Evidence for an Association Between Prostate Cancer and Chromosome 8q24 and 10q11 Genetic Variants in African American Men: The Flint Men's Health Study

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BACKGROUND. Prostate cancer is the most commonly diagnosed non-skin cancer in men in the United States and the second leading cause of cancer-related mortality. African American men have substantially increased risk of both being diagnosed and dying from the disease. Recent genome-wide genetic association studies have identified a number of common single nucleotide genetic polymorphisms (SNPs) that are associated with prostate cancer in men of European descent. Only a small number of studies have evaluated the association between these genetic variants and prostate cancer in African Americans.

METHODS. We used logistic regression models to assess the association between prostate cancer in African American men and 24 SNPs from regions previously reported to be associated with prostate cancer in men of European descent.

RESULTS. We found nominal evidence ($P < 0.05$) for association between prostate cancer and three chromosome 8q24 (rs6983561, rs16901979, and rs7000448) and two 10q11 (rs7904463 and rs10740051) SNPs.

CONCLUSIONS. We confirm recent reports that 8q24 variants identified to be associated with prostate cancer in men of European descent are also associated with prostate cancer in African Americans. Our report is the first to find evidence of association between SNPs near *MSMB* and prostate cancer in African Americans. Of note, rs7000448 is in strong linkage disequilibrium with rs10761581 in *NCOA4*, a SNP that has been implicated to be independently associated, with respect to the widely reported SNP rs10993994 in the nearby gene *MSMB*, with prostate cancer in men of European descent. *Prostate 71: 225–231, 2011.*

KEY WORDS: **single nucleotide polymorphism; African American; prostate cancer**

INTRODUCTION

Prostate cancer is the most common cancer among men in the United States with 192,280 new cases diagnosed and 27,360 deaths estimated in 2009 [1]. In addition to increasing age, ethnicity is one of the most important recognized risk factors for the disease [2]. African American men have an ~1.6-fold greater chance of being diagnosed with prostate cancer

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compared to European American men and a 2.4-fold greater chance of dying from the disease [1,2].

Genome-wide association studies (GWASs) have been successful in identifying a number of common single nucleotide genetic polymorphisms (SNPs) that are associated with prostate cancer in men of European descent [3–6]. Many of these association findings have been replicated successfully across multiple studies of European men with prostate cancer. Unfortunately, despite their increased risk for developing the disease, African Americans are typically under-represented in genetic association studies of prostate cancer. To date, no GWASs for prostate cancer have been completed in African American men. The major impediment has been the limited availability of sufficient sample sizes of African American prostate cancer cases for individual investigators to have sufficient power to discover novel common genetic variants associated with prostate cancer in this population. Several recent replication-based studies for loci identified in European American prostate cancer GWASs have been conducted in cohorts and case–control studies of African American men [7–9]. The results from these replication studies have been mixed with only chromosome 8q24 consistently showing some evidence of association with prostate cancer. The difficulty in replicating previous findings from European populations can be attributed to different allele frequencies and linkage disequilibrium patterns in men of African and European descent and the modest sample sizes used in the replication studies. We describe association results for 24 SNPs, from regions previously identified to be associated with prostate cancer, based on a population-based sample of 127 unrelated African American prostate cancer cases and 345 unrelated disease-free controls. We show nominal evidence ($P < 0.05$) for association between prostate cancer and several 8q24 (rs6983561, rs16901979, and rs7000448) and 10q11 (rs7904463 and rs10740051) SNPs.

MATERIALS AND METHODS

The Flint Men's Health Study (FMHS)

In 1996, a probability sample of African-American men was selected from households located in Genesee County, Michigan to participate in a study of prostate cancer [10,11]. Seven hundred thirty eligible subjects were provided a detailed in-home interview and an option to participate in a comprehensive urologic examination (digital rectal exam (DRE), transrectal ultrasound (TRUS), and a screening serum PSA measurement). Prostate biopsy was recommended in individuals with an elevated PSA ($\geq$4.0 ng/ml) or suspicious DRE. Three hundred seventy-nine of the 730 men who completed the interview participated in the clinical examination component of the study. After exclusion of men who were determined to be biopsy positive for prostate cancer at baseline and/or who subsequently developed prostate cancer after baseline (included in the present analyses as cases), a sufficient DNA sample was available for genotyping on 345 of the remaining controls.

