The Oncologist®

Clinical Genetics and Genetic Counseling

Racial Disparities in the Association Between Variants on 8q24 and Prostate Cancer: A Systematic Review and Meta-Analysis

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Key Words. Prostatic neoplasms • Continental population groups • Single nucleotide polymorphisms • Meta-analysis • Risk assessment

Disclosures: The author(s) indicated no potential conflicts of interest.

ABSTRACT

Recent studies implicate single nucleotide polymorphisms (SNPs) within the 8q24 region as a risk factor for prostate cancer (PCa). New developments suggest that 8q24 encodes regulators of the nearby *MYC* gene, a known oncogene. In order to better understand the implications of SNPs in this region, we performed meta-analyses, stratified by race, of seven SNPs and one microsatellite marker previously identified as risk loci on the 8q24 region of the genome. In addition, we reviewed the literature examining the possible associations between these polymorphisms and clinicopathological features of PCa. The results of the meta-analyses indicate that rs6983267, rs1447295, rs6983561, rs7837688, rs16901979, and DG8S737 are significantly associated with a higher risk for PCa for at least one race, whereas the variants rs13254738 and rs7000448 are not. The degree of association and frequency of the causative allele varied among men of different races. Though several studies have demonstrated an association between certain 8q24 SNPs and clinicopathological features of the disease, review of this topic revealed conflicting results. *The Oncologist* 2012;17:312–320

INTRODUCTION

Prostate cancer (PCa) is the most common noncutaneous cancer among men in the U.S., with an estimated 240,890 new cases diagnosed and 33,720 deaths in 2010 [1]. The risk for prostate cancer varies considerably among men of different racial backgrounds. The rate per 100,000 men, is 146.3 in whites, 231.9 in African Americans, 82.3 in Asian Americans and Pacific Islanders, 82.7 in American Indians and Native Alaskans, and 131.1 in Hispanics [1]. In recent years, research has placed a considerable emphasis on the role of genetics in the development, progression, and treatment of this disease. The 8q24 region was first shown to confer a PCa risk in a genomewide linkage scan of 871 Icelandic men [2]. Since then, >30 studies have examined the relationship between 8q24 and PCa risk. Importantly, some of these investigations have compared this association in a variety of races including African Americans (AAs), American whites (AWs), European whites (EWs), Asians (As), and Hispanics (Hs). These studies suggest that single nucleotide polymorphism (SNP) genotype frequencies on 8q24 may vary by race and thus 8q24 may at least partially account for racial differences in PCa risk.

The mechanism by which 8q24 influences the course of PCa is poorly understood. The 8q24 region has been described as a "gene desert;" the 600-kbp gene-poor region appears to have little or no transcriptional activity. Despite this, evidence suggests that 8q24 may play an active role in PCa. First, 8q24 is a highly conserved genomic region. In addition, *POU5F1P1* has been identified on 8q24. Originally thought to be a pseu-

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dogene, it is now believed that *POU5F1P1* can encode a functional protein that contributes to carcinogenesis through its role as a weak transcriptional activator [3]. Additionally, recent studies have shown that 8q24 encodes enhancers of the nearby oncogene *MYC* [4–7]. Wasserman et al. [5] and Sotelo et al. [4] both identified an enhancer of MYC that contained rs6983267, a SNP located in region 3 of 8q24. Ahmadiyeh et al. [7] provided additional support, finding that all three regions of 8q24 independently interact with both *MYC* and with one another.

These new findings demonstrate a renewed importance in exploring the SNPs on 8q24 because of their potential predictive value and ability to guide the development of therapies. Though many studies have assessed these SNPs in men with PCa, the results have been inconsistent. In addition, the two previously published meta-analyses of 8q24 SNPs only included a small subset of the relevant studies [8, 9], assessed only a small number of SNPs [8], or were not stratified by race [8]. Consequently, we conducted a systematic review of the relationship between PCa and 8q24 SNPs as well as a meta-analysis stratified by race in order to identify those SNPs that are associated with PCa risk and thus warrant further investigation.

