A Common 8q24 Variant in Prostate and Breast Cancer from a Large Nested Case-Control Study

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Abstract

Two recent studies independently identified polymorphisms in the 8q24 region, including a single nucleotide polymorphism (rs1447295), strongly associated with prostate cancer risk. Here, we replicate the overall association in a large nested case-control study from the National Cancer Institute Breast and Prostate Cancer Cohort Consortium using 6,637 prostate cancer cases and 7,361 matched controls. We also examine whether this polymorphism is associated with breast cancer among 2,604 Caucasian breast cancer cases and 3,118 matched controls. The rs1447295 marker was strongly associated with prostate cancer among Caucasians ($P = 1.23 \times 10^{-13}$). When we exclude the Multiethnic Cohort samples, previously reported by Freedman et al., the association remains highly significant ($P = 8.64 \times 10^{-13}$). Compared with wild-type homozygotes, carriers with one copy of the minor allele had an $OR_{AC} = 1.34$ (99% confidence intervals, 1.19–1.50) and carriers with two copies of the minor allele had an $OR_{AA} = 1.86$ (99% confidence intervals, 1.30–2.67). Among African Americans, the genotype association was statistically significant in men diagnosed with prostate cancer at an early age ($P = 0.011$) and nonsignificant for those diagnosed at a later age ($P = 0.924$). This difference in risk by age at diagnosis was not present among Caucasians. We found no statistically significant difference in risk when tumors were classified by Gleason score, stage, or mortality. We found no association between rs1447295 and breast cancer risk ($P = 0.590$). Although the gene responsible has yet to be identified, the validation of this marker in this large sample of prostate cancer cases leaves little room for the possibility of a false-positive result. [Cancer Res 2007;67(7):2951–6]

Introduction

The chromosomal region 8q24 is amplified in many tumor types, including the prostate (1–3), endometrium (4), and breast (5, 6). Amundadottir et al. (7) recently reported an association between a common variant in the 8q24 region of the genome and prostate cancer. These authors initially identified the region through a linkage analysis of Icelandic families, and replicated the findings in three moderately sized case-control studies of men with European ancestry from Iceland, Sweden, and the U.S., and one case-control study among African Americans. The odds ratio (OR) reported for the rs1447295 marker minor allele (A) was 1.15 ($P = 0.29$) in African Americans, and 1.51 ($P = 1.0 \times 10^{-11}$) among those with European heritage, assuming a multiplicative model. Across the case-control studies, the authors reported a slightly greater risk for prostate cancer with a biopsy Gleason score of >6 at diagnosis, thus implying the involvement of 8q24 in prostate cancer aggressiveness. Freedman et al. (8) independently identified a significant peak (logarithm of odds = 7.2) in the 8q24 region using a whole-genome admixture scan of nearly 1,600 African Americans; the risk was greatest for men diagnosed before the age of 72. In addition to the admixture scan, they reported a significant association between the rs1447295 marker and prostate cancer in four ethnicities from the Multiethnic Cohort (MEC): Native Hawaiians, OR = 3.02 ($P_{one\text{-}sided} = 1.50 \times 10^{-4}$); Japanese Americans, OR = 1.48 ($P_{one\text{-}sided} = 3.40 \times 10^{-4}$); Latino Americans, OR = 1.48 ($P_{one\text{-}sided} = 1.40 \times 10^{-3}$); and European Americans, OR = 1.35 ($P_{one\text{-}sided} = 0.022$). Here, we validate the association between the rs1447295 marker and prostate cancer in a nested case-control study of 6,637 cases and 7,361 matched controls from the National

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

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Cancer Institute Breast and Prostate Cancer Cohort Consortium (BPC3), which included 1,132 cases and 1,091 controls from the MEC presented by Freedman et al. (8). Furthermore, we investigate whether the rs1447295 single nucleotide polymorphism (SNP) is a susceptibility marker for breast cancer in 2,604 cases and 3,118 matched controls included in the BPC3.

Materials and Methods

The BPC3 and individual cohorts have been described in detail elsewhere (9). Briefly, the BPC3 is a large consortium consisting of nine well-established cohorts: the American Cancer Society Cancer Prevention Study II (ACS-CPSII; ref. 10), the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC; ref. 11), the European Prospective Investigation into Cancer and Nutrition Cohort (EPIC—which is comprised of cohorts from Denmark, Great Britain, Germany, Greece, Italy, the Netherlands, Spain, and Sweden; ref. 12), the Health Professionals Follow-up Study (HPFS; ref. 13), the MEC Study (14), the Nurses' Health Study (15), the Physicians' Health Study (PHS; ref. 16), the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO; ref. 17), and the Women's Health Study (18), which collectively include >248,000 men and >390,000 women who have provided a blood sample. Cancer cases were identified from these prospectively followed cohorts through population-based registries or confirmation of self-report by medical records.

