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Prostate Cancer Predisposition Loci and Risk of Metastatic Disease and Prostate Cancer Recurrence

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Abstract

Background—Genome-wide association studies (GWAS) have identified multiple novel prostate cancer predisposition loci. Whether these common genetic variants are associated with incident metastatic prostate cancer or with recurrence after surgical treatment for clinically localized prostate cancer is uncertain.

Methods—Twelve SNPs were selected for study in relation to prostate metastatic cancer and recurrence, based on their genome-wide association with prostate cancer in the Cancer Genetic Markers of Susceptibility (CGEMS) (1,2). To assess risk for metastatic disease, we compared genotypes for the 12 SNPs by logistic regression of 470 incident metastatic prostate cancer cases and 1945 controls in 3 case-control studies. To assess the relationship of these SNPs to risk for prostate cancer recurrence, we used Cox regression in a cohort of 1412 men treated for localized prostate cancer, including 328 recurrences, and used logistic regression in a case-case study, comparing 450 recurrent versus 450 nonrecurrent prostate cancer cases. Study-specific RRs for risk of metastatic disease and recurrence were summarized using meta-analysis, with inverse variance weights.

Results—*MSMB* rs10993994 (per variant allele summary RR=1.24, 95% CI=1.05-1.48), 8q24 rs4242382 (RR=1.40, 95% CI=1.13-1.75) and 8q24 rs6983267 (RR=0.67, 95% CI=0.50-0.89) were associated with risk for metastatic prostate cancer. None of the 12 SNPs was associated with prostate cancer recurrence.

Conclusions—SNPs in *MSMB* and 8q24 which predispose to prostate cancer overall are associated with risk for metastatic prostate cancer, the most lethal form of this disease. SNPs

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predictive of prostate cancer recurrence were not identified, among the predisposition SNPs. GWAS specific to these two phenotypes may identify additional phenotype-specific genetic determinants.

Introduction

The success of genome-wide association studies (GWAS) has been to discover novel genetic associations with prostate cancer, and for a subset of the identified single nucleotide polymorphisms (SNP), replication has been achieved in multiple independent study populations (1-9). For all markers so far, the per allele risks have been estimated to be below 1.5, confirming the observation that the etiology of prostate cancer is complex.

Some of these risk variants showed a moderate trend of increasing frequency with increasing Gleason score, stage, or pre-operative PSA levels in several (3,6,9-14) but not all (2,5,15,16) studies. None of these studies, however, specifically considered whether these SNPs are also associated with the diagnosis of metastatic prostate cancer or with recurrence after surgical treatment for clinically localized prostate cancer.

Although prostate cancer is the second leading cause of cancer death in men, the majority of the more than 200,000 cases annually in the US are diagnosed when localized, often detected by PSA screening(17). Only 10-20% of diagnosed cases die from the disease (18). Thus, risk prediction tools that distinguish men at higher risk of prostate cancer that is likely to metastasize and cause death from those at lower risk are needed to target men for screening and chemoprevention while reducing the burden of over-detection and over-treatment. In addition, improved prognostic tools that distinguish men with early stage prostate cancer at higher risk of recurrence after treatment from those at lower risk are needed to improve the ability to target patients for treatment while reducing the burden of over-treatment.

With these translational goals in mind, here we investigated the association of 12 prostate cancer predisposition SNPs with risk of metastatic prostate cancer and with prostate cancer recurrence after prostatectomy for clinically localized diseases. The 12 SNPs that we chose for this study were those reported to be statistically significantly associated with prostate cancer risk in the GWAS conducted by the Cancer Genetic Markers of Susceptibility (CGEMS) (1,2).

Materials and Methods

Study Population

Metastatic prostate cancer—We included 470 incident metastatic prostate cancer (clinical stage T4, N+, or M+) cases and 1,945 controls in two case-control studies from Sanjay Gandhi Hospital, India-Weill Medical College of Cornell University (19) and Washington University in St. Louis (Wash U) (20), and one nested case-control study from the National Cancer Institute (NCI)'s Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (1). Controls were men without a diagnosis of prostate cancer. Detailed descriptions of each study and matching factors are described in the Supplement.