Methods

We obtained data from all available studies in MEDLINE that reported 8q24 genotype frequencies in patients with PCa and in healthy controls. Only those studies that stratified their analysis by race were included in the present study. We grouped studies by SNP and stratified by race (AA, AW, EW, A, and H) within each SNP. The only exception was that Australian Caucasians were grouped with EWs. Our final analysis only included those SNPs whose 8q24 allele frequencies were reported in at least three different studies. In some studies, multiple cohorts of a single race were examined. In these instances, each cohort was assessed separately in the meta-analysis, which is represented in Figure 1.

The random effects model described by DerSimonian and Laird (1986) was used for the meta-analyses [10]. In this method, each study in a population is weighted by the inverse sum of the estimated variances of the study itself and of all the individual studies from the population mean. The allelic odds ratio (OR) values and confidence intervals (CIs) were calculated using the Mantel–Haenszel method. This test assumes homogeneity, so we first used the Breslow–Day test to determine whether or not the assumption of homogeneity was valid in each population. If the test for homogeneity was not significant, the population was said to be homogeneous. The results of the Mantel–Haenszel test were deemed significant if the OR 95% CI did not include 1.

In addition to allele frequencies, we recorded any data that assessed the relationship between 8q24 SNPs and the clinicopathological features of PCa, including aggressiveness, prostate-specific antigen (PSA) level at diagnosis, Gleason score, tumor grade, surgical margin, age at onset, tumor stage, and hereditary or familial versus sporadic PCa. Because of a scarcity of studies on this topic, we were not able to perform any meta-analyses.

Associations Between 8q24 SNPs and PCa

In total, 29 studies examining seven SNPs and one microsatellite marker were included in the analyses. The location on 8q24, variant allele, total number of cases and controls, number of studies assessed, mean allele frequencies, and meta-analysis results are presented in Table 1.

rs6983267

We identified 20 studies that met the inclusion criteria for this SNP. Two of four AA, nine of 11 AW, one of four A, and all seven EW studies showed a significant association between the rs6983267 risk allele and PCa risk. The results of the meta-analysis indicated that the association between PCa risk and the variant allele at rs6983267 was significant in AWs and As (Fig. 1A, Table 1). The AA and EW groups had significant heterogeneity and therefore valid ORs could not be calculated.

rs1447295

Twenty-six studies reporting genotype frequencies for rs1447295 met the criteria for inclusion. Only one of seven studies of AAs found a significant association between this SNP and PCa risk whereas four of six studies of As, 15 of 18 studies of AWs, 14 of 15 studies of EWs, and all three studies of Hs were significant. Our meta-analysis (Fig. 1B, Table 1) showed a significant association in AW, A, H, and AA populations. We could not assess the EW subgroup because of heterogeneity. The significant OR for the AA subgroup contradicts the fact that only one of seven studies of AAs found that the association was significant. This may be explained by the fact the one significant study had the largest sample size, contributing to 32% of the total number of participants. In addition, though significant, the OR was only moderately greater than one.

rs13254738

Our literature search only identified five studies that reported genotype frequencies for rs13254738. Four of those studies assessed this SNP in AWs and two reported data for As. Yamada et al. [11] and Zheng et al. [12] both found a significant relationship between this SNP and PCa risk in As, but there was an insufficient number of studies to conduct a meta-analysis. No evidence suggests that the rs13254738 marker is associated with PCa risk in AWs [9, 13, 14]. Similarly, the present meta-analysis found no association between the variant allele at this SNP and PCa risk (Fig. 1C, Table 1).

rs6983561

Genotyping studies for rs6983561 generally indicated that the C allele is associated with a higher risk for PCa. Of those analyzed here, two of three AA, three of six AW, and four of four A studies demonstrated a significant association. Interestingly, some studies that did not find a significant relationship in the overall population did detect a significant association within a subset of patients. For example, Beebe-

