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Chromosome 8q24 Variants Are Associated With Prostate Cancer Risk in a High Risk Population of African Ancestry

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Abstract

BACKGROUND—Earlier studies on the role of germline variations in the disproportionate higher burden of prostate cancer in men of African ancestry have been largely unrewarding. However, the successful replication of recent genome-wide association findings implicating some regions of chromosome 8q24 in the disparate prostate cancer susceptibility in men of European and African ancestry have been encouraging. This case–control study was designed to evaluate the association between germline variations in chromosome 8q24 and prostate cancer risk in Afro-Caribbean Tobago men, a population of predominantly West African ancestry.

METHODS—High molecular weight genomic DNA was isolated from blood clots using Qiagen kits. Genotyping was performed on genomic DNA using a pre-designed TaqMan SNP assay according to the manufacture's protocol on a 7900HT Fast Real-Time PCR system (Applied Biosystems, Foster City, CA).

RESULTS—SNP rs16901979 in region 2 was associated with significantly increased risk of prostate cancer (OR = 1.41, 95% confidence interval [CI] 1.02–1.95, $P = 0.04$) with the risk stronger in men with early-onset prostate cancer (OR = 2.37, 95% CI 1.40–3.99, $P = 0.001$). There was a tendency towards significantly increased risk for SNPs rs1447295 and rs6983267 in men with early-onset prostate cancer.

CONCLUSIONS—The replication of the association of chromosome 8q24 variants with increased prostate cancer risk in Tobago men and the higher frequency of the risk alleles in controls in populations of African ancestry further strengthens the possible role of this genomic region in the disproportionate higher burden of prostate cancer in men of African ancestry.

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Keywords

Tobago prostate survey; Afro-Caribbean men; germline variations

INTRODUCTION

In the United States (US), an estimated 27,130 new cases of prostate cancer were expected to be diagnosed in African American men in 2009, constituting 34% of all new cancers in African American males for that year 1. Between the years 2001 and 2005, the incidence of prostate cancer in African American men (248.5 per 100,000) was 1.6 times that in White men (156.7 per 100,000) and 2.6 times that in men of Asian/Pacific Island descent [1]. Data from the same period also show that African American men were 2.4 times as likely to die from prostate cancer compared to White men in the US. We [2,3] and others [4–7] have reported similar high rates of prostate cancer incidence and mortality in other populations of African ancestry in the Caribbean and the United Kingdom.

Little is currently known about what causes prostate cancer; age, a positive family history of the disease and ethnic background are the only established risk factors. There is no doubt that genetic factors play some role in etiology of prostate cancer. However, effort to decipher the contribution of germline mutations to prostate cancer risk and its contribution to the disproportionate higher burden of the disease in men of African ancestry has been hampered by the poor yield of research in this area in the past two decades. Determining genetic variants that indisputably affect prostate cancer risk has proven challenging. Studies of candidate genes have detected a number of associations, but in general these have not been widely replicated—and such studies, by their very focus, necessarily ignore most of the genome [8].

The situation, however, improved slightly in the past decade with the landmark linkage studies of Amundadottir et al. [9] among Icelandic families and admixture mapping in African American men by Freedman et al. [10]. Employing genome-wide linkage analysis among Icelandic families with prostate cancer Amundadottir et al. [9] initially demonstrated a linkage signal at chromosome 8q24. Using positional cloning techniques, these authors traced the risk variants to allele -8 of the microsatellite DG8S737, a dinucleotide AC repeat located within a linkage disequilibrium (LD) block that spans 92 kb on chromosome 8q24.21 (128.414–128.506 Mb, NCBI Build 34) in the Utah Centre d'Etude du Polymorphisme Humain (CEPH) Europeans (CEU) HapMap samples. Further exploration implicated the A allele of SNP rs1447295 located within the same LD block as contributing to prostate cancer risk. These findings were replicated in three other populations of European ancestry but only the microsatellite repeat was significant among African American men. Although Freeman et al. [10] detected an admixture signal in the same chromosomal region of 8q24, these authors failed to replicate the findings of increased risk of prostate cancer associated with -8 allele of DG8S737 and rs1447295 detected by Amundadottir et al. in African American men suggesting a role for other risk variants at chromosome 8q24. Subsequent fine mapping by the same group led to the detection of risk alleles in adjacent regions of chromosome 8q24, designated regions 2 and 3.