Prostate cancer recurrence—We evaluated genotypes of 1,412 men treated for localized prostate cancer, including 328 men who experienced recurrence. The cohort of 1,412 men were treated by radical prostatectomy for clinically localized prostate cancer (T1-3a, N0, M0) and had not had prior hormonal or radiation treatment. The cohort combined subjects from 3 studies from the Fred Hutchinson Cancer Research Center (FHCRC)(21), the University of Pennsylvania School of Medicine (U PENN), and the

Moffitt Cancer Center (MCC). In addition, we evaluated genotypes for 450 recurrence cases and 450 nonrecurrence prostate cancer controls selected using incidence density sampling nested in a cohort of men with localized prostate cancer from the Johns Hopkins University (JHU); the diseased but nonrecurrent controls were matched to the recurrent cases on age at surgery, race, and pathological stage and grade. All prostate cancer patients were followed for disease recurrence as per the standard of care, usually based on serum PSA determinations and clinical assessment every 6 months for the first year and annually thereafter. Recurrence was defined as a rise in PSA from non-detectable to ≥ 0.2 ng/mL, development of metastasis, or initiation of systemic therapy including hormonal or radiation therapy (<1% of cases). For detailed descriptions of each study see Supplement.

Genotyping

DNA was extracted from white blood cells for the Cornell, Wash U, FHCRC and U Penn studies, from paraffin embedded prostate tissue blocks for the MCC study, and from unaffected paraffin-embedded lymph nodes or frozen seminal vesicles for the JHU study. Thirteen SNPs were selected for genotyping based on their genome-wide association with prostate cancer in the Cancer Genetic Markers of Susceptibility (CGEMS) (1,2) or, for assay design considerations, on high correlation ($r^2 > 0.8$) with such a SNP. SNPs were genotyped at list the sites here using the TaqMan assay system (ABI, Foster City, CA, USA), by SNPlex genotyping system (Applied Biosystems, Inc.) at FHCRC, and as part of a GWAS study (Cancer Genetic Markers of Susceptibility; CGEMS) for the NCI-PLCO study. Genotyping was successfully completed for the 12 SNPs with average completion rates for all centers > 95%. Replicate quality control samples included in the studies yielded >99% concordance for all successfully genotyped SNPs.

Statistical analysis

For the case-control study of metastatic cancer, logistic regression was used to estimate the RRs and 95% confidence intervals (95% CIs) for the association between SNPs and metastatic prostate cancer, adjusting for age, and in the Washington University study, which included African Americans, for race. For the cohort recurrence analyses in the FHCRC, Penn, and MCC datasets, Cox proportional hazards regression was used to estimate relative risks (RRs) and 95% confidence intervals (CIs) for recurrence, adjusting for age at radical prostatectomy, race, and pathological stage and grade. Men were at risk from the date of prostatectomy until the date of first recurrence (PSA elevation), death from other cause, or last contact. For the case-case recurrence analyses in the JHU study, conditional logistic regression was used to estimate the RRs and 95% CI. For combining across studies results from the log-additive model in which the number of variant alleles for each of the 12 SNPs was entered as a single variable are presented. Co-dominant models were also run to confirm that the log-additive model was a reasonable assumption.

We used a meta-analytic approach to combine across the 3 studies for assessment of risk for metastatic prostate cancer. We also used this approach for the 4 studies on recurrent prostate cancer. To do so, we calculated summary RRs and 95% CIs using random-effects models that weighted individual study-specific \log_e RRs by the inverse of their variances. Between-study heterogeneity was tested by the I² statistic (22). Analyses were conducted using SAS version 9.1, software (SAS Institute, Inc., Cary, NC) and STATA 7.0 (College Station, TX). Two-sided statistical tests were performed.

Results

Population characteristics

Selected characteristics of each study are described in Table 1. The mean age by study ranged from 57.9 to 67.9 years. The majority of men were Caucasian, however, the Cornell study was of Asian Indians and the Washington University study included 39.5% African Americans. Clinical Gleason score distributions were similar among the three metastatic disease case-control studies. Among the three radical prostatectomy cohorts for the recurrence study, cases in the MCC cohort had a higher mean Gleason score.