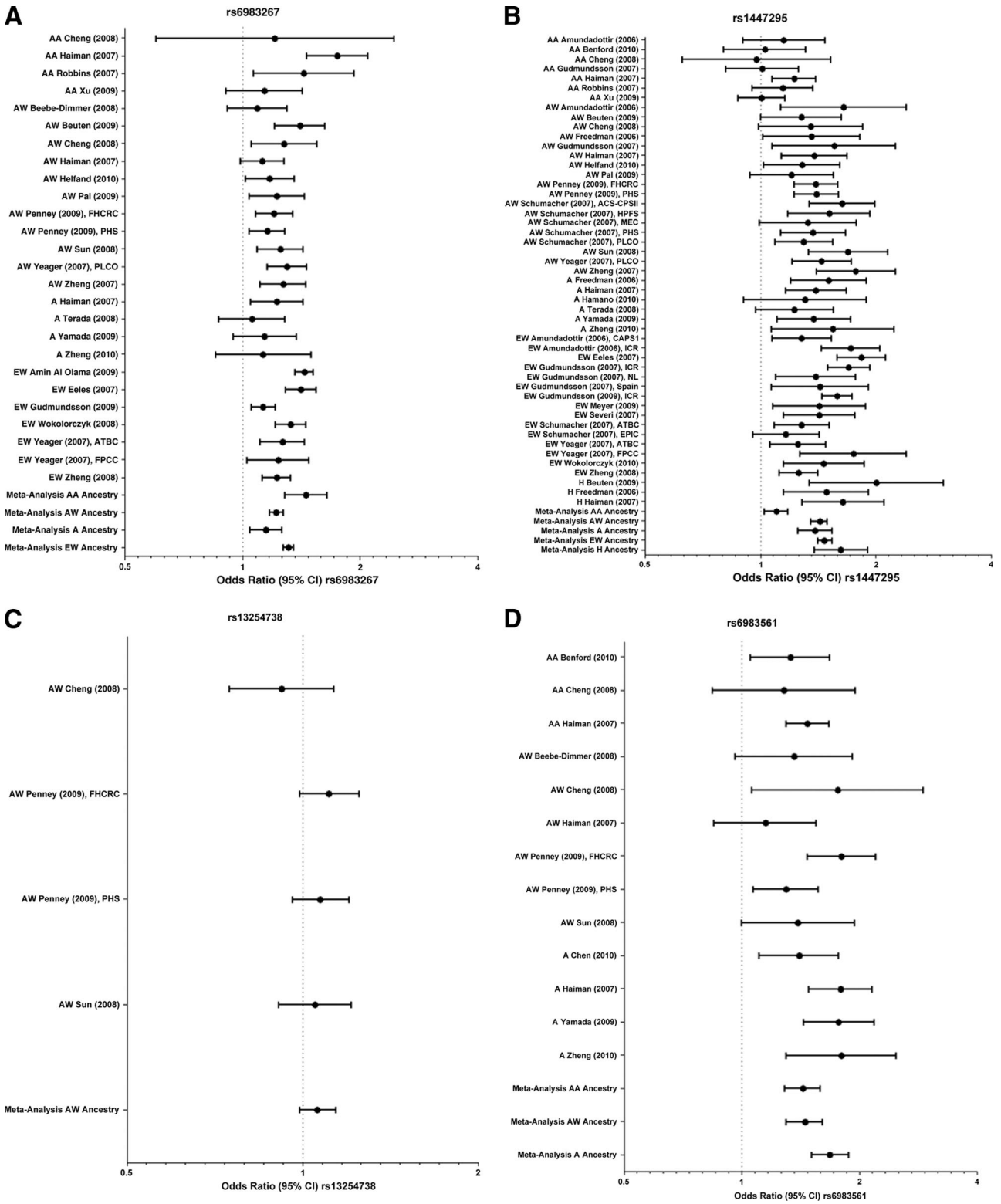