Prostate cancer case recruitment from the same community was initiated in 1999. Eligible men include those who were between the ages of 40–79 at time of prostate cancer diagnosis (between 1995 and 2002). Cases completed a detailed epidemiologic interview and provided a blood sample. Diagnosis of prostate cancer was confirmed by review of pathology reports or medical records, and age at diagnosis calculated from the date of the first biopsy positive for prostate cancer.

A total of 136 cases were ultimately recruited to participate in the study. A sufficient DNA sample was available for genotyping on 127 cases. Informed consent was obtained from all study participants and the research protocol was approved by the University of Michigan Institutional Review Board. For both cases and controls, genomic DNA was isolated from whole blood using the Puregene DNA Purification Kit (Gentra Systems, Inc., Minneapolis, MN).

Genotyping Methods

We genotyped 24 SNPs, in 127 FMHS cases and 345 FMHS controls. Genomic DNA was isolated from whole blood using the Puregene kit (Gentra Systems, Inc.). The 24 SNPs were genotyped using Taqman SNP Genotyping Assays (Applied Biosystems, Foster City, CA). Briefly, these assays consisted of a 40× mix of PCR primers and dye-labeled TaqMan MGB probes that were designed to interrogate a specific SNP within a given sequence. PCR reactions were conducted in a 384-well plate format, with 2.0 μl genomic DNA (5 ng/μl), 0.125 μl 40× SNP Genotyping Assay Mix, and 2.5 μl Taqman Genotyping PCR Mastermix (Applied Biosystems) for a 5 μl total volume reaction. All assays were optimized to use a universal thermal cycling protocol with an initial hold at 95°C for 10 min, followed by 40 cycles of denaturation at 92°C for 15 sec, and a combined annealing extension step at 60°C for 1 min. Allelic discrimination was carried out using the ABI PRISM 7900HT Sequence Detection System and the SDS version 2.1 software (Applied Biosystems). Approximately 5% of the samples were duplicated on this platform for verification purposes. No discrepancies were observed. Results for one SNP, rs1447295 at 8q24, were reported previously [12].

Statistical Analyses

For each SNP, the observed genotype distribution was tested for consistency with Hardy–Weinberg equilibrium expected proportions using Pearson's chi-square test. Lewontin's D′ statistic [13] and the squared correlation statistic r^2 were used to estimate the degree of linkage disequilibrium and correlation between all possible pair-wise combinations of SNPs in the same chromosomal region using the computer software Haploview [14]. Estimated proportion of West African ancestry for each study participant was obtained using the statistical software Structure [15] as described previously [12].

Unconditional single-variable and multivariable logistic regression models were used to test whether individual SNP genotypes were associated with prostate cancer using likelihood ratio tests implemented in SAS (SAS version 9.1, Cary NC). Specifically, we conducted a 1 degree-of-freedom test assuming a multiplicative (or log-additive) genetic model. Genotype was scored as the number of copies of the allele previously described as the risk allele in prostate cancer studies of men of European descent. In addition to unadjusted logistic models, covariate-adjusted models were also analyzed including age and the estimated proportion of West African ancestry. Finally, for chromosomal regions that contained at least 1 nominally significant SNP result ($P < 0.05$), additional analyses were performed: a joint analysis of SNPs in the proximity of the associated SNP to assess the cumulative evidence of association in the region and multivariable logistic regression analyses that included the most strongly associated SNP as a covariate to assess whether there was evidence for multiple independently associated SNPs in the region.

RESULTS

The sample consisted of 472 (127 prostate cancer cases, 345 disease-free controls) African-American subjects with both genotype and phenotype data. Median age overall was 58 years (interquartile range = 50–67) with cases being older than controls (cases median age = 62 years, interquartile range = 55–69.5; controls median age = 55 years, interquartile range = 49–69; $P < 10^{-7}$). 19.7% of cases and 20.2% of controls reported a family history of prostate cancer in a first degree relative. There was no statistical difference in mean percent African descent between cases (70.3%) and controls (70.9%). Characteristics for the 127 prostate cancer cases are presented in Table I.