Incidence of Metastatic Prostate cancer

The variant (T) allele of rs10993994 in *MSMB* was associated with a higher risk of metastatic prostate cancer (per variant allele summary RR=1.24; 95% CI: 1.05-1.48, p=0.012; Table 2). The variants allele of two 8q24 SNPs, rs4242382 (A allele, summary RR=1.40, 95% CI 1.13-1.75, p=0.003) and rs6983267 (T allele, summary RR=0.67, 95% CI 0.50-0.89, p=0.006), were also associated with metastatic prostate cancer. Findings are consistent across studies. None of the other SNPs examined was statistically significantly associated with metastatic disease. Results were consistent when we analyzed data based on Caucasians only (Table 2), and when we excluded the PLCO study (previously published data; data not shown).

Recurrence of Prostate Cancer

None of the SNPs was associated with recurrence in the 4 studies or after combing their results (Table 3). Findings are consistent across studies. Results were consistent across subgroups by race, clinical stage, and Gleason score (data not shown).

Discussion

By combining data from multiple studies in our consortium, we report risk profiles for metastatic prostate cancer and for prostate cancer recurrence following treatment for localized disease in relation to 12 established prostate cancer predisposition loci. In our study, three independent SNPs, rs10993994 in *MSMB* and rs4242382 and rs6983267 in 8q24 were associated with metastatic prostate cancer, while we discovered no risk associations for these loci in relation to prostate cancer recurrence. The strengths of this study include relatively large sample sizes and multiple independent populations.

Several studies show that the T allele of rs10993994 in *MSMB* is associated with a higher risk of prostate cancer overall. Xu et al. reported that this association did not differ when comparing T3/N+/M+ or Gleason score 7+ versus T2/N0/M0 and Gleason score 6 or lower) (16); however, most of the more aggressive cases in this series were based on a relatively non-stringent Gleason score characterization (7: 49%). Furthermore, there is evidence that this allele could also be associated with higher PSA concentrations (23), suggesting that the SNP may be associated with prostate cancer indirectly, because modest genetically mediated increases in constitutive PSA could lead to an increased biopsy rate, similar to potentially spurious associations with *KLK3* SNPs, the gene which encodes for PSA (24). Our findings that the T allele of rs10993994 is associated with an increased risk of metastatic cancer provides evidence that the SNP marks for genetic variation associated with primary carcinogenesis, because the detection of prostate cancer that is already metastatic is less likely to be the result of early diagnosis by routine PSA screening. Further support that the association with metastatic prostate cancer is causal comes from the observation that *MSMB* expression levels decrease progressively during prostate cancer development from early to late stages (25-27) and from *in vitro* functional studies showing that the T allele of

rs10993994, located in the 5' untranslated region of *MSMB*, confers decreased expression of *MSMB* (28,29).

Our finding of a significant positive association of the A variant of rs4242382 and a significant inverse association of the T variant of rs6983267 in 8q24 with metastatic prostate cancer are generally consistent with previous studies which examined less stringent groupings of aggressive disease. Several (3,11-14), although not all (2,5,15,16) report stronger associations with high Gleason score cancers for rs1447295, which is in high linkage disequilibrium with rs4242382 ($r^2 = 1.0$ in HapMap CEU samples) (30). A set of loci across 8q24 that spans a 1.2-Mb region and that is devoid of coding sequences has been strongly associated with breast, prostate, colorectal, ovarian, and bladder cancers (31,32). The plausible mechanism(s) of the association are not readily apparent and may relate to long-range regulation of the neighboring gene, *MYC*, or another locus on a distinct chromosome; recently, Jia et al. reported that rs11986220, which is strongly linked to rs4242382 at 8q24, localizes with embedded regulatory enhancers, potentially influencing binding activity of FoxA1 and androgen responsiveness (33).

Our findings of association of *MSMB* and 8q24 SNPs with metastatic prostate cancer indicate the importance of these SNPs for the most fatal form of this disease. The strength of the relative risks were, however, not substantially stronger than those observed for prostate cancer overall in earlier studies (1-9), indicating that risks are not specific for aggressive disease. GWAS discovery for metastatic disease specifically has not yet taken place, but should be a priority for identifying the gene variants that best predict risk of developing prostate cancer that is most likely to lead to death.