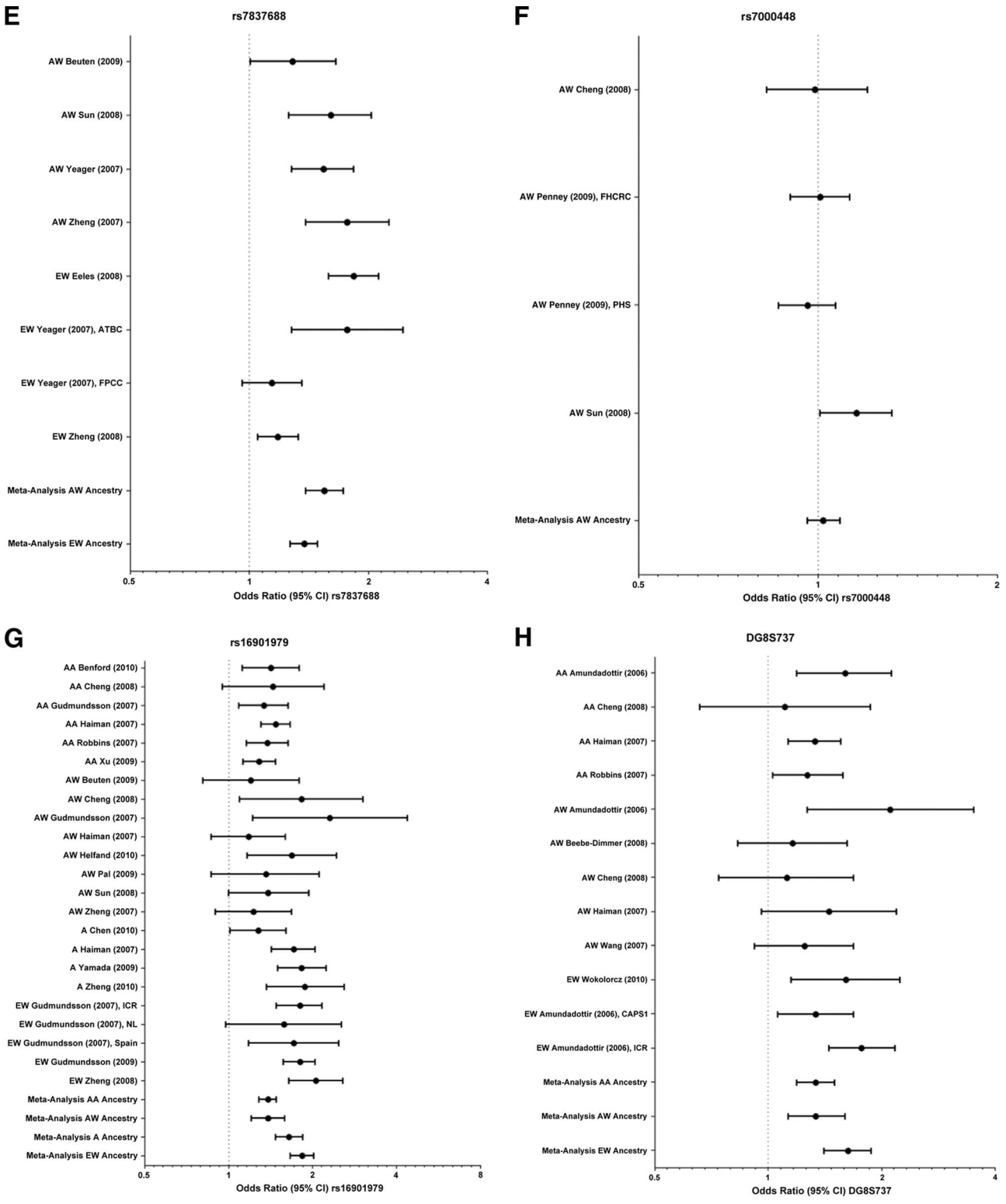