The rs1447295 marker was genotyped using a TaqMan assay and the ABI PRISM 7900 for sequence detection (TaqMan; Applied Biosystems, Foster City, CA) in four laboratories for the prostate samples and in two laboratories for the breast samples. All of the cohorts were represented in the prostate cancer genotyping and the breast cancer genotyping included four cohorts: the ACS-CPSII, the MEC, the Nurses' Health Study, and the Women's Health Study. The genotyping centers were blinded to the inclusion of duplicate or triplicate quality control samples (5–10%). Each genotyping center reported >99% concordance with the blinded samples and a genotyping completion rate >95%.

We restricted the majority of our prostate cancer analyses to Caucasians because ethnicity-specific results have been reported elsewhere by Freedman et al. (8) for the MEC samples. African Americans were included only in the analyses assessing effect modification by age. Assuming an additive genetic model, we used conditional logistic regression to estimate the ORs for disease associated with carrying one copy of the minor allele (A) relative to carrying no copies, and with carrying two copies relative to carrying no copies. All of the models were adjusted for age in 5-year intervals, cohort, and country where applicable. Ninety-nine percent confidence intervals (CI) are provided and the two-sided P values for association are from a 2 df likelihood ratio test (LRT) comparing the full model with the rs1447295 genotypes versus the intercept-only model. We used in-house SAS v.9.1 (SAS Institute, Cary, NC) macros to perform our analyses, and SAS default options were modified to obtain very small P values in scientific notation.

We tested for heterogeneity in OR estimates across age at diagnosis, body mass index (BMI), height, and family history. The cut-points for the stratifying variables were defined prior to the analyses. We used WHO recommendations to categorize BMI (<25, ≥25 and <30, and ≥30 kg/m^2), whereas the ethnicity and cohort specific tertile cut-points from controls were used for height. BMI was calculated from self-reported height and weight. Because the average age at diagnosis for prostate cancer was ~65 years old before PSA screening, we used this as one of the age cut-points. This age at diagnosis cut-point has been commonly used in the literature to define early and late prostate cancer diagnoses (19, 20). The effects of age at diagnosis were explored further by using the ages of 60 and 70 as cut-points. We defined a positive family history as having at least one first-degree relative diagnosed with prostate cancer. When performing a stratified analysis, a LRT for heterogeneity was used to compare models with and without the cross-product terms. The stratified results according to cohort did not show statistically significant heterogeneity; thereafter, we did a pooled analysis across cohorts. Statistical tests for heterogeneity were assessed at the 0.05 level to minimize the chance of both false-positive and false-negative results.

We used multinomial logistic regression to assess the marker association with prostate cancer aggressiveness. In multinomial logistic regression, a referent group (e.g., controls) was compared with two or more groups (e.g., nonaggressive and aggressive cases) allowing the logits to be calculated simultaneously for each comparison. The aggressive and nonaggressive logits were then compared using a LRT to assess for the presence of heterogeneous effects across aggressiveness. In the multinomial logistic regression, the P values for the marker genotypes were calculated from a Wald χ^2 test.

Prostate cancer tumor aggressiveness was defined using three different clinical measures: (a) Gleason score at diagnosis, (b) the Whitmore-Jewett staging system, and (c) prostate cancer metastasis or death. Gleason score was categorized by those who had a combined score of ≥8 at diagnosis and those with a combined Gleason score of <8. When using tumor stage, we grouped cases diagnosed with stage A (T_1 in the tumor-node-metastasis staging system) or B (T_2) prostate cancer and had not died from prostate cancer or developed metastases during follow-up. The other staging group included cases with stage C (T_3) or stage D (metastases) at diagnosis, developed metastases during follow-up, and died from prostate cancer. For the final classification, cases with metastases at diagnosis, or who developed metastases during follow-up or died from prostate cancer, were grouped and compared with those who had not died or developed metastases during follow-up. Cases with missing Gleason score, staging, or follow-up information were excluded from their respective analyses.

