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Research Article

Evaluating Genetic Risk for Prostate Cancer among Japanese and Latinos

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Abstract

Background: There have been few genome-wide association studies (GWAS) of prostate cancer among diverse populations. To search for novel prostate cancer risk variants, we conducted GWAS of prostate cancer in Japanese and Latinos. In addition, we tested prostate cancer risk variants and developed genetic risk models of prostate cancer for Japanese and Latinos.

Methods: Our first-stage GWAS of prostate cancer included Japanese (cases/controls = 1,033/1,042) and Latino (cases/controls = 1,043/1,057) from the Multiethnic Cohort (MEC). Significant associations from stage I ($P < 1.0 \times 10^{-4}$) were examined *in silico* in GWAS of prostate cancer (stage II) in Japanese (cases/controls = 1,583/3,386) and Europeans (cases/controls = 1,854/1,894).

Results: No novel stage I single-nucleotide polymorphism (SNP) outside of known risk regions reached genome-wide significance. For Japanese, in stage I, the most notable putative novel association was seen with 10 SNPs ($P \leq 8.0 \times 10^{-6}$) at chromosome 2q33; however, this was not replicated in stage II. For Latinos, the most significant association was observed with rs17023900 at the known 3p12 risk locus (stage I: OR = 1.45; $P = 7.01 \times 10^{-5}$ and stage II: OR = 1.58; $P = 3.05 \times 10^{-7}$). The majority of the established risk variants for prostate cancer, 79% and 88%, were positively associated with prostate cancer in Japanese and Latinos (stage I), respectively. The cumulative effects of these variants significantly influence prostate cancer risk (OR per allele = 1.10; $P = 2.71 \times 10^{-25}$ and OR = 1.07; $P = 1.02 \times 10^{-16}$ for Japanese and Latinos, respectively).

Conclusion and Impact: Our GWAS of prostate cancer did not identify novel genome-wide significant variants. However, our findings show that established risk variants for prostate cancer significantly contribute to risk among Japanese and Latinos. *Cancer Epidemiol Biomarkers Prev; 21(11); 2048–58. ©2012 AACR.*

Introduction

Prostate cancer displays dramatic differences in incidence rates across racial/ethnic populations. In the United States, African-Americans have the highest incidence rate of prostate cancer followed by European Americans, Latinos, and Asians. The contribution of genetic variants to prostate cancer risk likely varies across race/ethnicity and may play a key role in the unequal burden of disease across racial/ethnic groups (1). The first wave of genome-wide association studies (GWAS) of prostate cancer were heavily weighted by studies of European men (2–10), revealing more than 40 prostate cancer risk variants, many of which replicated in subsequent studies of non-European populations (1, 11–17). More recently, GWAS

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of prostate cancer have been conducted in non-Europeans (18, 19), identifying 5 new risk variants in Japanese (19) and 1 novel risk variant in men of African ancestry (18). Identifying the full spectrum of prostate cancer risk alleles, in terms of numbers and frequencies, requires conducting GWAS of prostate cancer in all possible racial/ethnic populations. With differences in allele frequencies, linkage disequilibrium (LD) patterns, and population-specific risk of disease across race/ethnicities, evaluating the generalizability of known risk variants is important to increase our understanding of the genetic contributions to prostate cancer. Equally important is defining the genetic risk profiles relevant for each racial/ethnic group.

In this study, we conducted 2-stage GWAS to search for novel risk variants for prostate cancer in Japanese and Latinos, respectively. We also tested known risk variants for prostate cancer and used these variants to develop genetic risk models of prostate cancer for Japanese and Latinos.

Methods

Stage I of the GWAS included Japanese and Latino prostate cancer cases and controls from the Multiethnic Cohort (MEC). *In silico* replication of the most significant associations from stage I were conducted in GWAS of prostate cancer in Japanese (19) and Europeans (7). Below is a brief description of the first and second-stage study populations.

The MEC is a large population-based cohort study of more than 215,000 individuals from Hawaii and California (20). Further methodologic details of this cohort are provided elsewhere (20). Briefly, incident prostate cancer cases were identified by cohort linkage to Surveillance, Epidemiology and End Results cancer registries covering Hawaii and California. Controls had no diagnosis of prostate cancer, were randomly selected from the random control pool of participants, and provided blood specimens for genetic analysis. Controls were frequency matched to cases by age (5, year categories) and ethnicity. Through January 1, 2008, the Japanese and Latino nested case–control studies of prostate cancer included 1,033 cases and 1,042 controls and 1,043 cases and 1,057 controls, respectively.

In silico replication of findings in Japanese men was conducted in a GWAS of prostate cancer of 1,583 Japanese with prostate cancer and 3,386 controls, who were part of the BioBank Japan at the Institute of Medical Science at the University of Tokyo (Tokyo, Japan; ref. 19). The 1,583 cases were diagnosed as having prostate cancer based on the pathologic evaluation of prostatic biopsy. The controls were 2,480 individuals registered in the BioBank Japan as subjects with 13 diseases other than prostate cancer and 906 healthy volunteers collected at the Osaka-Midosuji Rotary Club (Osaka, Japan). All participants provided written informed consent. Study subjects were genotyped using either the Illumina Infinium Human610-Quad BeadChip or Infinium HumanHap550v3 BeadChip.