All 24 SNPs had observed genotype frequencies consistent with Hardy–Weinberg equilibrium expected proportions ($P > 0.001$) in study controls. Nominal evidence (two-sided $P < 0.05$) for association between prostate cancer and genotype was observed for 5 SNPs (rs6983561, rs16901979, and rs7000448 at 8q24; rs7904463 and rs10740051 at 10q11) using unadjusted logistic regression models (Table II). Results were similar for multivariable models that included covariate adjustment for age and estimated proportion of West African ancestry (data not shown). Four SNPs that have been previously reported to be associated with prostate cancer (exception rs10740051) had direction of effects that were consistent with previous reports. Rs10740051 had a higher frequency of the minor allele in controls, which appears to contradict a previous report by Chang et al. [16] that reported results based on imputed genotype data for this SNP in an European case–control sample (see the Discussion Section). Estimates of the linkage disequilibrium measures D′ and r^2 for SNPs at 8q24 and 10q11 are presented in Table III.

Multiple-SNP models for 8q24-associated SNPs suggested that the observed single-SNP associations between rs6983561 and rs16901979 and prostate cancer represent the same association signal. When modeling rs16901979 jointly with rs6983561, there was overall evidence for an association between the two SNPs and prostate cancer ($P = 0.0079$ for the 2 degree-of-freedom

TABLE I. Characteristics of Men With Prostate Cancer (n = 127)

Characteristic	Median [interquartile range] or n (%)
Age at diagnosis (years)	62 [55–69.5]
Serum prostate-specific antigen at diagnosis (ng/ml)	6.3 [4.3–11.925]
Surgery	69 (54.3)
Family history[a]	25 (19.7)
Stage[b]	
Localized	97 (78.2)
Locally advanced	21 (16.9)
Metastatic	6 (4.8)
Gleason	
5–6	35 (28.7)
7	74 (60.7)
8–10	13 (10.7)
Clinically aggressive prostate cancer[c]	45 (35.4)

[a]Family history defined as PCa diagnosed in a first-degree relative.
[b]Localized = T1 or T2, N0, and M0, or PSA > 20 ng/ml if treated w/o surgery; locally advanced = T3 or T4, N0, and M0, or PSA < 20 ng/ml or >100 ng/ml; metastatic = N1, or M1, or PSA > 100 ng/ml if treated w/o surgery.
[c]Gleason > 7, or T3b or T4; Gleason = 7; and pos surgical margin or PSA >10, or >15 ng/ml, or M1.

TABLE II. Association Results Assuming a Multiplicative Model

SNP	CHR	BP	Risk allele[a]	Frequency in cases	Frequency in controls	Odds ratio (95% CI)[b]	2-sided *P*-value	1-sided *P*-value[c]
rs721048 (A/G)	2p15	63,043,382	A	0.03	0.03	0.98 (0.40, 2.18)	0.96	0.52
rs9364554 (C/T)	6q25	160,804,075	T	0.07	0.06	1.11 (0.59, 2.00)	0.74	0.37
rs10486567 (A/G)	7p15	27,749,803	G	0.75	0.72	1.16 (0.83, 1.64)	0.38	0.19
rs3747531 (C/G)	8p22	16,057,019	G	0.05	0.07	0.69 (0.33, 1.34)	0.28	0.86
rs1016343 (C/T)	8q24	128,162,479	T	0.17	0.20	0.78 (0.52, 1.16)	0.22	0.89
rs13254738 (A/C)	8q24	128,173,525	C	0.68	0.63	1.24 (0.91, 1.70)	0.17	0.085
rs6983561 (A/C)[d]	**8q24**	**128,176,062**	**C**	**0.56**	**0.45**	**1.55 (1.15, 2.09)**	**0.0039**	**0.0020**
rs16901979 (A/C)	**8q24**	**128,194,098**	**A**	**0.54**	**0.42**	**1.60 (1.17, 2.19)**	**0.0030**	**0.0015**
rs6983267 (G/T)	8q24	128,482,487	G	0.93	0.88	1.64 (0.99, 2.87)	0.057	0.028
rs7000448 (C/T)	**8q24**	**128,510,352**	**T**	**0.73**	**0.65**	**1.41 (1.03, 1.94)**	**0.030**	**0.015**
rs1447295 (A/C)	8q24	128,554,220	A	0.32	0.31	1.03 (0.75, 1.41)	0.84	0.42
rs4242382 (A/G)	8q24	128,586,755	A	0.33	0.34	0.98 (0.73, 1.31)	0.90	0.55
rs10090154 (C/T)	8q24	128,601,319	T	0.18	0.17	1.04 (0.72, 1.49)	0.82	0.41
rs10993994 (C/T)	10q11	51,219,502	T	0.65	0.61	1.18 (0.87, 1.60)	0.29	0.15
rs7904463 (C/T)	**10q11**	**51,229,475**	**T**	**0.72**	**0.64**	**1.42 (1.05, 1.96)**	**0.024**	**0.012**
rs10740051 (A/G)	**10q11**	**51,240,158**	**A**	**0.07**	**0.13**	**0.51 (0.29, 0.85)**	**0.0088**	**1.00**
rs4962416 (C/T)	10q26	126,686,862	C	0.12	0.16	0.73 (0.47, 1.12)	0.16	0.92
rs7931342 (G/T)	11q13	68,751,073	G	0.80	0.80	1.01 (0.71, 1.46)	0.96	0.48
rs10896449 (A/G)	11q13	68,751,243	G	0.70	0.70	0.98 (0.73, 1.34)	0.90	0.55
rs4430796 (A/G)	17q12	33,172,153	A	0.35	0.35	1.03 (0.76, 1.40)	0.84	0.42
rs7501939 (C/T)	17q12	33,175,269	C	0.48	0.48	1.00 (0.75, 1.33)	0.99	0.50
rs1859962 (G/T)	17q24	66,620,348	G	0.29	0.31	0.92 (0.68, 1.23)	0.56	0.72
rs2735839 (A/G)	19q13	56,056,435	G	0.68	0.69	0.95 (0.70, 1.31)	0.77	0.62
rs5945619 (C/T)	Xp11	51,074,708	C	0.41	0.38	1.08 (0.87, 1.33)	0.48	0.24

