Int. J. Cancer: **122,** 2876–2879 (2008)

SHORT REPORT

Chromosome 8q24 markers: Risk of early-onset and familial prostate cancer

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Recent admixture mapping and linkage/association studies have implicated an ~1 Mb region on chromosome 8q24 in prostate cancer susceptibility. In a subsequent follow-up investigation, Haiman *et al.* (Nat Genet 2007;39:638-44) observed significant, independent associations between 7 markers within this region and sporadic prostate cancer risk in a multi-ethnic sample. To clarify the risk associated with hereditary prostate cancer, we tested for prostate cancer association with 6 of these 7 markers in a sample of 1,015 non-Hispanic white men with and without prostate cancer from 403 familial and early-onset prostate cancer families. Single nucleotide polymorphisms (SNPs) rs6983561 and rs6983267 showed the strongest evidence of prostate cancer association. Using a family-based association test, the minor ("C") allele of rs6983561 and the major ("G") allele of rs6983267 were preferentially transmitted to affected men ($p < 0.05$), with estimated odds ratios (ORs) of 2.26 (95% confidence interval of 1.06–4.83) and 1.30 (95% confidence interval of 0.99–1.71), respectively, for an additive model. Notably, rs6983561 was significantly associated with prostate cancer among men diagnosed at an early (<50 years) but not later age ($p = 0.03$ versus $p = 0.21$). Similarly, the association with rs6983267 was (not) statistically significant among men with(out) clinically aggressive disease ($p = 0.007$ versus $p = 0.34$). Our results confirm the association of prostate cancer with several of the SNPs on chromosome 8q24 initially reported by Haiman *et al.* In addition, our results suggest that the increased risk associated with these SNPs is approximately doubled in individuals predisposed to develop early onset or clinically aggressive disease.

Key words: prostate; cancer; genetics; chromosome 8; risk

Prostate cancer is now the most commonly diagnosed malignancy among men in the United States, with over 218,890 new cases and 27,050 deaths expected in 2007 according to the National Cancer Institute. Although the majority of prostate cancer cases are sporadic, twin and family-based epidemiological studies consistently provide clear evidence of a substantial heritable component of the disease.[1] However, given the late-onset nature, lack of distinguishing clinical features between sporadic, familial and hereditary forms, and likely genetic heterogeneity of the disease, the localization and validation of prostate cancer susceptibility genes has been difficult. In this context, recent studies of chromosome 8 have provided promising leads and new insights into the genetics underlying prostate cancer susceptibility.

Amundadottir *et al.*[2] recently identified a region on chromosome 8, namely 8q24, which was linked to prostate cancer in their Icelandic families. Further fine mapping of this region led to the identification of several markers that were associated with prostate cancer in men with European and African American ancestry. At the same time, Freedman *et al.*[3] independently implicated the 8q24 region in prostate cancer susceptibility in a whole genome admixture scan of African American men. In addition to the admixture scan, they (Haiman *et al.*)[4] later conducted a high-density association scan of the 8q24 region and reported 7 markers (within a span of ~500 kb) that were significantly and independently associated with prostate cancer in a multi-ethnic sample of African, European and Japanese Americans, Native Hawaiians and Latinos.

While the markers identified by Haiman *et al.*[4] have been well characterized in samples of men with sporadic prostate cancer, their influence on prostate cancer among men with a strong heritable component to their disease has not been specifically studied. For example, in the sample of Haiman *et al.*[4], only 16% of men with prostate cancer reported a family history of the disease, and 50% were more than 68 years old at diagnosis. To address the impact of variation on chromosome 8q24 in the context of hereditary prostate cancer, we examined prostate cancer association with the significantly associated markers from Haiman *et al.*[4] in our ongoing family-based association study of familial and early-onset prostate cancer.[5]

Material and methods

Study subjects

The University of Michigan Prostate Cancer Genetics Project (PCGP) has been described in detail elsewhere.[5] Briefly, enrollment into the PCGP is restricted to (*i*) men diagnosed with prostate cancer with at least one living first- or second-degree relative also diagnosed with prostate cancer or (*ii*) men diagnosed with prostate cancer at ≤55 years of age without a family history of the disease. For the present analysis, 421 families were identified in which DNA was available from at least one pair of brothers discordant for prostate cancer. The majority of these 421 families were non-Hispanic white ($n = 403$), although 16 African American and 2 Asian families were also recruited. Results below, however, were restricted to non-Hispanic white families as the number of African American and Asian families was too small to make meaningful inferences about prostate cancer risk in these minority groups.