These significant findings in the three regions of chromosome 8q24 were subsequently replicated in several genome-wide association studies (GWAS) employing a wide array of study designs and spanning different population groups. Although the risk alleles detected in regions 2 and 3 of chromosome 8q24 were found to account for the admixture signal detected in African Americans by Freedman et al. [10], there were concerns on the interpretation of the current results with many investigators in the field recommending more studies in diverse populations to fully explore the chromosome 8q24 regions. All the current studies on chromosome 8q24 risk alleles in populations of African ancestry are conducted predominantly in African American populations. A pertinent question is how these chromosome 8q24 risk alleles might influence prostate risk in other populations of African descent that share similar high prostate cancer risk but reside outside of the US and may have differing environmental exposure. To consolidate on the gains of the advances so far made on chromosome 8q24, we sought to evaluate the association of risk alleles in the three distinct regions of 8q24 with prostate cancer risk in Tobago men, a population of predominantly West African ancestry with little admixture [11]. Using informative ancestral markers, we and others have shown that Tobago men share genetic ancestry with African American men [11].

MATERIALSANDMETHODS

Population

This case–control study is based on data from The Tobago Prostate Cancer Survey, an ongoing population-based prostate cancer screening survey of all males, aged 40–79 years, on the Caribbean island of Tobago [2]. The first round of screening was completed in 2001 and second and thirds rounds were conducted in 2002–2003 and 2004–2007, respectively. Participants for the current study comprised 354 men with screening-detected prostate cancer and 438 non-cases with prostate-specific antigen (PSA) levels ≤4 ng/ml and normal digital rectal examination (DRE). All men were of Afro-Caribbean origin.

Recruitment

Recruitment relied primarily on public information campaigns and word of mouth. Over 60% of all age-eligible (40–79 years) men on the island have participated in the survey to date and participation is equally representative of all Tobago parishes. There were no specific indications for prostate cancer screening among study participants and no previous prostate cancer screening had ever been completed in this population prior to the current study. Written informed consent was obtained from participants prior to screening. All forms and procedures were approved by the University of Pittsburgh Institutional Review Board and the Institutional Review Board of the Division of Health and Social Services, Tobago House of Assembly.

Data Collection and Prostate Cancer Diagnosis

Detailed questionnaires were administered by trained interviewers. Data collected included ethnicity and other demographics, and medical history of co-morbidities. A detailed description of the prostate cancer screening protocol has been previously published [2]. Briefly, men were screened by DRE and serum PSA (≥4.0 ng/ml). Men with abnormal

screening results underwent sextant ultrasound guided prostate biopsy. Repeat biopsies were performed in cases with high-grade prostatic intraepithelial neoplasia (HGPIN) or atypia. Screening was repeated at 2-year intervals after study entry using the same screening procedures. Prostate carcinoma was confirmed histologically by a pathologist at the University of Pittsburgh Cancer Institute, Department of Pathology.

Case–Control Status

Men with elevated PSA levels or abnormal digital rectal exam and subsequent prostate cancer diagnosis based on biopsy results were classified as cases. Men presenting with a PSA levels <4 ng/ml and a normal digital rectal exam served as controls. Men with elevated PSA or abnormal digital rectal exam who had not undergone biopsy, or for whom biopsy results were normal, were excluded from these analyses in order to avoid possible misclassification of men with occult prostate cancer. All males with a prostate cancer diagnosis prior to study enrollment were excluded. Due to the small number of men of non-African descent, these analyses were limited to men who reported that three or four grandparents were of African descent.

Molecular Methods

High molecular weight genomic DNA was isolated from blood clots using Qiagen kits. The chromosome 8q24 SNP rs1447295 A → C (Position 128554822, Build 127), SNP rs16901979 A → C (Position 128194098, Build 127), and SNP rs6983267 G → T (Position 1284824487, Build 127) sites were amplified using the TaqMan assays according to the manufacturer's protocol. Genotyping was performed using a pre-designed TaqMan SNP assay (Applied Biosystems, Foster City, CA). Genotyping was completed on genomic DNA according to the manufacture's protocol on a 7900HT Fast Real-Time PCR system (Applied Biosystems). The reactions were cycled with standard TaqMan conditions (95°C for 10 min, 45 cycles of 95°C for 15 sec and 60°C for 1 min, and final cool down to 4°C). The genotypes were called with the Applied Biosystems SDS 2.2.2 software package. The average genotyping completeness rate was 95.6% and the average genotyping consensus rate among the 8.86% blind replicate samples was 99.2%, for both studies. Genotypes were in Hardy–Weinberg equilibrium in both study populations ($P > 0.05$). The C numbers for the chromosome 8q24 SNPs are: C__33280526_10 for rs16901979, C__2160574_10 for rs1447295, and C__29086771_20 for rs6983267.