In silico replication of findings in Latinos and those from the combined analysis of Japanese and Latinos was conducted in the United Kingdom GWAS of 1,854 prostate cancer cases diagnosed at age 60 years or younger with a family history of disease, and 1,894 controls, ages more than 50 years, with a prostate-specific antigen of less than 0.5 ng/mL (7).

Genotyping

Genotyping of the Japanese and Latinos in the MEC was conducted using the Illumina.Human660W_Quad_v1 bead array at the Broad Institute (Cambridge, MA). Samples with DNA concentrations less than 18.8 ng/μL were not scanned (53 Japanese and 52 Latinos). Samples were removed on the basis of the following exclusion criteria: (i) call rates less than 95% (5 Japanese and 4 Latinos); (ii) ancestry outliers (21 Japanese and 25 Latinos, discussed later); and (iii) related samples (88 Japanese and 57 Latinos, discussed later). We also removed single-nucleotide polymorphism (SNP) with minor allele frequencies less than 1% ($n = 16{,}793$). To assess genotyping reproducibility, we included 9 replicate samples; the average concordance rate was 99.99% ($\geq$99.3% for all pairs). The final analysis included 528,023 SNPs evaluated in 2,075 Japanese and 2,100 Latinos.

Statistical analysis

Ancestry estimation. The EIGENSTRAT software (21) was used to calculate eigenvectors that explained genetic differences in ancestry. The analysis included data from HapMap phase III populations and our study, so that comparisons with reference populations of known ethnicity could be made. An individual was subject to filtering from the analysis if his value along eigenvector 1 or 2 was outside of 4 SDs of the mean of each respective eigenvector. Twenty-one self-reported Japanese and 25 self-reported Latinos met this filtering criterion. Together the top 10 eigenvectors (used in the analysis) explained 8% of the global genetic variability among subjects.

Relatedness inference. We used PLINK (22) to calculate the probabilities of sharing 0, 1, and 2 alleles ($Z = Z_0$, Z_1, and Z_2) across all possible pairs of samples to determine individuals who were likely to be related to others. We identified 1 pair of monozygotic twins (confirmed), 57 half siblings, and 129 first-degree relative pairs (parent offspring/full siblings) based on the values of their observed probability vector Z being within 1 SD of the expected values of Z for their respective relationship. For the 187 pairs, 1 individual was removed from analysis. The criterion for removal was such that individuals that were related with a higher number of pairs were chosen for removal. In all other cases, 1 of the 2 members was randomly selected for removal.

SNP imputation. We carried out genome-wide imputation using the software MACH. Phased haplotype data from the founders of the Japanese in Tokyo, Japan (JPT), Utah residents with Northern and Western European ancestry (CEU), and Yoruba in Ibadan, Nigeria. HapMap phase II samples were used to infer LD patterns to impute untyped markers. The Rsq metric, defined as the observed variance divided by the expected variance, provides a measure of the quality of the imputation at any SNP and was used as a threshold in determining which SNPs to filter from analysis (Rsq < 0.3). For all imputed SNPs reported, Rsq was 0.3 or more.

Association testing. In stage I, we examined the observed versus the expected distribution of the χ^2-square test statistics from the 1-degree-of-freedom (*df*) trend test, comparing genotype counts in cases and controls. All tests of statistical significance were 2-sided. OR and 95% confidence intervals (95% CI) were estimated using unconditional logistic regression adjusting for age and the first 10 ancestry eigenvalues. For each SNP, we tested for a gene-dosage effect through a 1 *df* Wald χ^2-square trend test. To address the hypothesis that the same variants could be informative across populations as shown for the 8q24 locus (1) and combine risk estimates between Japanese and Latinos, we conducted a meta-analysis of stage I results for SNPs genotyped in Japanese and Latinos, using the inverse variance method (METAL; ref. 23). The genomic control value for the meta-analyzed results was 1.007.

For the replication studies, statistical tests for the association with each SNP were conducted by a 1 *df* Cochrane–Armitage trend test. Per-allele ORs were estimated using logistic regression.

Risk modeling. In each population of stage I, we examined the association of 56 known risk variants for prostate cancer—45 independent variants and 11 risk variants at 8q24 that had an association with prostate cancer risk in previous European, African, and Japanese studies ($r^2 \leq 0.16$ in Europeans and $r^2 \leq 0.27$ in Asians with the exception of $r^2 = 0.52$ between rs1016343 and rs6983561 at 8q24; refs. 1, 3, 10, 24–31). SNP rs10090154 was used in place of rs11986220, as it is located in a predicted enhancer site (24). The risk SNP BD11934905 (1) is not on the Illumina 660W array and was not genotyped in this study. To model the cumulative genetic risk for the 56 variants, we summed the number of risk alleles for each individual and estimated the OR per allele for this aggregate unweighted allele count variable, serving as an approximate risk score appropriate for unlinked variants with independent effects of roughly the same magnitude for each allele. For individuals missing genotypes (2.7%) for a given SNP (range = 0%–1.27%; mean = 0.05%), we assigned the average number of risk alleles (2× risk allele frequency) to replace the missing value for that SNP. We also tested for differences in the effect of the risk score by race/ethnicity, age group (median of 64< years vs. 64≥ years), family history of prostate cancer, and stage of disease (localized vs. regional/distant disease).