The majority of PCGP families were recruited directly from the University of Michigan Comprehensive Cancer Center. Diagnosis of prostate cancer was confirmed by review of pathology reports or medical records, and age at diagnosis was calculated from the date of the first positive biopsy for prostate cancer. Cases were classified as clinically aggressive if they met at least one of the following criteria: (*i*) pathologic Gleason score > 7, or (*ii*) pathologic stage T3b (pT3b) tumor (indicating seminal vesicle involvement) and higher, or (*iii*) N1 (positive nodal involvement), or (*iv*) pathologic Gleason score of 7 and a positive surgical margin, or (*v*) a pre-diagnostic serum prostate-specific antigen (PSA) value >15 ng/ml, or (*vi*) or a pre-diagnostic serum PSA level > 10 ng/ml and a Gleason score of 7. On the basis of data from D'Amico

The first two authors contributed equally to this work.

Grant sponsor: National Cancer Institute SPORE in Prostate Cancer; Grant numbers: P50 CA69568, R01 CA79596.

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Received 3 December 2007; Accepted after revision 16 January 2008
DOI 10.1002/ijc.23471
Published online 21 March 2008 in Wiley InterScience (www.interscience.wiley.com).

et al.[6] these criteria were developed by the Southwest Oncology Group (SWOG) to identify men at intermediate to high risk of clinical recurrence after primary therapy. Disease status of the unaffected brothers was confirmed through serum PSA testing whenever possible. The Institutional Review Board at the University of Michigan Medical School approved all aspects of the protocol, and all participants gave written informed consent, including permission to release their medical records.

Genotyping assays

We genotyped five SNPs (rs13254738, rs6983561, rs6983267, rs7000448 and rs10090154) using Taqman SNP Genotyping Assays (Applied Biosystems, Foster City, CA), and we used the ABI PRISM 7900HT Sequence Detection System and the SDS version 2.1 software (Applied Biosystems) to distinguish SNP alleles as previously described.[5] Note, we did not genotype the sixth prostate cancer-associated SNP identified by Haiman *et al*.[4] (Broad11934905) due to the low frequency of the minor allele in non-African populations (<1%). We genotyped microsatellite DG8S737 using a fluorescently labeled PCR followed by capillary electrophoresis. We electrophoresed PCR products on an ABI 3100 Genetic Analyzer and analyzed the resulting data using GeneMapper Software v4.0 (Applied Biosystems) as previously described.[7] For each SNP, ~9% of samples were duplicated on the same platform, and ~2% of samples were directly sequenced for verification purposes. For the microsatellite, ~5% of samples were repeated for verification purposes. No genotype discrepancies were observed.

Data analysis

On the basis of a subset of unaffected, unrelated men, we tested the observed genotype distributions for departures from Hardy-Weinberg equilibrium and estimated two-marker haplotype frequencies using the expectation-maximization algorithm. Haplotype frequencies were used to calculate the LD measure r^2 between each pair of markers. For association testing, we used conditional logistic regression with family as the stratification variable and a robust variance estimate that incorporates familial correlations due to potential linkage to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between genotypes and prostate cancer.[8] In parallel, we used the Family-Based Association Test (FBAT) program (version 1.7.3)[9,10] to test for association between genotypes and prostate cancer. We employed the empirical variance function in FBAT, which is a valid test of the null hypothesis of no association in the presence of linkage. To maximize power, we analyzed the combined sample of affected and unaffected men using the offset option. We also carried out analyses of affected men only to allow for the possibility of misclassification of unaffected men. Both conditional logistic regression analyses and FBATs were carried out assuming additive, dominant and recessive genetic models. For conditional logistic regression and affecteds-only FBATs, we also examined a general (2 degrees of freedom) genotype model. Predetermined stratified analyses were also performed to explore the relationship between genotypes and prostate cancer, stratifying on the presence of clinically aggressive prostate cancer, age at diagnosis (<50 years), and number of confirmed cases of prostate cancer within a family (≥3). All statistical tests were two-sided, and p-values <0.05 were considered statistically significant. Conditional logistic regression was conducted using version 8.2 of the SAS programming language (SAS Institute, Cary, NC). All remaining analyses (except where noted above) were conducted using the R language (version 2.1.1).