rs1447295 results reported previously in Amundadottir et al. [12]
[a]As reported previously in European Americans or in Xu et al. [9]
[b]Increased/decreased odds for each additional copy of risk allele.
[c]1-sided test based on previously reported risk allele.
[d]SNPs in bold were nominally associated with prostate cancer ($P < 0.05$).

TABLE III. Estimated Pairwise-Linkage Disequilibrium for Chromosomes 8q24 and 10q11 SNPs in FMHS Samples (R^2 Above Diagonal/D' Below Diagonal)

CHR 8	rs1016343	rs13254738	rs6983561	rs16901979	rs6983267	rs7000448	rs1447295	rs4242382	rs10090154
rs1016343	—	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
rs13254738	0.00	—	0.24	0.22	0.03	0.02	0.03	0.01	0.00
rs6983561	0.07	0.68	—	0.79	0.06	0.03	0.03	0.00	0.01
rs16901979	0.10	0.69	0.94	—	0.05	0.03	0.02	0.00	0.00
rs6983267	0.08	0.35	0.73	0.69	—	0.12	0.03	0.01	0.02
rs7000448	0.13	0.14	0.26	0.28	0.70	—	0.02	0.02	0.02
rs1447295	0.01	0.31	0.22	0.16	0.79	0.31	—	0.00	0.05
rs4242382	0.03	0.16	0.08	0.03	0.49	0.29	0.02	—	0.37
rs10090154	0.02	0.19	0.16	0.07	0.93	0.49	0.33	0.94	—

CHR 10	rs10993994	rs7904463	rs10740051
rs10993994	—	0.01	0.00
rs7904463	0.19	—	0.02
rs10740051	0.04	0.24	—

(df) test), but neither SNP was individually associated with prostate cancer and their associated odds ratios attenuated considerably compared to when the SNPs were modeled individually (data not shown). In the two-SNP model that included rs16901979 and rs7000448, there was evidence for an overall association ($P = 0.0036$ for the 2 df test) between these two SNPs and prostate cancer, rs16901979 remained significantly associated with prostate cancer ($P = 0.0081$; OR = 1.53), but rs7000448 but was no longer individually significantly associated with prostate cancer ($P = 0.14$, OR = 1.30).

Multiple-SNP models for SNPs at 10q11 near *MSMB* provided marginal evidence for multiple independently associated SNPs in the region. We performed two (rs7904463 and rs1074005) and three (addition of rs10993994) SNP logistic regression models in the region. The overall evidence for an association remained similar to when rs1074005 was analyzed alone (Table II) for the two ($P = 0.0070$ for the 2 df test) and three ($P = 0.0087$ for the 3 df test) SNP models. In both the two and three SNP models, rs1074005 remained nominally significantly associated with prostate cancer ($P = 0.027$ in both models) with only slight attenuation of the SNP's associated odds ratios (OR = 0.54 in both models) compared to the observed odds ratio when the SNP was analyzed alone (OR = 0.51). In the two and three SNP models, statistical significance and associated odds ratios for rs7904463 decreased modestly ($P = 0.069$ and OR = 1.34 for the 2 SNP model; $P = 0.054$ and OR = 1.37 for the three SNP model). The widely reported rs10993994 was not associated with prostate cancer in the three SNP model ($P = 0.21$, OR = 1.23), though the direction and size of the effect were similar to previous prostate cancer association studies in European Americans.