Our findings of null associations with prostate cancer recurrence indicate that these SNPs are not strongly related to poor outcome after treatment of localized prostate cancer by radical prostatectomy, despite the SNPs being consistently associated with risk of prostate cancer development, and for rs10993994, rs4242382, and rs6983267 associated with metastatic disease. Prostate cancer recurrence in men treated by radical prostatectomy for localized disease is measured indirectly by PSA rise, which is the most commonly used clinical indicator of poor long-term prostate cancer prognosis (34), although it may not be indicative of measurable metastasis for many years. Our null results differ from those of Huang et al. who reported that rs1447295 in 8q24 and rs10993884 in *MSMB* were associated with biochemical relapse after radical prostatectomy, after controlling for PSA, Gleason score, pathologic stage, surgical margin, in Chinese population (35). However, our findings are consistent with a prior report of no association between these 12 loci and death from prostate cancer in a cohort of men diagnosed with prostate cancer in Swedish population (36).

The 12 candidate SNPs were discovered in populations of European ancestry and the power may be limited for evaluating risk in other ethnicities, particularly because linkage patterns of these SNPs to underlying causal genetic variants may differ by ethnicity. Nonetheless, results remained largely unchanged when we limited the analysis to the Caucasians. Further studies in other ethnicities are warranted to examine these associations for these groups.

In summary, we observed a SNP marker in *MSMB* (rs10993994) and two SNP markers at 8q24 (rs4242382 and rs6983267) that were significantly associated with risk of metastatic prostate cancer, suggesting that gene variants in *MSMB* and the 8q24 region are related mechanistically to the development of aggressive cancer; however, the associations were not strong and may be of limited use in individualized risk prediction. Findings merit follow-up in additional studies with larger sample size to confirm the association and to investigate the underpinning of the genetic association. None of the 12 SNPs was associated clearly with

risk of prostate cancer recurrence following radical prostatectomy. Further GWAS of these two phenotypes are needed to discover genetic variants associated specifically with metastatic disease and with prostate cancer recurrence, subsequent to radical prostatectomy.

Translational Relevance

Because most prostate cancers have a favorable outcome, genetic markers predicting aggressive cancer outcome, such as metastatic disease and recurrence after treatment, are needed to assist in the identification of the subset of patients who will benefit from chemoprevention and aggressive treatment. In a large pooled analysis, we examined the possible association of recently identified genetic markers of prostate cancer risk through GWAS with risk of metastatic prostate cancer and with prostate cancer recurrence after prostatectomy for clinically localized diseases. Although these markers seem to be informative for the identification of men who may be at elevated risk for a prostate cancer diagnosis, they do not seem to be helpful in identifying men at risk for developing metastatic prostate cancer or recurrence after treatment. Additional studies directly comparing cases with more or less aggressive disease in the GWAS discovery phase should be pursued to identify genetic markers that predict these aggressive phenotypes of prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
 Characteristics of study populations, Consortium on genetic risk of metastatic and recurrent prostate cancer ^d

	Metastatic prostate cancer				Recurrence after radical prostatectomy			
	India-Cornell U	Wash U	PLCO	JHU ^c	FHCRC	U Penn	MCC	
Study design ^d	Case-control	Case-control	Nested case-control	Nested case-control	Cohort	Cohort	Cohort	Cohort
Cases/controls (N)	122/322	295/455	53/1168	450/450	NA	NA	NA	NA
Cases/cohort (N)	NA	NA	NA	NA	92/424	99/617	137/371	
Mean age at diagnosis (years)	64.5	64.0	67.6	58.9	57.9	67.9	61.6	
Non-white (%)	100.0 ^a	39.5 ^b	0	14.1	4.5	12.8	6.7	
Pathologic Gleason score (%) in cases								
<7	26.8	23.6	16.7	64.6	60.6	55.2	3.8	
7	32.7	37.3	40.0	30.2	33.0	38.7	70.6	
7+	40.5	39.1	43.3	5.2	6.4	6.1	25.6	
Stage (%) in cases								
I	0.0	0.0	0.0	0.0	72.6	28.0	2.9	
II	0.0	0.0	0.0	13.6	27.1	47.1	97.1	
III	0.0	0.0	0.0	51.7	0.2	25.0	0	
IV	100.0	100.0	100.0	0.0	0.0	0.0	0.0	

^a Study population was Asian Indian.