Results

For this analysis, we identified 542 affected and 473 unaffected men from 403 non-Hispanic white families with at least 1 discordant sibling pair (DSP). In total, the sample consisted of 624 DSPs from 421 sibships. The clinical characteristics of men with prostate cancer are summarized in Table I. The median age at diagnosis was 54 years, and 116 cases (21%) were diagnosed before 50 years of age. On the basis of SWOG criteria, ~30% of prostate cancer cases were classified as having clinically aggressive disease. Over 90% of unaffected men reported having been screened for prostate cancer. In addition, ~80% of unaffected men reported their most recent PSA test results and/or had their PSA values confirmed by medical record review, and nearly 95% of them had documented PSA levels < 4.0 ng/ml.

TABLE I – CHARACTERISTICS OF MEN WITH PROSTATE CANCER (n = 542)

Characteristic	No.[1] (%)
Age at diagnosis (years)[2]	54 (50–62)
Pre-diagnosis PSA (ng/ml)[2]	5.6 (4.2–9.3)
Surgery[3]	415 (77)
Stage:	
Localized	414 (79)
Locally advanced	92 (17)
Metastasized	19 (4)
Gleason:	
≤6	252 (47)
7	216 (41)
>7	62 (12)
Clinically aggressive CaP (%)	162 (30)

[1]Column subtotals do not sum to 542 due to missing data.–[2]Median and [interquartile range] are reported.–[3]Number and (percentage) of men with prostate cancer who underwent a radical prostatectomy.

Allele frequencies for all 6 markers are given in Table II. There were no significant differences in the distribution of alleles or genotypes between affected and unaffected men when ignoring family structure and treating all men as unrelated subjects (data not shown). On the basis of a sample of unrelated, unaffected men, the genotype distributions of all markers were consistent with Hardy-Weinberg equilibrium (p-value > 0.05), and all 10 SNP pairs exhibited weak LD ($r^2 \leq 0.2$). After collapsing the alleles of DG8S737 (−8 versus all others), DG8S737 also exhibited weak LD with the SNPs (maximum r^2 of 0.32 with rs10090154).

Tables II and III summarize association results (under an additive model) for all 6 markers from FBATs and conditional logistic regression analyses, respectively. For the FBAT results that follow, we report findings from the combined sample of affected and unaffected men, unless otherwise specified. Before conducting the conditional logistic regression analysis, we excluded 38 men (from 10 families) who were not brothers of the index case; the resulting sample consisted of 977 men and 604 DSPs. The strongest evidence of prostate cancer association was for SNPs rs6983561 and rs6983267. The minor allele ("C") of rs6983561 was preferentially transmitted to affected men (z = 2.21; p = 0.03), with an odds ratio of 2.26 (95%CI = 1.06, 4.83). In contrast, the major allele ("G") of rs6983267 was preferentially transmitted to affected men (z = 2.07; p = 0.04), with an odds ratio of 1.30 (95%CI = 0.99, 1.71). Under a dominant (but not additive) genetic model, rs7000448 revealed suggestive but nonsignificant evidence of prostate cancer association (z = 1.87; p = 0.06), with an odds ratio of 1.44 (95%CI = 0.97, 2.11) for carriers of the minor or "T" allele. None of the remaining markers (rs13254738, rs10090154 or DG8S737) were associated with prostate cancer risk.