Results

Genome-wide association study of prostate cancer

Study characteristics of the 2,075 prostate cancer cases and 2,100 controls in the MEC are presented in Supplementary Table S1 (Japanese cases/controls = 1,033/1,042; Latinos cases/controls = 1,043/1,057). The mean age for Japanese cases and controls was 64.0 and 63.9 years, respectively, and the mean age for both Latino cases and controls was 62.6 years. As expected, cases were more likely than controls (~1.7 times) to report a family history of prostate cancer. Among cases, approximately 47.6% and 37.7% of Japanese and Latinos presented with regional/distant disease, respectively.

Quantile–quantile plots of the distribution of test statistics for the comparison of genotype frequencies in prostate cancer cases versus controls showed no evidence of overinflation; the genomic inflation factor lambda (λ) was 0.986 and 1.008 in Japanese and Latinos, respectively (Supplementary Fig. S1A and S1B). For Japanese, in stage I, 69 SNPs (including 10 genotyped SNPs) had $P < 5 \times 10^{-8}$ (Fig. 1A). All of these genome-wide significant SNPs were at the 8q24 risk locus between 128.16 and 128.61 Mb and were correlated with the known risk variants in this region. No novel SNPs reached genome-wide significance ($P < 5 \times 10^{-8}$) in these stage I samples. The most notable putative novel association was seen with a cluster of 10 SNPs ($P < 8.0 \times 10^{-6}$; Table 1), spanning 802 kb at chromosome 2q33 that includes the genes *BOLL*, *PLCL1*, *COQ10B*, and *RFTN2*. For stage II, we selected the 69 genotyped SNPs with $P < 1.0 \times 10^{-4}$ and located outside of known risk regions for *in silico* replication in 1,583 Japanese prostate cancer cases and 3,386 Japanese controls (Supplementary Table S2). None of the associations with these 69 SNPs replicated with $P < 0.05$ and effect estimates in the same direction as in stage I. The results for the most significant SNPs in stage I ($n = 13$ with $P < 1 \times 10^{-5}$) are shown in Table 1.

For Latinos, in stage I, we observed no genome-wide significant associations ($P < 5 \times 10^{-8}$; Fig. 1B). We selected the 56 genotyped SNPs with $P < 1.0 \times 10^{-4}$ in stage I (Supplementary Table S3) to evaluate in stage II samples of 1,854 prostate cancer cases and 1,894 controls of European ancestry. The most significant association in stage I was with the imputed SNP, rs12873332 at 3q33 ($P = 1.41 \times 10^{-7}$); a genotyped proxy for this SNP (rs12874523; $r^2 = 0.7$ in HapMap MEX) did not replicate at $P < 0.05$ in stage II. SNP, rs17023900, at the known risk locus at 3p12 (6, 19) was associated with prostate cancer (stage I; OR = 1.45; $P = 7.01 \times 10^{-5}$) and replicated in the European population (stage II; OR = 1.58; $P = 3.05 \times 10^{-7}$). SNP rs17023900 was not correlated with the known risk variant, rs17181170 at 3p12, identified in Europeans (6; $r^2 = 0.07$ in CEU and $r^2 = 0.07$ in JPT) Yet, rs17023900 was somewhat correlated with the other 3p12 risk variant, rs9284813, identified in Japanese (19; $r^2 = 0.14$ in CEU and $r^2 = 0.65$ in JPT). The 3 top-ranked genotyped SNPs [rs4240731 (12q21), rs6102322 (*ZHX3*), and rs6129760 (*TOP1*); $P < 1.0 \times 10^{-5}$] for Latinos in stage I, outside of known risk regions, were not significantly associated with prostate cancer in stage II (Table 1). Of the remaining 53 stage I SNPs, only 2 SNPs (chromosome 13-rs9514490 and chromosome 8-rs11306015) were associated with prostate cancer in stage II, however, the effect estimates were in the opposite direction (Supplementary Table S3).