Statistical Analysis

Allele frequencies were estimated in cases and non-cases by gene counting, and departures from Hardy–Weinberg equilibrium were tested by chi-square goodness of fit statistics. Standardized linkage disequilibrium values (D′) were calculated for pairs of alleles at the chromosome 8q24 SNP rs1447295, SNP rs16901979, and SNP rs6983267 sites. We compared the characteristics of cases and non-cases using *t*-tests for continuous measures and chi-square tests for categorical variables. Differences in PSA between cases and non-cases were evaluated with a Wilcoxon rank sum test due to the skewed distribution of PSA. We used logistic regression models to estimate odds ratios (OR) and 95% confidence intervals (CI) for the associations between the chromosome 8q24 SNPs rs1447295,

rs16901979 and rs6983267 genotypes and prostate cancer. For rs1447295 and rs16901979, men with the C/C genotype formed the referent groups while for rs6983267 the referent group was the rs6983267 G/G genotype in these analyses. The logistic regression analysis was also carried out in men with early-onset prostate cancer. Statistical analyses were performed using the R Statistical Software Package.

RESULTS

Association of Chromosome 8q24 SNPrs1447295 (Region1) and Prostate Cancer Risk

The genotyping assays for chromosome 8q24 SNP rs1447295 were successful in 354 cases and 438 controls. As shown in Table I, the SNP rs1447295 is highly polymorphic in Tobago men. The C allele was more common in cases (0.67) than in controls (0.63) while the "at risk" A allele was less common in cases (0.33) compared to controls (0.37). Also, the genotype frequencies in cases (0.44, 0.46, and 0.10, for C/C, C/A, and A/A genotypes, respectively) were slightly different from the distribution of these genotypes in control subjects (0.40, 0.47, and 0.13 for the C/C, C/A, and A/A genotypes, respectively). The distribution of the allele and genotype frequencies of this SNP in men with early-onset prostate cancer (≤65 years at diagnosis) was similar to the frequencies reported above for all study participants as shown in Table II. SNP rs1447295 was not associated with prostate cancer risk overall (odd ratio [OR] = 0.83, 95% CI 0.62–1.10, $P = 0.19$) or in men diagnosed with prostate cancer at age ≥ 65 years (OR = 0.80, 95% CI 0.53–1.21, $P = 0.29$) as shown in Tables I and II, respectively.

Association of Chromosome 8q24 SNPrs16901979 (Region 2) and Prostate Cancer Risk

The genotyping assays for chromosome 8q24 SNP rs16901979 variant were successful in 338 cases and 426 control subjects. The chromosome 8q24 SNP rs16901979 variant was found to be highly polymorphic in the study population as shown in Table I. Allele frequencies for the C and the "at risk" A alleles were 0.47 and 0.53, respectively, among the cases and 0.54 and 0.46, respectively, among the control subjects. Frequencies for the C/C, C/A, and A/A genotypes in the cases (0.24, 0.47, and 0.29, respectively) were different from the distribution of these genotypes in the control subjects (0.31, 0.45, and 0.24, respectively). When compared with the homozygous C/C genotype carriers, individuals harboring A/A genotype had significantly increased risk of prostate cancer (OR = 1.57, 95% CI 1.06–2.32, $P = 0.02$). Harboring at least one "at risk" A allele (C/A + A/A genotypes) was associated with 41% increased risk of prostate cancer in Tobago men as shown in Table I (OR = 1.41, 95% CI 1.02–1.95, $P = 0.03$). This risk was more pronounced in men with early-onset prostate cancer (age at diagnosis ≤65 years) who had over twofold increased risk of prostate cancer as shown in Table II (OR = 2.21, 95% CI 1.30–3.75, $P = 0.003$, for the C/A genotype; OR = 2.46, 95% CI 1.38–4.37, $P = 0.002$, for men harboring the A/A genotype and OR = 2.30, 95% CI 1.40–3.77, $P = 0.001$, for the combined C/A and A/A genotypes). There was a dose effect with men carrying the homozygous A/A genotype at much higher risk of disease compared with men with the heterozygous C/A genotype.