Results

In both the prostate cancer and breast cancer controls, the rs1447295 marker was in Hardy-Weinberg equilibrium for each cohort and in the combined controls. The minor allele frequency among controls (11.0% for prostate and 10.3% for breast) was similar to frequencies published previously in Caucasian populations (7, 8). Of the prostate samples genotyped successfully, the study population was predominantly Caucasian (n = 12,679), with a smaller number of African Americans (n = 1,319). All of the non-Caucasian samples were from the MEC and these results have been reported by Freedman et al. (8). The breast cancer samples included only U.S. Caucasian women, as number of cases from the ethnicities were too limited for separate analyses.

As shown in Table 1, the overall prostate cancer risk in Caucasians, including the MEC Caucasian samples, was 1.34 (99% CI, 1.19–1.50) in men with one copy of the minor allele (A) and 1.86 (99% CI, 1.30–2.67) in men with two copies of the minor allele compared with wild-type homozygotes ($P = 1.23 \times 10^{-13}$). The overall results were nearly equivalent (OR_{AC} =1.34; 99% CI, 1.19–1.51; OR_{AA} = 1.82; 99% CI, 1.26–2.64; $P = 8.64 \times 10^{-13}$) when the MEC Caucasians were excluded. The magnitude of the ORs did not vary across cohort with or without the MEC samples, as indicated by the LRT of heterogeneity by cohort (P for heterogeneity by cohort = 0.410 with MEC and P for heterogeneity by cohort = 0.295 without MEC).

The large sample size provided sufficient power to examine whether the results varied by age at diagnosis and various definitions of tumor aggressiveness. As seen in Table 2, age at diagnosis modified the risk in the overall population (P for heterogeneity by age = 0.036). When age at diagnosis (≤65) was stratified by ethnicity, the effect modification remained statistically significant only in African Americans (P for heterogeneity by age = 0.037; Table 2). Age did not modify the risk in Caucasians excluding or including the MEC samples (P for heterogeneity by age = 0.164 with MEC and P for heterogeneity by age = 0.144 without MEC). The genotype association for the rs1447295 marker was statistically significant in African American men diagnosed at an early age

Table 1. The genotypic association results between prostate cancer and the rs1447295 marker for Caucasian participants in the BPC3 and by member cohorts

	Cohort	MAF*		Genotype	Cases (%)	Controls (%)	OR †	99% CI ‡		P§
		Cases	Controls					LCL	UCL	
Caucasian, w/o MEC		0.14	0.11	*CC*	4,057 (73.7)	4,991 (79.6)	Ref.			8.64×10^{-13}
(P_{het} = 0.295)‖				*AC*	1,319 (24.0)	1,195 (19.1)	1.34	1.19	1.51	
				AA	129 (2.3)	84 (1.3)	1.82	1.26	2.64	
Caucasian, w/MEC		0.14	0.11	*CC*	4,405 (73.9)	5,353 (79.7)	Ref.			1.23×10^{-13}
(P_{het} = 0.410)‖				*AC*	1,417 (23.8)	1,277 (19.0)	1.34	1.19	1.50	
				AA	139 (2.3)	88 (1.3)	1.86	1.30	2.67	
	ACS-CPSII	0.12	0.08	*CC*	862 (77.0)	949 (84.8)	Ref.			1.26×10^{-5}
				AC	237 (21.2)	162 (14.5)	1.59	1.19	2.13	
				AA	20 (1.8)	8 (0.7)	2.77	0.94	8.19	
	ATBC	0.21	0.17	*CC*	606 (62.9)	623 (68.6)	Ref.			0.012
				AC	312 (32.4)	260 (28.6)	1.23	0.95	1.60	
				AA	45 (4.7)	25 (2.8)	1.81	0.94	3.51	
	EPIC	0.13	0.12	*CC*	551 (75.3)	869 (78.0)	Ref.			0.258
				AC	169 (23.1)	233 (20.9)	1.17	0.87	1.58	
				AA	12 (1.6)	12 (1.1)	1.57	0.53	4.59	
	HPFS	0.14	0.10	*CC*	462 (74.2)	510 (81.7)	Ref.			4.18×10^{-3}
				AC	151 (24.2)	109 (17.5)	1.53	1.06	2.21	
				AA	10 (1.6)	5 (0.8)	2.21	0.54	9.15	
	MEC	0.13	0.10	*CC*	348 (76.3)	362 (80.8)	Ref.			0.105
				AC	98 (21.5)	82 (18.3)	1.25	0.81	1.94	
				AA	10 (2.2)	4 (0.9)	2.69	0.57	12.66	
	PHS	0.12	0.09	*CC*	760 (78.4)	1,054 (83.3)	Ref.			0.011
				AC	190 (19.6)	196 (15.5)	1.34	1.00	1.79	
				AA	19 (2.0)	14 (1.2)	1.85	0.73	4.67	
	PLCO	0.14	0.11	*CC*	816 (74.2)	986 (79.5)	Ref.			0.014
				AC	260 (23.7)	235 (18.9)	1.33	1.02	1.72	
				AA	23 (2.1)	20 (1.6)	1.39	0.63	3.10	