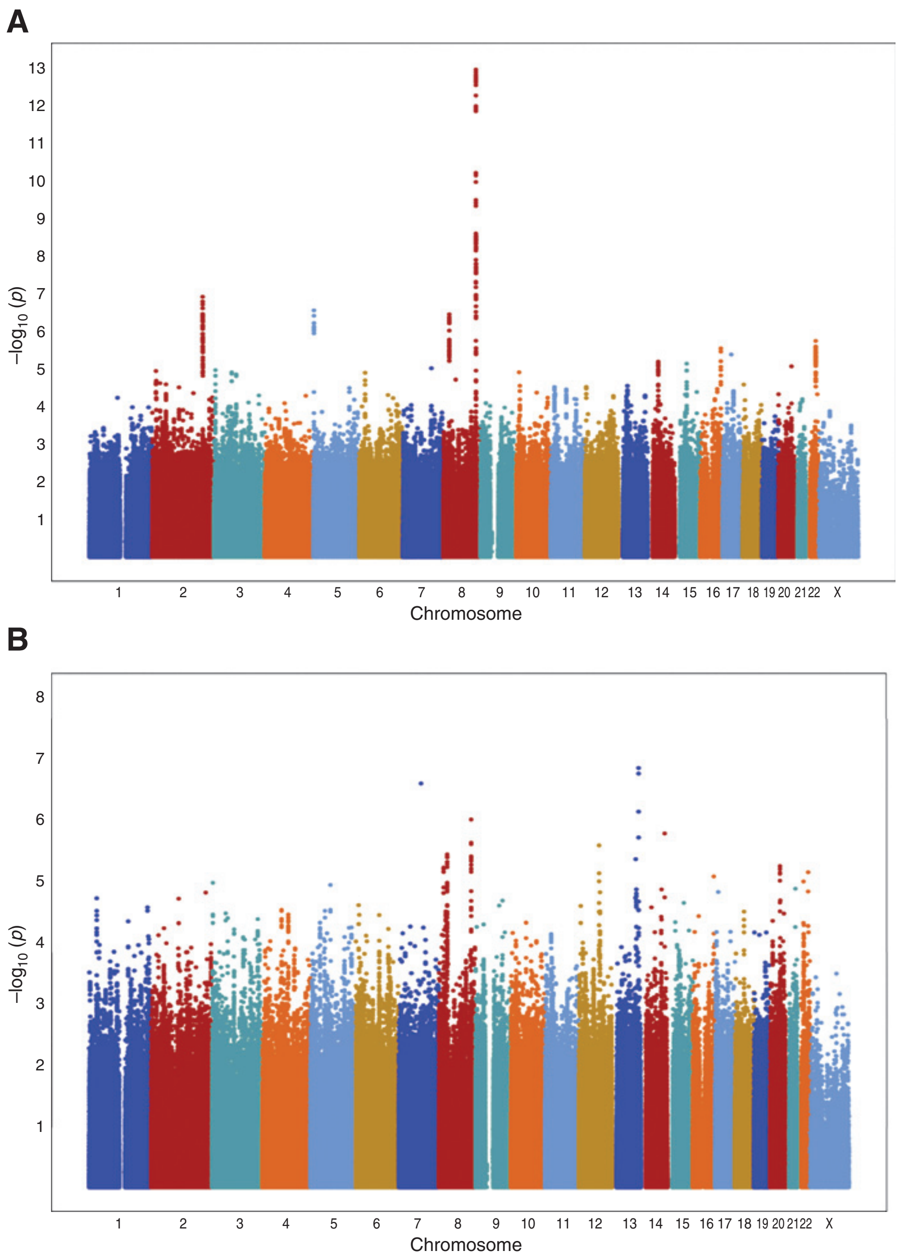

Figure 1. Manhattan plot for Latinos (A) and Japanese (B).

From the meta-analysis of stage I results for Japanese and Latinos, all genome-wide significant SNPs ($n = 10$; $P < 5 \times 10^{-8}$) were located at chromosome 8q24 (Supplementary Fig. S2). For SNPs with $P < 10^{-6}$ in the combined analysis (Supplementary Table S4), only 1 SNP, rs4999155 at 9q21 ($\mathrm{OR}_{\mathrm{meta}} = 1.32$; $P_{\mathrm{meta}} = 6.17 \times 10^{-7}$), was located outside of known risk regions. This SNP, rs4999155, was significantly associated with risk in both Japanese ($\mathrm{OR} = 1.31$; $P = 9.08 \times 10^{-4}$) and Latinos ($\mathrm{OR} = 1.33$; $P = 1.73 \times 10^{-4}$), but it did not replicate at $P < 0.05$ in the European GWAS of prostate cancer.

Testing of known risk variants

We tested, in stage I samples, 56 known prostate cancer risk variants located in 37 regions and in chromosome 8q24 (1–8, 18, 19, 26, 32–36); 51 were genotyped and 5 were imputed with high accuracy. The risk allele frequency ranged from 0.01 to 0.90 in Japanese and 0.12 to 0.92 in Latinos (Supplementary Fig. S3). Positive associations were observed with the majority of variants in each population (44 in Japanese and 49 in Latinos; Tables 2 and 3). Of the 56 risk variants, 18 SNPs were positively and significantly associated with prostate cancer risk in either

Table 1. SNPs outside of known risk regions at $P < 10^{-5}$ in Japanese and Latinos GWAS of prostate cancer