Figure 1. Forest plots of odds ratios (95% confidence interval [CI]) of individual studies and a meta-analysis for the variant allele at rs6983267 **(A)**, rs1447295 **(B)**, rs13254738 **(C)**, rs6983561 **(D)**, rs78737688 **(E)**, rs7000448 **(F)**, rs16901979 **(G)**, and DG8S737 **(H)**.

Abbreviations: A, Asian; AA, African American; ACS-CPSII, American Cancer Society Cancer Prevention Study II; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; AW, American white; CAPS1, Cancer of Prostate in Sweden 1; EPIC, European Prospective Investigation into Cancer and Nutrition Cohort; EW, European white; FHCRC, Fred Hutchinson Cancer Research Center King County; FPCC, French Prostate Case-Control Study; H, Hispanic; HPFS, Health Professionals Follow-up Study; ICR, Icelandic Cancer Registry; MEC, Multiethnic Cohort; NL, Netherlands; PHS, Physicians' Health Study; PLCO, Prostate, Lung, Colon, Ovarian Trial.



Dimmer et al. [15] found that this variant was associated with PCa in patients diagnosed before the age of 50 years. Sun et al. [14] showed a significant association for hereditary PCa but not non-hereditary PCa. The meta-analysis indicated a significant association between the risk allele for rs6983561 and PCa risk in AAs, AWs, and As (Fig. 1D, Table 1).

rs7837688

The PCa risk associated with rs7837688 was examined in AW and EW populations. The studies consistently found a significantly higher frequency of the risk allele, T, in cases than in controls for both races. Likewise, most of the studies found a significant association between this SNP and PCa risk. Our

Table 1. Summary of 8q24 allele frequencies and meta-analyses by race

SNP	8q24 region	Risk allele	Race (*n* cases/*n* controls)	Mean variant allele f_{case}	Mean variant allele $f_{control}$	OR (95% CI)	*p*-value for homogeneity	Reference
rs6983267	3	G	AA (3,132/2,310)	0.906	0.877	1.45 (1.28–1.65)	.032[b]	[9, 27, 28, 34]
			AW (14,570/10,036)	0.574	0.505	1.22 (1.17–1.27)[a]	.47	[8, 9, 13–15, 22, 27, 32, 33, 35]
			A (2,128/2,292)	0.403	0.344	1.15 (1.04–1.26)[a]	.71	[11, 12, 18, 27]
			EW (16,563/48,141)	0.57	0.536	1.31 (1.27–1.35)	3.00×10^{-6}[b]	[16, 19, 20, 35–37]
rs1447295	1	A	AA (3,953/3,560)	0.334	0.316	1.1 (1.02–1.18)[a]	.46	[2, 9, 27, 28, 34, 38, 39]
			AW (19,900/15,373)	0.161	0.111	1.43 (1.35–1.49)[a]	.71	[2, 8, 9, 13, 14, 22, 25, 27, 32, 33, 35, 39, 40]
			A (2,884/2,885)	0.228	0.175	1.39 (1.25–1.54)[a]	.85	[11, 12, 18, 27, 40, 41]
			EW (17,895/52,248)	0.163	0.112	1.47 (1.41–1.54)	.0002[b]	[2, 20, 23, 25, 26, 35–37, 39, 42]
			H (1,473/1,672)	0.136	0.085	1.62 (1.38–1.91)[a]	.46	[27, 32, 40]
rs13254738	2	C	AW (8,330/3,612)	0.338	0.325	1.06 (0.99–1.14)	.47	[9, 13, 14]
rs6983561	2	C	AA (1,904/1,375)	0.497	0.416	1.43 (1.29–1.59)[a]	.65	[9, 27, 38]
			AW (7,681/5,083)	0.071	0.057	1.45 (1.30–1.61)[a]	.11	[9, 13–15, 27]
			A (1,627/2,230)	0.295	0.191	1.68 (1.51–1.88)[a]	.37	[11, 12, 27, 29]
rs7837688	1	T	AW (4,946/4305)	0.126	0.091	1.55 (1.39–1.73)[a]	.35	[14, 22, 32, 35]
			EW (7,451/5,030)	0.155	0.115	1.38 (1.27–1.49)	3.00×10^{-6}[b]	[20, 35, 37]
rs7000448	3	T	AW (8,387/3,618)	0.395	0.384	1.02 (0.96–1.09)	.23	[9, 13, 14]
rs16901979	2	A	AA (3,608/3,196)	0.486	0.41	1.39 (1.29–1.49)[a]	.81	[9, 27, 28, 34, 38, 39]
			AW (7,115/4,921)	0.05	0.035	1.39 (1.21–1.59)[a]	.44	[8, 9, 14, 22, 27, 32, 33, 39]
			A (1,962/2,240)	0.304	0.199	1.65 (1.48–1.85)[a]	.09	[9, 11, 12, 27]
			EW (1,962/2,240)	0.065	0.041	1.84 (1.67–2.02)[a]	.78	[20, 36, 39]
DG8S737	1	−8	AA (2,368/1,766)	0.212	0.169	1.34 (1.19–1.50)[a]	.55	[2, 9, 27, 34]
			AW (2,971/2,092)	0.072	0.056	1.32 (1.12–1.56)[a]	.3	[2, 9, 15, 21, 27]
			EW (3,416/2,378)	0.107	0.071	1.56 (1.36–1.79)[a]	.08	[2, 23]

