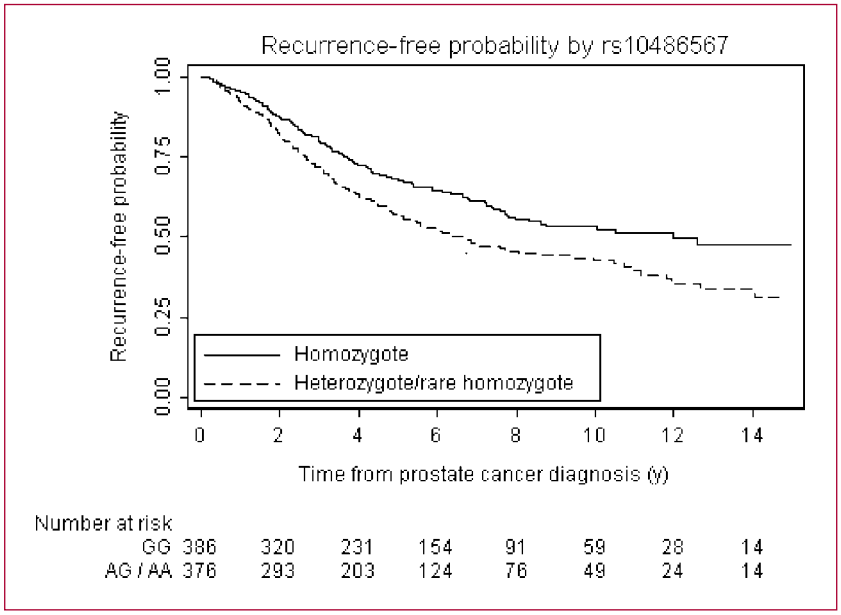

Fig. 2. Kaplan-Meier probability of freedom from biochemical recurrence common for individuals who are homozygote versus heterozygote or rare homozygote at rs10486567.

indicators currently available, and reliably predict aggressive disease are urgently needed. If they are associated with grade of disease, it is possible that susceptibility loci may also correlate with disease prognosis. Such seems to be the case for *BRCA* mutations, which are associated with increased risk for a higher grade of prostate cancer and independently with worse clinical outcome (17, 19).

Germ line variation has been associated with risk of prostate cancer and it has recently been appreciated that germ line variation might also be used to predict outcome after diagnosis. Initial studies investigating prognostic end points were disappointing, and efforts to associate susceptible loci with Gleason score and survival were unsuccessful (16, 21–23). However, others identified associations between rs2735839 in *KLK3* ($P = 8.4 \times 10^{-7}$), rs10993994 in *MSMB* ($P = 0.046$; ref. 29), rs2710646 at 2p15, and rs4054823 at 17p12, and more aggressive prostate cancer defined by histologic grade and clinical stage (7, 30). One study reported an association between rs7920517 and rs10993994 and PSA recurrence after prostatectomy (31). The current report is thus among the first to characterize susceptibility loci identified by genome-wide scans as potential prognostic indicators, and specifically to investigate clinically meaningful end points such as castration-resistant metastases and prostate cancer–specific mortality.

No biomarker has yet been identified that adds a clinically significant increment to the prognostic power of currently used clinical indicators, such as PSA, clinical stage, and Gleason score. Levels of serum markers such as human kallikrein–related peptidase 2 and soluble urokinase plasminogen activator receptor have been associated with clinical outcome (32, 33), and seem to improve the predictive accuracy of preoperative nomograms for biochemical recurrence (34, 35), but there is no evidence that any analyte improves significantly on the deficiencies of PSA testing. The somatic rearrangement *TMPRSS2-ERG* gene fusion that is identified in ~50% of PSA-screened primary prostate cancers and was initially associated with tumor progression has subsequently been associated with both favorable and worse outcome associations (36–38). The clinical utility of this marker is therefore currently uncertain. The inverse relationship between circulating tumor cell number and outcome (39), in addition to the potential of circulating tumor cells to provide somatic DNA for analysis (40), supports their candidacy as a potential biomarker. Prospective tests of circulating tumor cells are still pending. Germ line genetic variation provides attractive biomarker candidates which can be identified at the time of blood draw, do not change over time (i.e., are constitutional), and when using a dominant model or recessive model, are dichotomous (i.e., do not require adjustment or normalization).