						MEC Japanese (cases/controls = 1,033/1,042)		Japanese (cases/ controls = 1,583/3,386)	
Chromosome	**Locus**	**SNP**	**Position**	**Coded allele/ref allele**	**Coded allele frequency**	**OR**	***P***	**OR**	***P***
2	Intergenic	rs10931777	197851836	T/C	0.84	0.66	1.23×10^{-7}	1.04	0.48
2	Intergenic	rs16824376	198392587	T/C	0.17	1.49	5.00×10^{-7}	0.97	0.61
2	*BOLL*	rs1851779	198355353	A/G	0.17	1.49	5.41×10^{-7}	0.97	0.61
2	Intergenic	rs6707521	198421476	A/G	0.17	1.49	5.47×10^{-7}	0.97	0.56
2	Intergenic	rs996427	198393854	T/C	0.17	1.49	5.51×10^{-7}	0.97	0.61
2	*PLCL1*	rs1595825	198583709	A/G	0.16	1.47	1.47×10^{-6}	0.97	0.54
2	*COQ10B*	rs3754822	198035559	T/C	0.17	1.45	1.84×10^{-6}	0.96	0.43
2	*PLCL1*	rs1016883	198589913	T/C	0.16	1.46	2.56×10^{-6}	0.98	0.64
2	*RFTN2*	rs2045244	198214711	A/G	0.18	1.45	2.68×10^{-6}	0.97	0.62
16	Intergenic	rs7202575	81005610	T/C	0.08	1.62	2.92×10^{-6}	0.90	0.13
16	Intergenic	rs7202694	81005355	G/A	0.08	1.59	6.33×10^{-6}	—	—
22	*GTPBP1*	rs4821815	37435653	A/G	0.53	0.75	6.47×10^{-6}	0.95	0.24
2	*PLCL1*	rs6434955	198654796	A/G	0.16	1.43	8.00×10^{-6}	0.96	0.49
						MEC Latinos (cases/controls = 1,043/1,057)		**UK (cases/ controls = 1,854/3,748)**	
12	Intergenic	rs4240731	80786862	G/A	0.28	1.36	2.60×10^{-6}	1.00	0.94
20	*ZHX3*	rs6102322	39306182	T/C	0.36	1.33	5.70×10^{-6}	0.99	0.81
20	*TOP1*	rs6129760	39179817	G/A	0.39	1.32	9.83×10^{-6}	0.98	0.74

Japanese or Latinos (Tables 2 and 3), with rs1512268 at 8p21, rs10993994 at 10q11, and 5 SNPs at 8q24 (rs10086908, rs13254738, rs6983561, and rs10090154) reaching statistical significance ($P < 0.05$) in both populations. For both Japanese and Latinos, the strongest associations were noted at 8q24, albeit with different SNPs, rs6983561 in Japanese, OR = 1.87; 95% CI: 1.58 to 2.22; $P = 3.8 \times 10^{-13}$; and rs10090154 in Latinos, OR = 1.68; 95% CI: 1.35 to 2.09; $P = 3.4 \times 10^{-6}$. The strongest association outside of chromosome 8q24 was with rs12653946 at 5p15 in Japanese (OR = 1.39; 95% CI: 1.22–1.57; $P = 3.4 \times 10^{-7}$), and rs5759167 at 22q13 in Latinos (OR = 1.22; 95% CI: 1.08–1.39; $P = 2.0 \times 10^{-3}$). At 8q24, all 11 of the risk variants, except for rs12543663, were positively associated with risk in Japanese and Latinos. In Japanese, 9 of 11 variants were significantly associated with risk (Table 3) with 4 remaining showing statistically significant independent genetic associations (rs10086908-region 1, rs13254738-region 2, rs6983561-region 2, and rs6983267-region 4). In Latinos, 5 of the 11 8q24 risk variants were significantly associated with prostate cancer and 3 showed independent significant associations (rs10086908-region 1, rs13254738-region 2, and rs6983561-region 2). Notably, the per allele OR for rs6983561 was approximately 1.5 in both populations, which is considerably larger as compared with effect estimates observed for other known risk alleles for prostate cancer (OR ~1.1–1.2).

Risk modeling of prostate cancer variants

Using the 56 prostate cancer risk variants (see Methods), we modeled their cumulative effect in Japanese and Latinos in stage I samples (Table 4). For Japanese, a 10% increased risk of prostate cancer was associated with each additional risk allele ($P = 2.71 \times 10^{-25}$). Japanese men at the top quartile of the risk allele distribution had a 3.7-fold increased risk of prostate cancer as compared with those at the lowest quartile ($P = 1.17 \times 10^{-21}$). For Latinos, a 7% increased risk of prostate cancer was associated with each additional risk allele ($P = 1.02 \times 10^{-16}$) and those at the highest risk quartile had a 2.8-fold increased risk of disease in comparison with men at the lowest risk quartile ($P = 1.10 \times 10^{-14}$). Heterogeneity in effects of the risk score by race/ethnicity was not statistically significant ($P_{\text{het}} = 0.06$). Stratified analysis of the risk score revealed similar patterns of associations across age groups ($P_{\text{het}} \geq 0.16$) and family history of prostate cancer ($P_{\text{het}} \geq 0.77$; data not shown). In addition, similar effects were seen for localized ($\text{OR}_{\text{JA}} = 1.10$; $P = 1.11 \times 10^{-15}$; $\text{OR}_{\text{LA}} = 1.07$; $P = 3.36 \times 10^{-11}$) and regional/distant ($\text{OR}_{\text{JA}} = 1.08$; $P = 9.47 \times 10^{-11}$; $\text{OR}_{\text{LA}} = 1.08$; $P = 1.49 \times 10^{-10}$) disease for both populations [Japanese (JA) $P_{\text{het}} = 0.13$; Latinos (LA) $P_{\text{het}} = 0.61$].