Association of Chromosome 8q24 SNPrs6983267 (Region 3) and Prostate Cancer Risk

As shown in Table I, the rs6983267 variant was less polymorphic in Tobago men with allele frequencies of 0.95 and 0.05 for the G and T alleles, respectively, among the cases and 0.94 and 0.06 for the G and T alleles, respectively, among the control subjects. The distribution of the G/G, G/T, and T/T genotypes were not significantly different in cases (0.90, 0.11, and 0.005, respectively) and controls (0.88, 0.12, and 0.002, respectively). Only two cases and one control were homozygous for the T/T genotypes. In the logistic regression model, carrying the "at risk" T allele was not associated with increased risk of prostate cancer overall (OR = 0.83, 95% CI 0.53–1.29, $P = 0.40$) or in men with early-onset prostate cancer (age at diagnosis ≤65 years) (OR = 0.73, 95% CI 0.35–1.52, $P = 0.40$) as shown in Table II.

DISCUSSION

The search for genetic factors in prostate cancer susceptibility has been very challenging. Several earlier risk germline mutations reported in different population/racial groups could not be replicated in others. In addition, progress in the field of genome research has been hampered by the small sample sizes of earlier studies and the limited computational and bioinformatics tools and skills previously available. All these appear to be changing in the past decade. Progress in the Human Genome Project and advances in computational and bioinformatics techniques have permitted large-scale GWAS [8,9,12,13]. These GWAS studies have paved way for progress in the search for relevant germline mutations in prostate cancer etiology.

The distributions of chromosome 8q24 risk alleles in the Tobago control population parallels reports in the HapMap and the findings of various previous studies. The SNP rs1447295 (Position 128554822, Build 127, region 1) "at risk" A allele frequency of 0.37 in Tobago is similar to figures (range 0.31–0.39) reported in various populations of African ancestry [9,14,15] but considerably higher than the allele frequencies in European men (range 0.07–0.13) [9,12,13], Latinos (0.10), Native Hawaiians (0.16), and Japanese American men (0.17) [10] (Table III). Similarly, the "at risk" A allele frequency for rs16901979 (Position 128194098, Build 127, region 2) of 0.46 in Tobago controls is slightly lower than the 0.54 reported for Nigerian Yoruban (HapMap) but slightly higher than the frequencies in African American populations (0.33, Southwest USA [HapMap]; 0.42, Washington, D.C. 14; 0.42, Baltimore; 0.41 [12], King County, Seattle 15). Remarkably, the frequencies in populations of African ancestry are approximately 10-fold higher than the frequencies reported in controls in European populations (range 0.02–0.04) [12,15] as shown in Table IV. Likewise, we notice wide variation in the frequency of the T allele of rs6983267 (Position 1284824487, Build 127, region 3) between control populations of African ancestry (0.06, Tobago; 0.02, Nigerian Yoruban [HapMap]; 0.11, African Americans in King County, Seattle 15) and various populations of European ancestry (0.50) [13,15,16] (Table V).

Allele A of rs1447295 was not associated with risk of prostate cancer in Tobago men. Our findings support the reports of most studies that have evaluated rs1447295 in most populations of African ancestry. In a case–control study of 246 African American men with prostate cancer and 352 controls in Michigan, Amundadottir et al. [9] failed to replicate the association of the SNP rs1447295 A allele with prostate cancer. Similarly, Freedman et

al. [10] found no association of the A allele with prostate cancer among 989 African American men with prostate cancer and 804 controls (OR, 1.05; 95% CI = 0.95–1.16, *P* = 0.15). Likewise, Gudmundsson et al. [12] (OR, 1.01; 95% CI = 0.81–1.25, *P* = 0.96), Cheng et al. [15] (OR, 0.87, 95% CI = 0.55–1.40, *P* = 0.87) and Salinas et al. [16] (OR, 1.19; 95% CI = 0.66–2.14) all found no association of allele A of SNP rs1447295 with prostate cancer risk in African American men (Table III). However, in a recent meta-analysis by Cheng et al. [15], the authors reported that African American men carrying the "at risk" A allele were at increased risk of prostate cancer.