The strongest association with a genetic variant identified here involved rs10486567 which is located in the *7JAZF1* gene. In both the univariate and the multivariable analyses, this SNP predicted early biochemical recurrence for heterozygotes or rare homozygotes. This association remained significant after Bonferroni correction. Thomas et al. identified no association between this SNP and prostate cancer risk in their first genome-wide scan ($P = 0.04$), but reported a protective effect in a second larger analysis [OR of heterozygotes versus controls for nonaggressive disease 0.74 (0.66-0.83); OR of heterozygotes versus controls for aggressive disease 0.89 (0.80-0.98)], and the signal seemed to be more strongly associated with aggressive disease, defined as Gleason score > 7 or disease stage III/IV (12). A common translocation identified in endometrial stromal tumors brings together the *JAZF1* and *JJAZ1* genes (41); expression of the protein product protects cells from apoptosis caused by hypoxia. *JAZF1* seems to act as a transcriptional repressor of NR2C2, a nuclear

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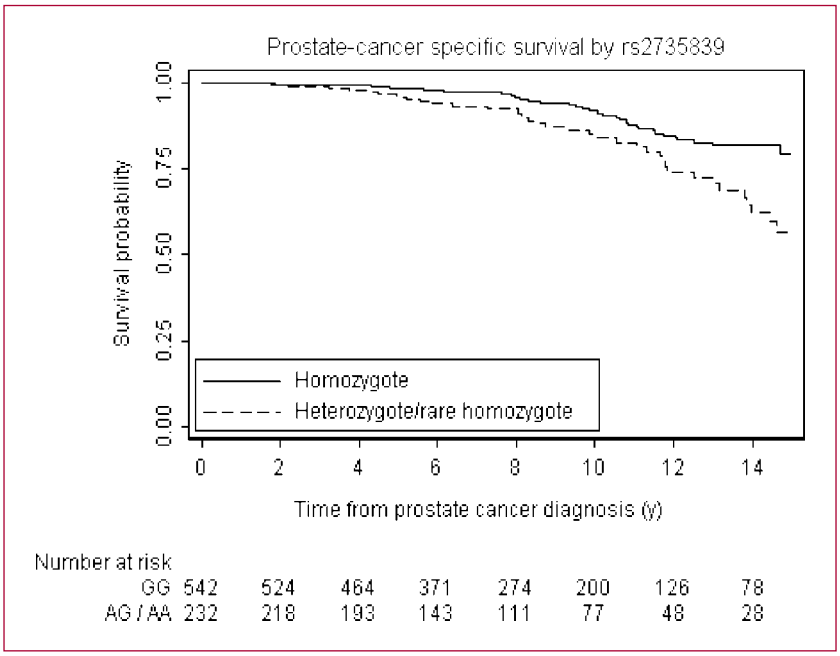

Fig. 3. Kaplan-Meier probability of freedom from prostate cancer–specific death for individuals who are homozygote versus heterozygote or rare homozygote at rs2735839.

orphan receptor that is highly expressed in prostate tissue and that reportedly interacts with the androgen receptor (12). This gene has not been functionally implicated in prostate cancer to date, and although the possibility of a false-negative association exists, this result highlights the potential for germ line association studies to identify molecular pathways that may be important in disease development.

We identified an association between rs2735839, located in the *KLK2-KLK3* intergenic region, and prostate cancer–specific mortality in both univariate ($P = 0.007$), and multivariable analyses (0.002). This SNP has been associated with prostate cancer predisposition, but again with a protective effect for the heterozygous and rare homozygous alleles (per allele odds ratio = 0.83; $P = 2 \times 10^{18}$; ref. 8). The protective allele has also been associated with poorly differentiated, high-stage prostate cancer. However, it has been reported that this association is confounded by a PSA bias (8, 21, 42). Individuals with the susceptibility allele might be biopsied earlier due to increased PSA levels but have lower Gleason scores. Individuals with this PSA-associated allele may therefore have an increased risk of being diagnosed because they have a higher PSA, and the SNP may not be etiologically involved in prostate cancer development. However, an association between a single