[a]Significant OR and no significant heterogeneity detected.
[b]Brewslow–Day test significant, OR invalid (does not meet assumption of homogeneity).
Abbreviations: A, Asian; AA, African American; AW, American white; CI, confidence interval; EW, European white; H, Hispanic; OR, odds ratio; SNP, single nucleotide polymorphism.

meta-analysis confirmed this relationship in AWs (Fig. 1E, Table 1). The EW group did not meet the assumption of homogeneity and therefore the association could not be assessed.

rs7000448

Three studies analyzed rs7000448 in AWs but none found a significant association between this SNP and PCa risk [9, 13, 14]. Consistent with these results, our meta-analysis found no evidence of this relationship (Fig. 1F, Table 1).

rs16901979

This region 2 8q24 SNP was genotyped in men with PCa in 16 studies. The results suggest a relationship between the rs16901979 risk allele and PCa. This pattern is consistent across AA (five of six studies), A (four of four studies), and EW (four of five studies) populations. There appears to be greater variability among studies of AWs because only four of eight studies found the relationship to be significant. Our meta-analysis demonstrated that the association between PCa risk and the variant allele for rs16901979 was significant in all four populations (Fig. 1G, Table 1).

DG8S737

The −8 allele of the DG8S737 satellite marker located on 8q24 has also been analyzed for a possible association with PCa risk. The association was significant in three of four studies of AAs and three of three studies of EWs, but only one of five studies of AWs. However, the results of our meta-analysis indicate that the association is significant for all three races (Fig. 1H, Table 1).

Association Between 8q24 SNPs and Clinical Features of PCa

Investigations into the possible links between these polymorphisms and specific clinicopathological features of PCa could reveal whether or not there is an association between these SNPs and a specific subset of PCa cases (i.e., aggressiveness, age at onset, family history, etc.) or suggest possible mechanisms by which 8q24 risk genotypes contribute to PCa risk and

Table 2. Summary of studies examining the relationship between prostate cancer clinicopathological features and 8q24 SNPs

SNP	Clinicopathological feature	Significant association	Nonsignificant association
rs6983267	Elevated PSA level	Penney et al. [13] (AWs)	Terada et al. [18] (As), Wiklund et al. [24] (EWs)
	Higher tumor grade	Wokolorczky et al. [16] (EWs)	Terada et al. [18] (As)
	Higher risk for a positive surgical margin	Bao et al. [17] (As)	
	High Gleason score	Penney et al. [13] (AWs)	Al Olama et al. [19] (EWs), Xu et al. [28] (EWs), Terada et al. [18] (As)
	Advanced stage		Wiklund et al. [24] (EWs)
	Hereditary, not sporadic		Wokolorczky et al. [16] (EWs), Zheng et al. [20] (EWs)
rs1447295	Greater aggressiveness	Terada et al. [18] (As) Wang et al. [21] (AWs)	
	Higher PSA level at diagnosis		Wiklund et al. [24] (EWs), Zheng et al. [22] (EWs)
	Higher risk for a positive surgical margin	Bao et al. [17] (As)	
	High Gleason score	Amundadottir et al. [2] (AWs), Hamano et al. [41] (As)	Amundadottir et al. [2] (EWs), Wokolorczky et al. [23] (EWs), Wang et al. [21] (AWs), Schumacher et al. [25] (AWs and AAs), Severi et al. [26] (EWs)
	Advanced stage	Zheng et al. [22] (EWs), Bao et al. [17] (As), Terada et al. [18] (As)	Schumacher et al. [25] (AWs and AAs), Wiklund et al. [24] (EWs)
	Younger age at onset	Zheng et al. [22] (EWs); Schumacher et al. [25] (AAs)	Schumacher et al. [25] (AWs), Zheng et al. [20] (EWs)
	Hereditary, not sporadic	Wang et al. [21] (AWs), Wokolorczky et al. [23] (EWs)	Schumacher et al. [25] (EWs), Severi et al. [26] (EWs), Zheng et al. [20] (EWs)
rs6983561	Higher tumor grade	Wokolorczky et al. [23] (EWs)	
	Advanced stage	Haiman et al. [27] (AAs)	
	Young age at onset	Beebe-Dimmer et al. [15] (AWs), Haiman et al. [27] (AAs)	
	Hereditary, not sporadic	Sun et al. [14] (AWs)	Haiman et al. [27] (AAs)
rs16901979	Higher PSA level at diagnosis		Chen et al. [29] (As), Wiklund et al. [24] (EWs)
	Higher tumor grade		Chen et al. [29] (As)
	Advanced stage		Wiklund et al. [24] (EWs)
	Young age at onset	Gudmundsson et al. [36] (EWs)	
	Hereditary, not sporadic	Sun et al. [14] (AWs)	
DG8S737−8	Higher Gleason score	Amundadottir et al. [2] (EW, AWs, AAs), Haiman et al. [27] (AAs)	Wokolorczky et al. [23] (EWs)
	Hereditary, not sporadic	Wokolorczky et al. [23] (EWs)	