Given the strongest associations at 8q24 noted in Japanese in stage I, we also examined the effects of a risk score composed of only 11 variants at chromosome 8q24 (see Methods; Supplementary Table S5). The

Table 2. Associations with established risk variants for prostate cancer in Japanese (1,033 cases, 1,042 controls) and Latinos (1,043 cases, 1,057 controls)

			Japanese			Latinos		
Chr., marker	Position, alleles[d]	RAF[a] Europeans	RAF	Per allele OR (95% CI)[b]	*P*[c]	RAF	Per allele OR (95% CI)[b]	*P*[c]
2p24, rs13385191	20751746, G/A	0.2	0.57	1.03 (0.91–1.17)	0.66	0.27	1.16 (1.01–1.32)	0.037
2p21, rs1465618	43407453, T/C	0.23	0.66	1.19 (1.04–1.35)	1.0×10^{-2}	0.41	1.03 (0.91–1.17)	0.63
2p15, rs721048[e,g]	62985235, A/G	0.19	0.04	0.93 (0.68–1.27)	0.65	0.16	1.26 (1.07–1.48)	5.2×10^{-3}
2p15, rs2710647	63067474, C/T	0.55	0.73	1.05 (0.91–1.2)	0.50	0.58	1.07 (0.95–1.21)	0.28
2p11, rs10187424	85647807, T/C	0.55	0.64	0.98 (0.86–1.11)	0.73	0.64	1.16 (1.02–1.33)	0.026
2q21, rs12621278	173019799, A/G	0.94	0.77	1.13 (0.97–1.31)	0.11	0.92	1.34 (1.05–1.71)	0.018
2q37, rs2292884	238107965, G/A	0.26	0.25	1.11 (0.96–1.27)	0.16	0.28	1.10 (0.96–1.27)	0.16
3p12, rs2660753	87193364, T/C	0.11	0.24	1.14 (0.98–1.31)	0.08	0.19	1.23 (1.06–1.44)	7.2×10^{-3}
3q21, rs10934853	129521063, A/C	0.28	0.52	0.93 (0.82–1.05)	0.24	0.40	0.97 (0.86–1.10)	0.65
3q23, rs6763931	142585522, A/G	0.43	0.35	1.16 (1.02–1.32)	0.019	0.40	1.03 (0.91–1.16)	0.68
3q26, rs10936632[g]	171612795, A/C	0.52	0.42	1.16 (0.99–1.36)	0.06	0.39	1.04 (0.90–1.21)	0.60
4q22, rs12500426	95733632, A/C	0.46	0.44	1.05 (0.93–1.19)	0.43	0.54	1.13 (1.00–1.28)	0.046
4q22, rs17021918	95781900, C/T	0.66	0.62	0.99 (0.88–1.13)	0.93	0.72	1.08 (0.94–1.24)	0.27
4q24, rs7679673[f,g]	106280983, C/A	0.55	0.27	1.02 (0.87–1.21)	0.79	0.47	1.01 (0.88–1.15)	0.94
5p15, rs401681	1375087, C/T	0.55	0.67	0.97 (0.85–1.1)	0.59	0.61	0.93 (0.82–1.05)	0.25
5p15, rs12653946	1948829, T/C	0.42	0.43	1.39 (1.22–1.57)	3.4×10^{-7}	0.49	1.02 (0.90–1.15)	0.78
5p12, rs2121875	44401301, C/A	0.35	0.47	1.02 (0.9–1.16)	0.71	0.55	0.98 (0.87–1.12)	0.80
6p21, rs130067	31226489, G/T	0.23	0.36	0.99 (0.87–1.12)	0.82	0.29	0.92 (0.80–1.06)	0.23
6p21, rs1983891	41644405, T/C	0.27	0.42	1.04 (0.92–1.18)	0.52	0.38	1.16 (1.02–1.31)	0.025