Our finding of increased risk of prostate cancer in men carrying the "at risk" A allele of rs16901979 in region 2 of chromosome 8q24 in Tobago men is in agreement with reports of several other investigators in both populations of African [12,14,15] and European ancestry [12,15]. However, Cheng et al. [15] reported a non-significant 37% increased risk of prostate cancer among African American men in King County, Seattle; the lack of association may be due to the small sample size of their study. Across various populations of European ancestry, the A allele of SNP rs16901979 is significantly associated with increased risk of prostate cancer [12,15]. The finding of a stronger association of rs16901979 with early-onset prostate cancer (age at diagnosis ≤65 years) has been similarly reported by other investigators among African Americans and Caucasians suggesting that carriers of rs16901979 A allele are at increased risk for early-onset cases in both populations.

We did not detect any association of allele T of rs6983267 in region 3 of chromosome 8q24 with prostate cancer risk in Tobago men similar to the findings of some investigators that have evaluated this SNP in populations of African ancestry. Cheng et al. [15] reported no association between this SNP and prostate cancer risk among 89 African American men with prostate cancer and 89 controls in King County, Seattle. Robbins et al. [14] noted a tendency towards significance for the G allele among African American men in Washington, D.C. with prostate cancer (OR, 1.4; 95% CI = 0.9–2.4, *P* = 0.07). Among all populations of European ancestry evaluated to date, the G allele of rs6983267 is significantly associated with increased risk of prostate cancer. In a GWAS study of 550,00 SNPs in 1,172 European American men with prostate cancer and 1,157 controls in the Prostate, Lung, Colon and Ovarian (PLCO) Trial [17,18], Yeager et al. [13] reported significant association of the G allele of rs6983267 with prostate cancer risk. These authors also replicated the findings of increased risk of prostate cancer associated with the G allele in four other studies among men of European ancestry [19–22] (Table V). Similarly, Cheng et al. [15] replicated the strong association of the G allele of rs6983267 with prostate cancer risk among European Americans in Seattle, Washington (OR, 1.39; 95% CI = 1.14–1.70, *P* = 0.001).

In a recent meta-analysis, Cheng et al. [15] evaluated the association of these three risk alleles in chromosome 8q24 with prostate cancer in populations of both European and African ancestry. All three variants were significantly associated with prostate cancer risk in all groups combined and as well in stratified analysis of populations of European and African ancestry [15]. These authors reported that combining the effects of these three SNPs with that of the −8 allele of micro-satellite DG8S737 in region 1 of chromosome 8q24 gave an estimated joint population attributable fractions of 15% and 41% in European and African populations, respectively [15]. Some of the reported differences in the association of

chromosome 8q24 risk alleles with prostate cancer risk between populations of European and African ancestry might be related to differences in the LD block structure in chromosome 8q24 in the two populations. Examination of a 92-kb LD block in chromosome 8q24.21 in the Nigerian Yoruban (YRI) Hapmap sample by Amundadottir et al. [9] revealed both greater genetic diversity and weaker LD in the YRI sample than in populations of European ancestry. Such greater genetic diversity in African populations could provide greater resolution to pinpoint the unknown prostate cancer risk variants in chromosome 8q24.

Despite the evidence for a role for chromosome 8q24 variants in prostate cancer risk, the direct biological mechanisms for this association remain largely obscure. The three genomic regions on chromosome 8q24 showing association to prostate cancer are in a gene-poor area. Two known genes, FAM84B (also known as NSE2) and c-MYC oncogene (a key regulator in cellular proliferation), are located centromeric and telomeric to this interval, respectively, but most studies have not observed any association between variants of these genes and prostate cancer [12]. Somatic genetic data independently highlight the chromosome 8q24 region as one of the most frequently amplified regions in prostate tumors [23,24]. Overexpression of c-MYC has been shown to induce tumors in mice and to create a cancer phenotype in benign prostatic epithelium [25,26]. It is possible that c-MYC could be the gene responsible for the prostate cancer risk, but no structural or regulatory variant has yet been identified.

The distal end of the common fragile site 8C (FRA8C) has been mapped to this genomic interval [27], as have multiple integration sites for human papilloma virus in cervical cancer [28]. Although studies investigating the role of HPV infections in the development of prostate cancer have yielded conflicting results [29], the current results warrant further investigation into this issue. In addition, the fact that chromosome 8q24 is the most frequently gained chromosomal region in prostate tumors [30] raises the possibility that the risk variants described here could predispose to prostate cancer through increased genomic instability. Recently, Jia et al. [31] have provided data suggesting that the chromosome 8q24 variants could influence prostate cancer risk through epigenetic mechanisms. Using a combination of high-density tiling arrays, transcript and epigenetic profiling, and computational analysis, these authors identified several transcript enhancers within the same chromosome 8q24 regions associated with prostate cancer; two of these transcript enhancers interact with the androgen receptor to facilitate both stronger FoxA1 and androgen responsiveness.