Abbreviations: A, Asian; AA, African American; AW, American white; EW, European white; H, Hispanic; PSA, prostate-specific antigen; SNP, single nucleotide polymorphism.

disease development. We found 17 papers that assessed the relationship among one or more of the 8q24 SNPs of interest, but there was insufficient data to perform a meta-analysis. The findings are summarized in Table 2.

rs6983267

Some studies have also analyzed potential associations between rs6983267 and various clinical features of PCa. The findings indicated an association between the risk allele at

rs6983267 and PSA level at diagnosis in EWs [13], higher grade tumors in EWs [16], and a higher risk for a positive surgical margin in As [17]. Penney et al. [13] found that AWs heterozygous at rs6983267 had a lower risk for Gleason score 8–10 tumors than men who were homozygous for the risk allele.

Contrary to those findings, Terada et al. [18] found no relationship between the risk allele for this SNP and PSA level or tumor stage in their study of Japanese men. In fact, they found an association between the variant allele and a low Gleason score in PCa patients, compared with controls. Similarly Al Olama et al. [19] failed to detect a relationship between this SNP and Gleason score in EW men.

According to Wokolorczyk et al. [16] and Zheng et al. [20], the risk allele frequency for rs6983267 did not differ significantly between sporadic and familial cases of PCa. However, Sun et al. [14] found that this SNP was associated with nonhereditary PCa but not with hereditary PCa.

rs1447295

The risk allele at rs1447295 may be associated with several PCa clinical features, including greater tumor aggressiveness in As [18] and AWs [21], advanced stage disease in EWs [22] and As [17, 18], and a higher risk for a positive surgical margin [17]. Amundadottir et al. [2] showed that the rs1447295 risk allele tended to be more strongly associated with Gleason score 7–10 tumors than with Gleason score 2–6 tumors in AAs and AWs. This trend does not appear to translate to EW populations [2, 23]. The relationship between PCa risk and this SNP did not appear to be affected by PSA level in EWs [22, 24]. Zheng et al. [22] showed that this allele was associated with a younger age at onset in EWs, but Schumacher et al. [25] and Zheng et al. [20] found no such evidence. The risk allele may be associated with a younger age at onset in AA populations [25].

Schumacher et al. [25], Severi et al. [26], and Zheng et al. [20] failed to find a significant difference in rs1447295 risk allele frequencies between sporadic and familial cases in EWs. However, Wang et al. [21] found that, for AWs, this risk allele was associated with familial PCa but not with sporadic PCa. Likewise, Wokolorczyk et al. [23] found that this risk allele was more strongly associated with familial PCa than with sporadic PCa in EWs.

rs6983561

The A allele at rs6983561 may be associated with clinicopathological features of PCa. For example, Wokolorczyk et al. [16] found that the risk allele was more strongly associated with high-grade tumors than with low-grade tumors in EWs. In addition, the variant allele was moderately more frequent among AA individuals with high-stage PCa than among AA controls [27]. This SNP may also be associated with the risk for younger age at onset in AWs [15] and AAs [27]. Lastly, Sun et al. [14] found that the rs6983561 risk allele was associated with hereditary PCa but not with nonhereditary PCa in AWs, whereas Haiman et al. [27] found that the effect of this SNP was greater in nonhereditary cases among AAs.

rs16901979

According to Wiklund et al. [24], the rs16901979 risk allele is also associated with an elevated PSA level. However, Xu et al. [28] and Chen et al. [29] found conflicting evidence. In addition, this risk allele appears to be associated with lower tumor grade [29]. Finally, according to Sun et al. [14], the association between PCa risk and this variant allele is only significant in hereditary PCa, not nonhereditary PCa.