NOTE: The overall results are shown including and excluding the MEC samples.
*Minor allele frequency (*A*) for rs1447295.
†All conditional logistic regression models were frequency adjusted for age in 5-y intervals across all cohorts; EPIC was adjusted for country as well.
‡99% CI; lower and upper confidence limits.
§The *P* value for association from a LRT with 2 *df*.
‖The *P* value for heterogeneity by cohort with 5 *df* when excluding MEC samples and 6 *df* when including MEC samples.

(P = 0.011) and was nonsignificant for those diagnosed at a later age (P = 0.924). Conversely, Caucasian carriers of the minor allele were at greater risk regardless of the age stratum (Table 2). We further explored the effect of age using two additional cut-points (≤60 and ≤70). Heterogeneity by age was not statistically significant among Caucasians, however, at the age cut-point of ≤60, effect modification remained statistically significant for African Americans (P for heterogeneity by age ≤60 = 0.027; Supplementary Table S1).

In contrast to the findings of Amundadottir et al., but in concordance with Freedman et al. (8), we found no difference in the main effects between tumors classified by Gleason score (<8 versus ≥8) at diagnosis. As shown in Table 3, the heterozygote and variant homozygote point estimates among Caucasian cases with a Gleason score of <8 (OR_{AC} = 1.29; OR_{AA} = 1.68) and a Gleason score of ≥8 (OR_{AC} = 1.31; OR_{AA} = 2.12) at diagnosis were similar. The main effects did not differ significantly (P for heterogeneity by staging = 0.153) in high stage prostate cancers (OR_{AC} = 1.33; 99% CI, 0.94–1.87; OR_{AA} = 2.38; 99% CI, 1.29–4.40) versus low stage cancers (OR_{AC} = 1.36; 99% CI, 1.11–1.66; OR_{AA} = 1.70; 99% CI, 1.13–2.56) compared with controls (Table 3). Likewise, the main effects for diagnosis or development of metastases or death due to prostate cancer were not statistically different (P for heterogeneity by metastases/death = 0.373; OR_{AC} = 1.09; 99% CI, 0.61–1.95; OR_{AA} = 2.87; 99% CI, 1.22–6.74) contrasted to localized and nonfatal prostate cancer cases (OR_{AC} = 1.38; 99% CI, 0.85–2.24; OR_{AA} = 2.08; 99% CI, 0.51–3.53).

To further evaluate the role of this marker in prostate cancer aggressiveness, we did several additional analyses (results not shown). The risk estimates varied very little when Gleason score at diagnosis was categorized into three groups: ≤6, 7, and ≥8 (Supplementary Table S2). We also examined several additional definitions of prostate cancer aggressiveness: Gleason score and tumor stage combinations (Supplementary Table S3), age at diagnosis stratified by Gleason score or tumor stage (Supplementary Table S4), and tumor stage C only versus controls (Supplementary Table S5). The rs1447295 marker remained statistically significant in nearly every stratum and the risk estimates were similar regardless of tumor classification.

A substantial portion of the aggressiveness information was missing (see the legend in Table 3 for a list of the number of cases missing information according to cohort). However, the genotype distribution for individuals missing either tumor stage (*CC*, 73.2%; *AC*, 24.6%; *AA*, 2.2%), Gleason score (*CC*, 73.9%; *AC*, 23.7%; *AA*, 2.2%), or mortality (*CC*, 73.9%; *AC*, 24.1%; *AA*, 2.0%) was nearly identical to the genotype distribution among those with complete information (*CC*, 73.9%; *AC*, 23.8%; *AA*, 2.3%). This provides confidence in the validity of our findings for prostate cancer aggressiveness.

Finally, we assessed the presence of effect modification by several prostate cancer risk factors in Caucasians. The LRT for heterogeneity was not statistically significant for family history (P = 0.471), BMI (P = 0.534), or height (P = 0.353). The rs1447295 marker remained statistically significant across all strata (results not shown).