After stratification, the minor allele ("C") of rs6983561 was preferentially transmitted to men diagnosed with prostate cancer before the age of 50 years relative to their unaffected brothers (z = 2.19; p = 0.03 for an additive model), with an odds ratio of 4.69 (95% CI = 0.86, 25.6). Similarly, the major allele of rs6983267 ("G") was preferentially transmitted to men diagnosed with clinically aggressive disease (z = 2.69; p = 0.007 for an additive model), with an odds ratio of 1.90 (95% CI = 1.09, 3.31). These stratified results are consistent with the FBAT results based

TABLE II – ALLELE FREQUENCIES BY PROSTATE CANCER AFFECTION STATUS AND FAMILY-BASED ASSOCIATION TEST (FBAT) RESULTS

Marker	Region[1]	Major > minor allele	Minor allele frequency in		FBAT[2]		
			Affected men (n = 542)	Unaffected men (n = 473)	N^3	Z-score	p-value
rs13254738	2	A>C	0.34	0.35	191	-0.29	0.78
rs6983561	2	A>C	0.08	0.06	49	2.21	0.03
rs6983267	3	G>T	0.41	0.43	189	2.07	0.04
rs7000448	3	C>T	0.41	0.40	187	0.72	0.47
DG8S737	1	−8[4]	0.08	0.07	62	0.71	0.48
rs10090154	1	C>T	0.13	0.13	106	0.06	0.95

[1]Defined by Haiman *et al.*[4]–[2]Under an additive model for the minor allele, except for rs6983267 (major allele).–[3]Number of informative families.–[4]Minor allele after collapsing alleles of DG8S737, i.e., −8 versus all others.

TABLE III – ODDS RATIOS (ORS) (AND 95% CONFIDENCE INTERVALS) IN CURRENT STUDY[1] AND FROM HAIMAN *ET AL.*[4]

	Non-Hispanic whites[2]	European Americans[1]	Multi-ethnic sample[1]
rs13254738	0.97 (0.74, 1.27)	1.11 (0.97, 1.26)	1.26 (1.18, 1.36)
rs6983561	2.26 (1.06, 4.83)	1.16 (0.86, 1.58)	1.51 (1.37, 1.67)
rs6983267	1.30 (0.99, 1.71)	1.13 (0.99, 1.28)	1.18 (1.09, 1.27)
rs7000448	1.11 (0.85, 1.44)	1.14 (0.93, 1.40)	1.26 (1.15, 1.38)
DG8S737	1.24 (0.74, 2.07)	1.45 (0.96, 2.19)	1.39 (1.23, 1.57)
rs10090154	1.05 (0.72, 1.53)	1.44 (1.17, 1.76)	1.43 (1.30, 1.58)

Note – as in Table II, ORs are based on an additive model for the minor allele, except for rs6983267 (major allele).

[1]Based on unconditional logistic regression of (1) 2,124 European American men and (2) after adjustment for population and study, 7,518 men from a multi-ethnic sample, including African, European, and Japanese Americans, Native Hawaiians, and Latinos.–[2]Based on conditional logistic regression of 977 non-Hispanic white men (604 DSPs in total).

on all families. In contrast, rs6983561 and rs6983267 were not significantly associated with prostate cancer in men diagnosed at a later age ($p = 0.21$) or with nonaggressive disease ($p = 0.34$), respectively. We found no significant evidence of an association between rs13254738, rs10090154 or DG8S737 and prostate cancer in any of the stratified analyses.

Discussion

In summary, we have confirmed that 2 of the 7 prostate cancer-associated markers on chromosome 8q24 identified by Haiman *et al.*[4] in their multi-ethnic sample of sporadic prostate cancer are associated with early-onset and familial prostate cancer in our sample of non-Hispanic white men. Our 2 significantly associated markers, SNPs rs6983561 and rs6983267, had the strongest evidence of association in the subset of families in which men were diagnosed with prostate cancer at an early age or with clinically aggressive disease, respectively. To our knowledge, we are the first group to validate the association of prostate cancer with SNP rs6983561 and the first to report a significant association between clinically aggressive prostate cancer and SNP rs6983267. Notably, we estimate that men with one risk allele at SNP rs6983561 are nearly 5 times more likely to develop early-onset prostate cancer than men with no risk alleles. Similarly, men with 2 risk alleles at SNP rs6983267 are nearly 4 times more likely to develop clinically aggressive prostate cancer than men with no risk alleles.