The findings reported here and in other studies [10,13,32] could have substantial public health implications, as the associated variants may explain a large proportion of prostate cancers and the higher disease risk among African Americans. Whereas the individual associations of the chromosome 8q24 variants with prostate cancer are relatively modest, a combination of multiple variants showed considerably larger associations [13,32]. Furthermore, the risk alleles are fairly common, especially among populations of African ancestry, raising the possibility of higher population attributable risks in men of African descent. Further functional studies are recommended to unravel the mechanisms of increased prostate cancer risk associated with chromosome 8q24 variants.

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TABLE I

Distribution of 8q24 Genotypes in Relation to Prostate Cancer Risk

	Cases (n = 354)	Controls (n = 438)	OR	95% CI	*P*-value
rs1447295					
rs1447295 (C allele)	0.67	0.63			
rs1447295 (A allele)	0.33	0.37			
rs1447295 (C/C)	156 (44.1)	173 (39.5)	1.00		
rs1447295 (C/A)	162 (45.8)	207 (47.3)	0.87	0.73–1.12	0.35
rs1447295 (A/A)	36 (10.1)	58 (13.2)	0.69	0.43–1.10	0.11
rs1447295 (C/A) + (A/A)	198 (55.9)	265 (60.5)	0.83	0.62–1.10	0.19

	Cases (n = 338)	Controls (n = 426)	OR	95% CI	*P*-value
rs16901979					
rs16901979 (C allele)	0.47	0.54			
rs16901979 (A allele)	0.53	0.46			
rs16901979 (C/C)	81 (24.0)	131 (30.7)	1.00		
rs16901979 (C/A)	158 (46.7)	193 (45.3)	1.32	0.94–1.87	0.11
rs16901979 (A/A)	99 (29.3)	102 (24.0)	1.57	1.06–2.32	0.02*
rs16901979 (C/A) + (A/A)	257 (76.0)	295 (69.2)	1.41	1.02–1.95	0.03*

	Cases (n = 343)	Controls (n = 426)	OR	95% CI	*P*-value
rs6983267					
rs6983267 (G allele)	0.95	0.94			
rs6983267 (T allele)	0.05	0.06			
rs6983267 (G/G)	307 (89.5)	373 (87.6)	1.00		
rs6983267 (G/T)	34 (10.0)	52 (12.2)	0.79	0.50–1.26	0.32
rs6983267 (T/T)	2 (0.5)	1 (0.2)	2.43	0.22–26.93	0.46
rs6983267 (G/T) + (T/T)	36 (10.5)	53 (12.4)	0.83	0.53–1.29	0.40

*Significant predictors of prostate cancer risk.

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TABLE II

Distribution of 8q24 Genotypes in Relation to Prostate Cancer Risk in Men ≤65 Years

	Cases	Controls	OR	95% CI	*P*-value
rs1447295	(n = 156)	(n = 231)			
rs1447295 (C allele)	0.68	0.65			
rs1447295 (A allele)	0.32	0.35			
rs1447295 (C/C)	74 (47.4)	97 (42.0)	1.00		
rs1447295 (C/A)	63 (40.4)	108 (46.8)	0.76	0.50–1.18	0.22
rs1447295 (A/A)	19 (12.2)	26 (11.2)	0.96	0.49–1.86	0.89
rs1447295 (C/A) + (A/A)	82 (52.6)	134 (58.0)	0.80	0.53–1.21	0.29
rs16901979	(n = 151)	(n = 224)			
rs16901979 (C allele)	0.43	0.55			
rs16901979 (A allele)	0.57	0.45			
rs16901979 (C/C)	28 (18.6)	77 (34.4)	1.00		
rs16901979 (C/A)	73 (48.3)	91 (40.6)	2.21	1.30–3.75	0.003*
rs16901979 (A/A)	50 (33.1)	56 (25.0)	2.46	1.38–4.37	0.002*
rs16901979 (C/A) + (A/A)	123 (81.4)	157 (65.6)	2.30	1.40–3.77	0.001*
rs6983267	(n = 149)	(n = 225)			
rs6983267 (G allele)	0.96	0.95			
rs6983267 (T allele)	0.04	0.05			
rs6983267 (G/G)	137 (91.9)	201 (89.3)	1.00		
rs6983267 (G/T)	11 (7.4)	24 (10.7)	0.67	0.32–1.42	0.29
rs6983267 (T/T)	1 (0.7)	0 (0.0)	—	—	—
rs6983267 (G/T) + (T/T)	12 (8.1)	24 (10.7)	0.73	0.35–1.52	0.40

*Significant predictors of prostate cancer risk.