6q22, rs339331	117316745, T/C	0.64	0.63	1.14 (1–1.29)	0.046	0.73	1.03 (0.89–1.18)	0.72
6q25, rs9364554	160753654, T/C	0.29	0.34	1.09 (0.95–1.24)	0.22	0.21	1.06 (0.91–1.23)	0.44
7p15, rs10486567	27943088, G/A	0.77	0.09	1.22 (0.99–1.5)	0.06	0.53	1.13 (1.00–1.28)	0.052
7q21, rs6465657	97654263, C/T	0.46	0.90	1.06 (0.86–1.3)	0.61	0.70	0.96 (0.84–1.10)	0.53
8p21, rs2928679	23494920, A/G	0.42	0.09	0.90 (0.73–1.12)	0.34	0.32	1.03 (0.91–1.18)	0.61
8p21, rs1512268	23582408, T/C	0.45	0.36	1.35 (1.19–1.53)	4.5×10^{-6}	0.44	1.21 (1.07–1.37)	2.8×10^{-3}
10q11, rs10993994	51219502, T/C	0.4	0.46	1.19 (1.05–1.34)	6.4×10^{-3}	0.35	1.19 (1.05–1.35)	6.4×10^{-3}
10q26, rs4962416	126686862, C/T	0.27	0.01	1.11 (0.61–2.08)	0.73	0.24	1.05 (0.91–1.22)	0.47
11p15, rs7127900	2190150, A/G	0.2	0.08	1.18 (0.95–1.47)	0.14	0.31	1.17 (1.02–1.33)	0.025
11q13, rs12418451[g]	68691995, A/G	0.28	0.09	0.90 (0.67–1.21)	0.49	0.22	1.08 (0.92–1.27)	0.34
11q13, rs11228565[g]	68735156, A/G	0.2	0.04	1.03 (0.75–1.41)	0.88	0.12	1.26 (1.05–1.52)	0.015
11q13, rs7931342	68751073, G/T	0.51	0.22	1.00 (0.86–1.16)	0.99	0.38	1.11 (0.98–1.26)	0.10
11q13, rs10896449	68751243, G/A	0.52	0.04	1.17 (0.88–1.56)	0.27	0.35	1.10 (0.97–1.25)	0.14
12q13, rs10875943	47962276, C/T	0.28	0.81	1.13 (0.96–1.32)	0.14	0.32	1.06 (0.93–1.21)	0.42
13q22, rs9600079	72626140, T/G	0.47	0.36	1.2 (1.06–1.36)	4.1×10^{-3}	0.39	1.02 (0.90–1.16)	0.71
17p12, rs4054823	13565749, T/C	0.56	0.57	1.08 (0.96–1.22)	0.20	0.49	1.09 (0.97–1.23)	0.17
17q12, rs11649743	33149092, G/A	0.8	0.71	1.08 (0.94–1.23)	0.28	0.82	1.27 (1.08–1.50)	3.8×10^{-3}
17q12, rs4430796	33172153, A/G	0.53	0.64	1.13 (0.99–1.29)	0.06	0.59	1.09 (0.96–1.24)	0.16
17q12, rs7501939	33175269, C/T	0.58	0.68	1.21 (1.06–1.38)	4.9×10^{-3}	0.67	1.04 (0.91–1.18)	0.56
17q24, rs1859962	66620348, G/T	0.46	0.25	1.06 (0.92–1.21)	0.43	0.60	1.14 (1.00–1.29)	0.045
19q13, rs8102476	43427453, C/T	0.54	0.37	0.87 (0.77–0.99)	0.030	0.49	1.07 (0.95–1.21)	0.29
19q13, rs266849	56040902, A/G	0.8	0.64	1.15 (1.01–1.31)	0.034	0.76	1.13 (0.98–1.31)	0.10
19q13, rs2735839	56056435, G/A	0.85	0.59	1.20 (1.05–1.36)	5.6×10^{-3}	0.76	1.15 (0.99–1.33)	0.07
22q13, rs5759167	41830156, G/T	0.53	0.66	1.11 (0.97–1.27)	0.13	0.58	1.22 (1.08–1.39)	2.0×10^{-3}
Xp11, rs5945572	51246423, A/G	0.35	0.08	1.10 (0.94–1.27)	0.23	0.16	1.09 (0.97–1.22)	0.15