Although our results were not all statistically significant, none were significantly different from the study of Haiman *et al.*[4] (see Table III). In fact, based on their European American sample, 5 of the 6 markers tested by Haiman *et al.*,[4] including rs6983561 and rs6983267, were nonsignificantly associated with prostate cancer, possibly reflecting the effects of clinical and genetic heterogeneity in a smaller sample. Notably, in their pooled, multi-ethnic sample, the effect of rs6983561 was significantly greater among men diagnosed with prostate cancer below the median age of 68 years, consistent with both our overall and stratified results for rs6983561. Further, indirect support for this association was also recently given by Gudmundsson *et al.*,[11] who reported early-onset prostate cancer association with SNP rs16901979, which is perfectly correlated with rs6983561 in the HapMap† CEU sample ($r^2 = 1$). Finally, like us, Yeager *et al.*[12] also reported a stronger association between clinically aggressive prostate cancer and SNP rs6983267, although their result was not statistically significant, perhaps again owing (in part) to the adverse effects of clinical and genetic heterogeneity.

Several other groups have also identified markers on chromosome 8q24 as being associated with prostate cancer. For example, multiple studies have reported prostate cancer association with SNP rs1447295.[2,3,11–17] Because of the perfect correlation between rs1447295 and one of our tested SNPs, rs10090154, in the HapMap† CEU sample ($r^2 = 1$), we did not initially genotype rs1447295. However, in subsequent genotyping, we found no association between this SNP and prostate cancer (data not shown), consistent with our original result for rs10090154. Lastly, several studies have also reported prostate cancer association with the –8 allele of microsatellite DG8S737,[2,4,15,16] including one study that reported a stronger association between the –10 allele and clinically aggressive prostate cancer.[16] Still, we found no association between DG8S737 and clinically aggressive and/or nonaggressive prostate cancer.

We acknowledge several study limitations. First, our modestly powered sample limited our ability to detect prostate cancer-marker associations with the small effect sizes (e.g., odds ratios less than 1.5) previously reported by Haiman *et al.*[4] and confirmed by others. For example, based on our current sample of ~400 DSP families and a significance level of 5%, we had a maximum of 26–64% power to detect prostate cancer association with a single SNP for odds ratios of 1.2–1.4 and risk allele frequencies from 5 to 95% (under an additive genetic model). Second, because our sample largely included non-Hispanic white men with early onset and/or familial prostate cancer, we were unable to generalize our findings, *e.g.,* the association between clinically aggressive prostate cancer and SNP rs6983267, to other populations. Third, the possibility of preclinical disease among the unaffected men in our study may have undermined our ability to detect genetic differences

†http://www.hapmap.org

between men with and without prostate cancer. Still, when we restricted analyses to the sample of affected men only, our findings were consistent with those based on analyses of the combined sample of affected and unaffected men, suggesting that the impact of any misclassification of unaffected men was likely minimal.

In conclusion, results from a number of studies indicate that genetic variation on chromosome 8q24 is associated with prostate cancer, primarily sporadic prostate cancer. Data from our family-based study, however, suggest that these associations also extend to early-onset and familial prostate cancer. Furthermore, results from our stratified analyses indicate that the genetic risk conferred by these SNPs may be substantially increased, *e.g.,* ~2-fold higher, in men predisposed to develop early-onset or clinically aggressive prostate cancer. These findings hint at the potential for early genetic screening to identify a subset of men who are at greater risk of developing prostate cancer, even in the absence of a family history of the disease.

Acknowledgements

We thank all the men and their families who generously volunteered their time to participate in our study.

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