TABLE III

Frequency of A Allele of SNP rs1447295 in Various Populations

Study	No. of cases	No. of controls	Frequency in cases	Frequency in controls	Odd ratios	95% CI	*P*-value
African ancestry							
Bunker et al. [2,3] (Tobago men)	354	438	0.33	0.37	0.83	0.62–1.1	0.19
Robbins et al. [14] (African Americans)	490	567	0.34	0.31	1.4	0.7–1.3	0.131
Gudmundsson et al. [12] (AA, Baltimore)	373	372	0.315	0.313	1.01	0.81–1.25	0.96
Amundadottir et al. [9] (AA, Michig Gleason [7–10]	112	352	0.352	0.313	1.19		0.28
Amundadottir et al. [9] (AA, Michig Gleason [2–6]	121	352	0.341	0.313	1.14		0.43
Freedman et al. [10] (African Americans)	989	804			1.05	0.95–1.16	0.15
Cheng et al. [15] (African Americans)	91	89	0.315	0.320	0.87	0.55–1.40 (adjusted)	0.574 (adjusted)
Salinas et al. [16] (African Americans)	144	79			1.19	0.66–2.14	0.57
European ancestry							
Amundadottir et al. [9] (Iceland) Gleason [7–10]	289	997	0.179	0.106	1.84		7.3×10^{-6}
Amundadottir et al. [9] (Iceland) Gleason [2–6]	548	997	0.170	0.106	1.73		6.7×10^{-7}
Amundadottir et al. [9] (Sweden) Gleason [7–10]	625	779	0.167	0.133	1.29		2.0×10^{-2}
Amundadottir et al. [9] (Sweden) Gleason [2–6]	678	779	0.158	0.138	1.25		3.4×10^{-2}
Amundadottir et al. [9] (European Americans, Chicago) Gleason [7–10]	149	247	0.151	0.081	2.03		2.7×10^{-3}
Amundadottir et al. [9] (European Americans, Chicago) Gleason [2–6]	306	247	0.116	0.081	1.50		5.1×10^{-2}
Gudmundsson et al. [12] Iceland	1,453	3,064	0.165	0.104	1.71	1.49–1.95	1.6×10^{-14}
Gudmundsson et al. [12] Spain	385	892	0.103	0.074	1.44	1.07–1.94	0.017
Gudmundsson et al. [12] The Netherlands	367	1,302	0.144	0.108	1.39	1.09–1.78	9.0×10^{-3}
Gudmundsson et al. (Eur Am, Chicago)	458	251	0.124	0.083	1.56	1.08–2.27	0.019
All Europeans				0.088	1.44	1.21–1.70	2.5×10^{-5}

	No. of cases	No. of controls	Frequency in cases	Frequency in controls	OR (CA)	OR (AA)	*P*-value
Yeager et al. [13] PLCO	1,172	1,157	0.14	0.10	1.42 (1.16–1.73)	2.78 (1.32–5.86)	9.75×10^{-5}
Yeager et al. [13] ACS	1,150	1,142	0.12	0.08	1.53 (1.23–1.90)	2.82 (1.30–6.14)	2.26×10^{-5}
Yeager et al. [13] ATBC	894	896	0.21	0.17	1.24 (1.01–1.52)	1.64 (0.98–2.72)	2.88×10^{-2}

	No. of cases	No. of controls	Frequency in cases	Frequency in controls	OR (CA)	OR (AA)	*P*-value
Yeager et al. [13] FPCC	455	459	0.12	0.07	1.71 (1.20–2.43)	3.11 (0.62–15.71)	4.35×10^{-3}
Yeager et al. [13] HPFS	625	636	0.13	0.09	1.56 (1.18–2.06)	2.51 (0.77–8.20)	2.74×10^{-3}
Yeager et al. [13] ALL	4,296	4,299	0.11	0.11	1.43 (1.29–1.59)	2.23 (1.58–3.14)	1.53×10^{-14}
Freedman et al. [10] (European Americans)	455	447	0.131	0.10	1.35	1.01–1.80	0.022 (one tailed)
Freedman et al. [10] (Latino Americans)	640	567	0.135	0.095	1.48	1.14–1.91	0.0014 (one tailed)
Freedman et al. [10] (Japanese Americans)	449	465	0.238	0.172	1.48	1.18–1.86	0.00034 (one tailed)
Freedman et al. [10] (Native Hawaiians)	70	68	0.370	0.162	3.02	1.66–5.50	0.00015 (one tailed)
Cheng et al. [15] (European Americans)	417	417	0.121	0.092	1.46 (adjusted)	1.06–2.02 (adjusted)	0.020 (adjusted)
Salinas et al. [16] (Caucasians)	1,252	1,263	0.14	0.10	1.36 (1.12–1.65) (GT)	2.08 (1.07–3.95) (TT)	0.0012