In the breast cancer analysis, we found no association between rs1447295 and breast cancer risk in any of the four cohorts (Supplementary Table S6). The EPIC breast cancer samples were not genotyped due to the null results observed in the cohorts reported here. As there was no heterogeneity in the risk estimates between cohorts (P for heterogeneity = 0.619), we pooled the data, and still found no association between this SNP and breast cancer risk (OR_{AC} = 0.99; 95% CI, 0.87–1.14; OR_{AA} = 0.77; 95% CI, 0.47–1.27; P = 0.590), compared with the CC homozygotes were the reference group. We also saw no evidence of association when the tumors were classified as *in situ*, localized, or metastatic. We did not observe any significant effect modification after stratification by estrogen or progesterone receptor status, age, or menopausal status (results not shown).

Discussion

We have replicated the association previously reported between a novel locus in the 8q24 region and prostate cancer using a large study of nearly 7,000 cases. In addition, we show that the risk estimates remained statistically significant and equivalent among aggressive and nonaggressive prostate cancer tumors defined by Gleason score at diagnosis, tumor stage, and metastases/death due to prostate cancer. Additionally, we show that the effect modification according to age in African Americans, described by Freedman et al. (8), was not observed among Caucasians using several age cut-points.

The population-attributable risk for this locus, using the minor allele frequencies in controls (Caucasian = 0.11; African

Table 2. The genotypic association results between prostate cancer and the rs1447295 marker in African Americans and Caucasians stratified by age at diagnosis (≤65 and >65) in the BPC3

Ethnicity	MAF*		Age at diagnosis	Genotype	Cases (%)	Controls (%)	OR†	99% CI‡		P§
	Cases	Controls						LCL	UCL	
All (P_{het} = 0.036)‖	0.17	0.13	≤65	*CC*	1,235 (69.1)	1,675 (75.8)	Ref.			7.82×10^{-9}
				AC	479 (26.8)	490 (22.2)	1.40	1.15	1.71	
				AA	73 (4.1)	44 (2.0)	2.61	1.55	4.38	
	0.16	0.12	>65	*CC*	3,457 (71.6)	3,971 (77.3)	Ref.			4.09×10^{-7}
				AC	1,221 (25.3)	1,064 (20.7)	1.27	1.12	1.44	
				AA	149 (3.1)	103 (2.0)	1.49	1.05	2.09	
African American (P_{het} = 0.037)‖	0.40	0.31	≤65	*CC*	64 (37.4)	119 (46.5)	Ref.			0.011
				AC	77 (45.1)	116 (45.3)	1.26	0.73	2.18	
				AA	30 (17.5)	21 (8.2)	2.63	1.14	6.05	
	0.32	0.31	>65	*CC*	238 (47.1)	187 (48.3)	Ref.			0.924
				AC	213 (42.2)	162 (41.9)	1.01	0.70	1.46	
				AA	54 (10.7)	38 (9.8)	1.10	0.60	2.01	
Caucasian, w/MEC (P_{het} = 0.164)‖	0.15	0.11	≤65	*CC*	1,171 (72.5)	1,556 (79.7)	Ref.			6.12×10^{-7}
				AC	402 (24.9)	374 (19.1)	1.42	1.15	1.76	
				AA	43 (2.6)	23 (1.2)	2.50	1.27	4.93	
	0.14	0.11	>65	*CC*	3,219 (74.5)	3,784 (79.6)	Ref.			6.06×10^{-8}
				AC	1,008 (23.3)	902 (19.0)	1.30	1.14	1.49	
				AA	95 (2.2)	65 (1.4)	1.65	1.09	2.52	
Caucasian, w/o MEC (P_{het} = 0.144)‖	0.15	0.11	≤65	*CC*	1,070 (72.0)	1,410 (79.4)	Ref.			1.03×10^{-6}
				AC	376 (25.3)	343 (19.3)	1.44	1.15	1.80	
				AA	41 (2.7)	22 (1.3)	2.48	1.24	4.97	
	0.14	0.11	>65	*CC*	2,972 (74.4)	3,568 (79.6)	Ref.			2.29×10^{-7}
				AC	936 (23.4)	851 (19.0)	1.31	1.14	1.50	
				AA	87 (2.2)	62 (1.4)	1.61	1.04	2.48	

NOTE: Age at diagnosis was missing for 37 Caucasians (23 cases and 14 controls). The Caucasian results are shown including and excluding the MEC samples.

*Minor allele frequency (*A*) for rs1447295.