DG8S737

Some evidence suggests a possible link between this genomic marker and Gleason score. Two studies found that the variant −8 allele frequency was higher among men with high Gleason scores than among those with low Gleason scores in AAs [2, 27], AWs [2], and EWs [2]. However, Wokolorczky et al. [23] did not find the relationship to be significant in EWs. The DG8S727 −8 allele was also more strongly associated with familial PCa than with sporadic PCa.

Conclusions

Many studies have investigated the role of 8q24 variants as genetic indicators of PCa risk and clinicopathological features of PCa. These studies have produced conflicting results, but it is hoped that the present meta-analysis will help elucidate which variants are most critical in specific races.

Interestingly, the frequency of the risk alleles varied considerably across races. For example, the variant allele frequency was highest among AAs for all the SNPs included in the present analysis. For three of the four SNPs, A men had the second highest relative frequency of the variant allele. In general, the frequencies were similar between AWs and EWs and tended to be lower than those of other ethnic populations. As seen in Table 1, in most cases, these differences in allele frequency among races were quite pronounced.

These frequency data both complement and contradict variations in the incidence of PCa, suggesting that 8q24 may modify other genetic risk factors within races. For example, AA men have the highest incidence of PCa [30] and a higher frequency of the variant alleles for 8q24 SNPs than men of other ethnicities. In contrast, As have the lowest incidence of PCa but tend to have higher variant allele frequencies than EWs and AWs.

The relative strength of the association between PCa risk and the 8q24 variant alleles also appeared to vary among races and among SNPs within the same race. Although our meta-analysis helps to clarify these associations relative to the null hypothesis (i.e., no effect on risk in individual populations), the overlapping CIs of many of the estimated ORs suggest that comparisons between them should be interpreted with caution. It is worth noting that CIs did not overlap for rs1447295 (lower in AAs than in other races) and rs6983267 (lower in AAs and AWs than in EWs), whereas overlap was observed for all other comparisons. Therefore, future studies should account for the

possibility that certain 8q24 SNPs confer greater risk in certain populations.

Despite these differences, the risk alleles at rs6983267, rs1447295, rs6983561, rs16901979, and DG8S737 were consistently associated with PCa risk across races. The only SNPs that did not appear to be related to PCa risk were rs13254738 and rs7000448.

Haplotype analyses indicate that certain SNPs are in linkage disequilibrium; thus, there may be multiple interacting regions on 8q24 that confer a PCa risk [12, 29, 31, 32]. For instance, multiple studies report that rs6983561 and rs16901979 are in strong linkage disequilibrium [19, 29]. Despite these interactions, it is clear that many 8q24 SNPs, including five of the seven SNPs assessed herein, independently predict PCa risk. This is supported by research assessing the cumulative risk associated with 8q24 polymorphisms. These studies suggest that the risk alleles interact additively or even synergistically [11, 13, 14, 17, 20, 22, 32, 33]. For example, one study found that each additional risk allele increased the risk for PCa by 19% [13]. This has important implications because it suggests that 8q24 may contain multiple functional variants.

Many factors aside from race are associated with PCa, including age at onset, family history, tumor aggressiveness, PSA level, Gleason score, tumor stage, and surgical margins. Few studies have examined the relationship between 8q24 SNPs and these clinicopathological features and thus we were not able to include them in the meta-analyses. Of those studies that have been conducted, the results have been generally inconsistent. In subsequent studies of 8q24 polymorphisms in PCa patients, the association between 8q24 SNPs and these prognostic factors must be assessed.

In addition, future studies of 8q24 should look to explain the mechanism by which 8q24 increases the risk for PCa. It will be important to explore the association between these SNPs and gene variants on nearby regions such as *MYC* and *POU5F1P1*. A clear association exists between 8q24 and PCa, but the value of this relationship for drug development and prognostics will continue to be limited until future studies can identify the mechanism of action.

Author Contributions

Conception/Design: Sarah M. Troutman
Provision of study material or patients: Sarah M. Troutman
Collection and/or assembly of data: Sarah M. Troutman, Cheryl D. Cropp
Data analysis and interpretation: Tristan M. Sissung, Cheryl D. Cropp, David J. Venzon
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Final approval of manuscript: William D. Figg

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