TABLE IV

Frequency of A Allele of SNP rs16901979 in Various Populations

Study	No. of cases	No. of controls	Frequency in cases	Frequency in controls	Odd ratios	95% CI	*P*-value
African ancestry							
Bunker et al. [2,3] (Tobago men)	338	426	0.53	0.46	1.41	1.02–1.95	0.03
Robbins et al. [14] (African Americans)	567	490	0.50	0.42	1.15	1.1–2.2	0.008
Gudmundsson et al. [12] (African Americans, Baltimore)	373	372	0.497	0.425	1.34	1.09–1.64	4.9×10^{-3}
Cheng et al. [15] (African Americans)	89	88	0.50	0.41	1.37	0.88–2.13	0.167
European ancestry							
Gudmundsson et al. [12] Iceland	1,453	3,064	0.073	0.042	1.80	1.47–2.20	9.9×10^{-9}
Gudmundsson et al. [12] Spain	385	892	0.066	0.040	1.71	1.49–1.95	1.6×10^{-14}
Gudmundsson et al. [12] The Netherlands	367	1,302	0.034	0.022	1.58	0.96–2.58	0.070
Gudmundsson et al. [12] (European Americans, Chicago)	458	251	0.053	0.023	2.43	1.32–4.50	4.6×10^{-3}
All Europeans				0.028	1.79	1.36–2.34	2.4×10^{-5}
Cheng et al. [15] (European Americans)	417	416	0.052	0.029	1.98	1.18–3.31	0.009

TABLE V

Frequency of T Allele (African Populations) and G Allele (European Populations) of SNP rs6983267

Study	No. of cases	No. of controls	Frequency in cases	Frequency in controls	OR	95% CI	*P*-value
African ancestry							
Bunker et al. [2,3] (Tobago men)	343	426	0.05	0.06	0.83	0.53–1.29	0.40
Robbins et al. [14] (African Americans)	567	490	0.08	0.11	1.4 (associated with G allele)	0.9–2.4	0.123 0.068 (adju. for age and W.A. ancestry)
Cheng et al. [15] (African Americans)	89	89	0.09	0.11	1.15 (associated with G allele)	0.57–2.35	0.693
Salinas et al. [16] (African Americans)	145	78			0.57	0.28–1.18	0.13

	No. of cases	No. of controls	G allele	G allele	OR (GT genotype)	OR (GG genotype)	*P*-value
European ancestry							
Yeager et al. [13] PLCO (G)	1,172	1,157	0.55	0.49	1.40 (1.14–1.73)	1.73 (1.37–2.19)	2.43×10^{-5}
Yeager et al. [13] ACS	1,140	1,151	0.55	0.50	1.27 (1.03–1.56)	1.49 (1.18–1.89)	3.16×10^{-3}
Yeager et al. [13] ATBC	894	896	0.57	0.51	1.26 (0.99–1.60)	1.66 (1.28–2.16)	1.89×10^{-3}
Yeager et al. [13] FPCC	455	459	0.56	0.51	1.13 (0.81–1.59)	1.45 (1.00–2.10)	1.17×10^{-1}
Yeager et al. [13] HPFS	625	636	0.57	0.51	1.15 (0.87–1.53)	1.58 (1.15–2.16)	9.54×10^{-3}
Yeager et al. [13] ALL	4,284	4,299	0.56	0.50	1.26 (1.13–1.41)	1.58 (1.40–1.78)	9.42×10^{-13}
Cheng et al. [15] (European Americans) (G)	417	417	0.56	0.50	1.39	1.14–1.70	0.001
Salinas et al. [16] (Caucasians)	1,258	1,238	0.45	0.50	0.91 (0.75–1.10) (GT genotype)	0.67 (0.54–0.85) (TT genotype)	0.0017