^b 39.5% was African Americans.

^c Cases and controls matched on age at radical prostatectomy, race, and pathological stage and grade. Controls sampled using incidence density sampling.

^d In metastatic cases (India-Cornell U, Wash U, PLCO), in recurrence cohorts (FHCRC, U Penn, HLMCC), and in the cases in the recurrence nested case-control study (JHU).

Table 2

Association of 12 prostate cancer susceptibility SNPs with risk of metastatic prostate cancer, Consortium on genetic risk of metastatic and recurrent prostate cancer

SNP	Gene	Alleles	India (Cornell U) RR (95% CI) ^b	Wash U RR (95% CI) ^b	PLCO RR (95% CI) ^b	Summary RR (95% CI) ^c (212 cases and 1442 controls) Caucasians only	Summary RR (95% CI) ^d (470 cases and 1945 controls) All study participants
rs10486567	JAZF1	C/T	0.59 (0.41-0.85)	0.74 (0.57-0.97)	1.21 (0.77-1.89)	0.98 (0.69-1.41)	0.79 (0.55-1.12)
rs10896449	11q13	G/A	0.70 (0.52-0.94)	0.82 (0.65-1.04)	1.16 (0.80-1.71)	0.95 (0.65-1.37)	0.85 (0.66-1.10)
rs10993994	MSMB	C/T	1.41 (1.02-1.95)	1.21 (0.96-1.53)	1.12 (0.75-1.66)	1.18 (0.96-1.51)	1.24 (1.05-1.48)
rs12771728	10q23	T/C	1.15 (0.83-1.59)	1.07 (0.83-1.38)	1.21 (0.82-1.79)	1.10 (0.86-1.41)	1.12 (0.94-1.34)
rs4072111	IL16	C/T	0.97 (0.71-1.33)	0.90 (0.59-1.37)	0.88 (0.46-1.70)	0.88 (0.59-1.32)	0.94 (0.74-1.18)
rs4242382	8q24	G/A	1.38 (0.95-2.02)	1.47 (1.08-1.98)	1.24 (0.68-2.26)	1.31 (0.98-1.91)	1.40 (1.13-1.75)
rs4430796	HNF1B	T/C	1.05 (0.77-1.43)	0.80 (0.64-1.00)	1.02 (0.68-1.52)	0.92 (0.71-1.18)	0.91 (0.76-1.09)
rs4782726	CDH13	G/A	0.57 (0.37-0.89)	1.04 (0.78-1.38)	0.90 (0.53-1.51)	0.93 (0.67-1.30)	0.83 (0.57-1.21)
rs4961199	CPNE3	G/A	1.50 (0.48-4.72)	1.10 (0.77-1.55)	0.49 (0.24-1.00)	0.81 (0.33-1.96)	0.90 (0.50-1.63)
rs4962416	CTBP2	A/G	1.26 (0.91-1.73)	1.01 (0.78-1.31)	1.05 (0.81-1.31)	1.02 (0.78-1.32)	1.10 (0.89-1.36)
rs6982080	8p21	G/T	1.03 (0.75-1.42)	1.04 (0.82-1.34)	0.79 (0.51-1.23)	0.93 (0.72-1.20)	0.99 (0.83-1.18)
rs6983267	8q24	G/T	0.88 (0.65-1.19)	0.59 (0.45-0.77)	0.55 (0.37-0.83)	0.55 (0.43-0.71)	0.67 (0.50-0.89)

^bRR per risk allele assuming a log-additive model, adjusted for age, and race (Wash U only).

^cThe summary RRs and 95% CIs were calculated using a random-effects model, based on Caucasians only.

^dThe summary RRs and 95% CIs were calculated using a random-effects model, based on all study populations.