†All conditional logistic regression models were frequency adjusted for age in 5-y intervals, cohort, and country.

‡99% CI; lower and upper confidence limits.

§The P value for association from a LRT with 2 *df*.

‖The P value for the LRT for heterogeneity across age with 1 *df*.

Table 3. The genotypic association results between prostate cancer aggressiveness (tumor staging, Gleason score at diagnosis, and mortality) and the rs1447295 marker among Caucasians in the BPC3

Aggressiveness		Genotype	Cases (%)	Controls (%)	OR*	99% CI†		P‡
						LCL	UCL	
Tumor stage (P_{het} = 0.153)§	C, D, or CaP death	*CC*	500 (70.1)	4,367 (79.7)	Ref.			7.56×10^{-6}
		AC	189 (26.5)	1,042 (19.0)	1.33	0.94	1.87	
		AA	24 (3.4)	68 (1.3)	2.38	1.29	4.40	
	A and B	*CC*	2,317 (75.3)	4,367 (79.7)	Ref.			
		AC	693 (22.5)	1,042 (19.0)	1.36	1.11	1.66	
		AA	67 (2.2)	68 (1.3)	1.70	1.13	2.56	
Gleason score (P_{het} = 0.929)§	≥8	*CC*	378 (71.9)	4,367 (79.7)	Ref.			8.73×10^{-5}
		AC	134 (25.4)	1,042 (19.0)	1.31	0.96	1.78	
		AA	14 (2.7)	68 (1.3)	2.12	1.20	3.75	
	<8	*CC*	2,153 (74.2)	4,367 (79.7)	Ref.			
		AC	677 (23.4)	1,042 (19.0)	1.29	1.06	1.59	
		AA	70 (2.4)	68 (1.3)	1.68	1.11	2.53	
Mortality (P_{het} = 0.373)§	Metastatic or fatal	*CC*	345 (69.1)	4,367 (79.7)	Ref.			9.46×10^{-3}
		AC	134 (26.9)	1,042 (19.0)	1.09	0.61	1.95	
		AA	20 (4.0)	68 (1.3)	2.87	1.22	6.74	
	Localized and nonfatal	*CC*	1,973 (74.8)	4,367 (79.7)	Ref.			
		AC	602 (22.7)	1,042 (19.0)	1.38	0.85	2.24	
		AA	61 (2.3)	68 (1.3)	2.08	0.51	3.53	

NOTE: Tumor stage information was missing for 2,171 cases (cases by cohort: 31 ACS-CPSII, 376 ATBC, 329 EPIC, 83 HPFS, 20 MEC, 233 PHS, and 1,099 PLCO); Gleason score was missing for 2,535 cases (cases by cohort: 160 ACS-CPSII, 389 ATBC, 634 EPIC, 73 HPFS, 12 MEC, 168 PHS, and 1,099 PLCO); mortality/metastases information was missing for 2,826 cases (cases by cohort: 31 ACS-CPSII, 371 ATBC, 622 EPIC, 75 HPFS, 404 MEC, 224 PHS, and 1,099 PLCO).

*All multinomial logistic regression models were frequency adjusted for age in 5-y intervals, cohort, ethnicity, and country.

†99% CI; lower and upper confidence limits.

‡The *P* value for association from a Wald χ^2 test with 4 *df*.

§The *P* value for the LRT for heterogeneity across prostate cancer aggressiveness with 2 *df*.

Americans = 0.31) and risk estimates from a multiplicative model ($OR_{Caucasian}$ = 1.34; $OR_{African\ American}$ = 1.17), was ~6.6% and 8.2% in Caucasians and African Americans, respectively. Because the rs1447295 marker is not the causative locus, this is the minimum population-attributable risk. Within the BPC3 study, men with a positive family history of prostate cancer were more likely to be diagnosed with prostate cancer compared with men without a positive family history (OR = 1.73; 99% CI, 1.47–2.00). The association between family history and prostate cancer was only slightly attenuated (OR = 1.70; 99% CI, 1.46–1.99) when adjusted for the rs1447295 marker. Again, the causative locus may have a greater effect on the association between prostate cancer and family history.

The absence of any association between this marker and breast cancer suggests that the 8q24 locus may not be harboring a gene that is a general cause of hormone-related cancers. The lack of a significant difference between several definitions of early versus late prostate cancers suggests that the unknown gene is associated with prostate cancer at all stages. Our large sample size leaves little room for the possibility of a false-positive result between this locus and prostate cancer risk.

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