DISCUSSION

We describe results for a prostate cancer association study from a community-based sample of African American men on 24 SNPs found in regions previously reported to be associated with prostate cancer in men of European descent. We found nominal evidence for an association between prostate cancer and SNPs at 8q24 (rs6983561, rs16901979, and rs7000448) and 10q11 (rs7904463 and rs10740051) near *MSMB*. Our results at 8q24 replicate findings from other African American prostate cancer association studies that have found evidence for associated SNPs in the region [7,9]. The signals for the two most strongly associated SNPs at 8q24, namely rs6983561 (8q24 region 2) and rs16901979 (8q24 region 2), were not independent given the strong LD between the two SNPs (Table III) and the strongly attenuated odds ratios for each SNP when including both in the same model (data not shown). The nominal evidence for association at rs7000448 (8q24 region 3) disappeared when including rs16901979 in the model. However, the associated odds ratio for rs7000448 remained relatively high (OR = 1.30 in the two SNP model compared to OR = 1.41 when rs7000448 was analyzed separately) after adjustment for rs16901979, suggesting that there is more than one independent risk factor in the region and that we had low power to detect one risk factor in the presence of the other.

Our study is the first study to report an association between SNPs at (rs7904463) and near (rs10740051) *MSMB* and prostate cancer in African American men. Interestingly, our most strongly associated SNP at 10q11, rs10740051, is in a neighboring gene *NCOA4*. This SNP is in LD with rs10761581 [estimated R^2/D' in HapMap CEU = 0.58/1.00, YRI = 0.15/1.00] (www.hapmap.org), which was suggested by Chang et al. [16] to be a second independent locus near *MSMB* to be associated with prostate cancer. *NCOA4* [otherwise known as ARA70] is an interesting candidate gene because it is known to increase androgen receptor transcriptional activity in human prostate cancer cells [17]. Chang et al. evaluated imputed genotype data for rs10740051 and found nominal evidence of association with prostate cancer ($P = 0.036$). Consistent with Chang et al., our results at rs10740051 appear to be independent of results for the widely reported *MSMB* SNP rs10993994, which was not significant in our study despite having an estimated odds ratio that was identical in direction and similar in magnitude to previous reports in European Americans. The direction of effect for rs10740051 appears to differ between our findings and those of Chang et al., with the minor allele in our study being less frequent in African American cases. The frequency of the minor allele for rs10740051 was also lower in our African American controls (0.13) than in the European American controls used by Chang et al. (estimated based on imputation to be 0.24 using CEU HapMap samples as the reference sample; frequency = 0.36 in CEU samples). The quality score of the imputed genotype data was not reported for this SNP in Chang et al. It remains a question whether our result at rs10740051 represents corroboration of a second independent locus near *MSMB* or a false positive finding.

A major limitation with prostate cancer studies on African Americans has been small sample sizes for individual studies. One obvious ramification of limited sample size is the impact on statistical power to detect significant genetic effects when present. Our study is not immune to this limitation and we note in most instances that our effect size estimates, presented as odds ratios and their associated 95% confidence intervals, were not significantly different than those

from previous prostate cancer association reports based on European ancestry populations. None of our top results would meet formal statistical significance if a strict Bonferroni significance threshold were applied to our findings using two-sided hypothesis tests. We note however that we have identified two independent regions containing SNPs with evidence of association ($P < 0.01$). Further, we note that results at 8q24 for two SNPs (rs6983561 and rs16901979) would be statistically significant after Bonferroni correction using one-sided hypothesis tests that factored in the consistent direction of effects observed for these SNPs in this report with those from previous reports. Future larger meta-analyses will be necessary to definitively assess the association of common genetic variants with prostate cancer in African American men. Given the relatively small number of African American prostate cancer cases available to genetic researchers, the FMHS will continue to be a valuable resource for identifying and validating genetic variants associated with prostate cancer in this understudied population.

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