Note: all 12 statistics were < 20%, indicating no strong evidence of heterogeneity among studies.

Table 3

Association of 12 prostate cancer predisposition SNPs with prostate cancer recurrence after prostatectomy for clinically localized prostate cancer, Consortium on genetic risk of metastatic and recurrent prostate cancer

SNP	Gene	Allele	JHU RR (95% CI) ^b	FHCRC RR (95% CI) ^c	U Penn RR (95% CI) ^c	MCC RR (95% CI) ^c	Summary RR (95% CI) ^d Caucasians only	Summary RR (95% CI) ^e All study participants
rs10486567	JAZF1	C/T	1.02(0.82-1.26)	1.16 (0.81-1.68)	0.94 (0.67-1.33)	1.18 (0.88-1.58)	1.06 (0.91-1.24)	1.13 (0.96-1.32)
rs10896449	11q13	G/A	1.07(0.88-1.30)	0.76 (0.56-1.06)	1.13 (0.86-1.49)	1.03 (0.79-1.34)	1.02 (0.88-1.18)	0.95 (0.83-1.10)
rs10993994	MSMB	C/T	0.95(0.79-1.14)	1.13 (0.83-1.55)	1.02 (0.77-1.36)	1.15 (0.91-1.44)	1.02 (0.91-1.14)	1.04 (0.92-1.18)
rs12771728	10q23	T/C	0.93(0.76-1.13)	1.10 (0.80-1.50)	1.09 (0.80-1.48)	1.14 (0.90-1.46)	1.05 (0.93-1.17)	1.07 (0.93-1.23)
rs4072111	11L16	C/T	1.28(0.91-1.78)	1.34 (0.85-1.98)	0.83 (0.48-1.45)	1.05 (0.70-1.58)	1.14 (0.89-1.46)	1.08 (0.87-1.34)
rs4242382	8q24	G/A	0.86(0.65-1.14)	1.27 (0.86-1.85)	1.60 (1.12-2.29)	1.08 (0.79-1.49)	1.15 (0.83-1.58)	1.14 (0.96-1.35)
rs4430796	HNF1B	T/C	0.99(0.83-1.18)	0.90 (0.68-1.24)	1.11 (0.83-1.47)	1.01 (0.80-1.28)	0.99 (0.89-1.11)	1.00 (0.88-1.14)
rs4782726	CDH13	G/A	1.08(0.85-1.38)	1.01 (0.72-1.50)	0.62 (0.39-0.99)	0.94 (0.70-1.25)	0.92 (0.77-1.11)	0.94 (0.80-1.12)
rs4961199	CPNE3	G/A	1.10(0.83-1.45)	1.14 (0.77-1.72)		1.13 (0.84-1.53)	1.15 (0.92-1.44)	1.09 (0.89-1.32)
rs4962416	CTBP2	A/G	0.93(0.77-1.13)	0.98 (0.69-1.37)	1.02 (0.76-1.37)	1.18 (0.86-1.61)	0.96 (0.86-1.07)	0.91 (0.74-1.12)
rs6982080	8p21	G/T	0.95(0.78-1.16)	0.84 (0.61-1.14)	1.11 (0.83-1.48)	0.96 (0.74-1.24)	0.96 (0.85-1.09)	0.96 (0.84-1.10)
rs6983267	8q24	G/T	0.97(0.80-1.17)	0.91 (0.66-1.29)	1.11 (0.81-1.52)	0.73 (0.56-0.95)	0.93 (0.80-1.08)	0.91 (0.79-1.06)

^b RR per risk allele assuming a log-additive model, estimated by conditional logistic regression; cases and controls (incidence density sampled) matched on age at radical prostatectomy, race, pathological stage and grade.

^c RR per risk allele assuming a log-additive model, adjusted for age at radical prostatectomy, race, pathological stage, and grade.

^d The summary RR and 95% CIs were calculated using a random-effects model, based on Caucasians only.

^e The summary RRs and 95% CIs were calculated using a random-effects model, based on all study populations.

Note: all I2 statistics were < 20%, indicating no strong evidence of heterogeneity among studies.