Table 3. Multivariable analysis for SNPs and prostate cancer outcomes

SNP	No. of patients	Biochemical recurrence			Clinical metastases			Prostate cancer–specific death		
		n = 351			*n* = 146			*n* = 91		
		HR	95% CI*	*P*	HR	95% CI	*P*	HR	95% CI	*P*
rs10486567	635	1.29	1.00-1.65	0.046	1.42	0.96-2.10	0.083	1.1	0.66-1.82	0.7
rs4962416	628	1.08	0.84-1.39	0.5	0.87	0.58-1.29	0.5	0.85	0.50-1.45	0.6
rs7920517	631	1.53	1.17-2.01	0.002	1.11	0.73-1.68	0.6	1.06	0.61-1.84	0.8
rs7931342	632	1.03	0.80-1.32	0.8	2.01	1.35-3.00	0.0006	1.81	1.07-3.05	0.027
rs10896449	649	1.01	0.79-1.28	1	1.88	1.28-2.77	0.001	1.83	1.10-3.04	0.021
rs2735839	643	0.88	0.67-1.17	0.4	1.26	0.84-1.87	0.3	2.22	1.35-3.66	0.002
rs7008482	617	0.85	0.66-1.09	0.19	0.87	0.59-1.28	0.5	1	0.60-1.65	1

NOTE: Each SNP is individually assessed in separate multivariable models, controlling for age at prostate cancer diagnosis, PSA at diagnosis, clinical stage, and biopsy Gleason grade. Shown are SNPs with univariate associations at $P < 0.05$ by the 2 *df* test.
*The first *P* value shown for each SNP was determined by a 2 *df* test for a global difference across genotypes; the second *P* value shown was determined by a log-additive (linear trend) model.

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PSA test and subsequent prostate cancer progression has been repeatedly reported, supporting an etiologic role for this locus (3, 43–45), and the relationship between this SNP and PSA values at later stages of disease would be worthy of investigation. Furthermore, the association with prostate cancer–specific death remained ($P = 0.002$) in a multivariable model that included PSA and stage (46). Finally, the strong association of an additional polymorphism in Asp-Asn *KLK3* (rs61752561), which is in linkage disequilibrium with rs2735839 (26) with prostate cancer–specific mortality in our second analysis, strengthens the hypothesis that this locus is important in influencing outcome.

The association between rs2735839 and rs61752561 and prostate cancer–specific mortality may be explained by an interaction between *KLK* genes and the androgen receptor. Androgen deprivation therapy is the mainstay of treatment for recurrent prostate cancer; however, response duration is limited and prostate cancer evolves to regain the ability to grow despite low levels of circulating androgens (47). Upon the development of hormone-refractory progression of disease, most tumors maintain dependence on the androgen receptor despite low levels of circulating androgens, and novel therapeutic strategies targeting androgen receptor signaling in this setting have recently been developed. Functional data suggesting that a polymorphism in the androgen response element, located in the promoter of *KLK3* gene, confers greater androgen responsiveness and a greater affinity for the androgen receptor provides an example of how mutations in *KLK* genes might correlate with the development of hormone-refractory disease (46).

We recently reported that *BRCA* mutation was associated with worse outcome in Ashkenazi men with prostate cancer by predicting earlier biochemical recurrence, hormone-refractory progression of disease, and death due to prostate cancer (48). The different associations between clinical end points and SNPs in this study may be related to their differential function. For example, different loci may contribute to different stages of disease progression. Rs7008482 was associated with biochemical recurrence in the univariate analysis but not in the multivariable analysis that included PSA. Although an increase in PSA in both hormone-sensitive and castration-resistant prostate cancer predicts overall survival (49), this study was limited to PSA determination at the time of diagnosis, and PSA at a later time point might more accurately predict survival. Furthermore, our choice of definition for biochemical recurrence may also have obscured the associations with this end point (24). Patients in this study received different primary therapies for their prostate cancer, and consequently, different definitions were used for biochemical recurrence. As a result, biochemical recurrence might be the least robust of the clinical end points used.

The results reported here are limited by the small number of patients in genetically defined subsets; larger studies are required to verify these findings. Population heterogeneity may induce false-positive findings in genomic association studies; the limitation of the current analysis to those of Ashkenazi heritage was intended to address this potential concern. It is also possible that the associations reported are unique to the genetic isolate we have investigated; however, "founder" alleles for cancer risk have, thus far, been representative of genetic variants in the general population. Although the major finding of an association of rs10486567 and biochemical recurrence survives Bonferroni correction, the significance of the point estimates of the other associations is limited by small sample size and multiple comparisons. For these reasons, the current findings are hypothesis-generating and require prospective validation. Investigation of SNP associations in a large cohort in which clinical data is prospectively collected is needed. If confirmed, these and other findings which emerge could be incorporated into existing nomograms to allow more accurate risk predications than those based on PSA and common clinical markers. Investigation of the genetic candidates implicated by reported SNP associations with clinical outcome may also improve our understanding of the pathways of progression of prostate cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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