[a] RAF, risk allele frequency in populations of European ancestry from previous reports or HapMap CEU population.

[b] Adjusted for age and the 1st 10 eigenvalues.

[c] Test of trend (1-df).

[d] Risk allele/reference allele.

[e] rs721048 not typed in Japanese and Latinos. Results for rs17432497 are shown for these groups ($r^2 = 0.98$ with rs721048 in HapMap CEU).

[f] rs7679673 not on Illumina 1M/660.

[g] Imputed SNP.

Table 3. Associations with known risk variants at 8q24 in Japanese and Latinos

Block[a], position	Marker, alleles[b]	RAF[c]	RAF	OR (95% CI)[d]	*P* value[e]	OR (95% CI) adjusted[f]	*P*-value
Japanese (1,033 cases and 1,042 controls)							
1, 127,993,841	rs12543663, C/A	0.31	0.08	0.98 (0.78–1.23)	8.30×10^{-1}	1.02 (0.79–1.31)	8.77×10^{-1}
1, 128,081,119	rs10086908, T/C	0.70	0.80	1.26 (1.08–1.48)	3.92×10^{-3}	1.27 (1.07–1.51)	7.11×10^{-3}
2, 128,162,479	rs1016343, T/C	0.20	0.26	1.48 (1.30–1.69)	5.23×10^{-9}	1.10 (0.90–1.34)	3.61×10^{-1}
2, 128,164,338	rs13252298, A/G	0.70	0.63	1.41 (1.24–1.61)	3.25×10^{-7}	0.97 (0.79–1.19)	7.92×10^{-1}
2, 128,173,525	rs13254738, C/A	0.35	0.54	1.59 (1.38–1.84)	4.23×10^{-10}	1.34 (1.06–1.69)	1.35×10^{-2}
2, 128,176,062	rs6983561, C/A	0.04	0.18	1.87 (1.58–2.22)	3.84×10^{-13}	1.52 (1.21–1.92)	3.88×10^{-4}
3, 128,404,855	rs620861[g], G/A	0.61	0.53	1.05 (0.93–1.19)	4.29×10^{-1}	1.08 (0.92–1.26)	3.42×10^{-1}
3, 128,410,090	rs16902104, T/C	0.14	0.24	1.13 (0.99–1.30)	8.02×10^{-2}	1.06 (0.89–1.26)	5.13×10^{-1}
4, 128,482,487	rs6983267, G/T	0.51	0.31	1.25 (1.10–1.42)	5.69×10^{-4}	1.21 (1.04–1.40)	1.13×10^{-2}
4, 128,510,352	rs7000448, T/C	0.36	0.22	1.20 (1.01–1.41)	3.33×10^{-2}	1.09 (0.90–1.31)	3.79×10^{-1}
5, 128,601,319	rs10090154, T/C	0.09	0.16	1.62 (1.38–1.92)	5.56×10^{-9}	1.06 (0.63–1.78)	6.89×10^{-2}
Latinos (1,043 cases and 1,057 controls)							
1, 127,993,841	rs12543663, C/A	0.31	0.37	0.92 (0.81–1.04)	1.93×10^{-1}	0.97 (0.84–1.11)	6.43×10^{-1}
1, 128,081,119	rs10086908, T/C	0.70	0.64	1.24 (1.09–1.41)	1.10×10^{-3}	1.22 (1.07–1.40)	3.91×10^{-3}
2, 128,162,479	rs1016343, T/C	0.20	0.13	1.19 (1.00–1.42)	5.66×10^{-2}	1.05 (0.86–1.29)	6.26×10^{-1}
2, 128,164,338	rs13252298, A/G	0.70	0.66	1.03 (0.91–1.18)	6.14×10^{-1}	0.96 (0.82–1.11)	5.52×10^{-1}
2, 128,173,525	rs13254738, C/A	0.35	0.44	1.19 (1.04–1.37)	9.93×10^{-3}	1.20 (1.02–1.40)	2.58×10^{-2}
2, 128,176,062	rs6983561, C/A	0.04	0.04	1.68 (1.25–2.26)	5.78×10^{-4}	1.49 (1.10–2.04)	1.13×10^{-2}
3, 128,404,855	rs620861[g], G/A	0.61	0.62	1.11 (0.98–1.26)	9.95×10^{-2}	1.09 (0.95–1.25)	2.03×10^{-1}
3, 128,410,090	rs16902104, T/C	0.14	0.11	1.19 (0.99–1.44)	7.09×10^{-2}	1.15 (0.94–1.40)	1.86×10^{-1}
4, 128,482,487	rs6983267, G/T	0.51	0.62	1.08 (0.95–1.23)	2.23×10^{-1}	1.06 (0.93–1.22)	3.85×10^{-1}
4, 128,510,352	rs7000448, T/C	0.36	0.32	1.09 (0.95–1.25)	2.39×10^{-1}	1.07 (0.92–1.25)	3.81×10^{-1}
5, 128,601,319	rs10090154, T/C	0.09	0.08	1.68 (1.35–2.09)	3.40×10^{-6}	1.30 (0.71–2.45)	4.68×10^{-1}

[a] As defined in Al Olama and colleagues (10).

[b] Risk/reference alleles.

[c] RAF, risk allele frequency in populations of European ancestry (EA) as reported previously (2–8, 26, 32–36) and in Japanese (JA) and Latinos (LA).

[d] Adjusted for age and the 1st 10 eigenvalues.

[e] Test of trend ($1 - df$).

[f] From multivariate model. OR adjusted for age and the 1st 10 eigenvalues and all other 8q24 risk variants.

[g] Imputed ($R^2 > 0.89$). rs445114 was not typed and could not be imputed.

associations of the 8q24 risk score were greater in each population than the risk score comprised all prostate cancer variants, highlighting the importance of this region in these populations. For Japanese, a 1.16-fold increased risk of prostate cancer was observed for each additional 8q24 risk allele ($P = 8.75 \times 10^{-19}$), whereas for Latinos, a 1.10-fold increased risk of disease was seen ($P = 1.83 \times 10^{-6}$). There was little evidence of heterogeneity in effects of the 8q24 risk score across race/ethnicity ($P_{\text{het}} = 0.15$).

A risk score composed of risk variants outside of the 8q24 locus (SNPs = 45) was associated with an 8% and 7% increased risk of disease, per additional risk allele, for Japanese ($P = 8.75 \times 10^{-13}$) and Latinos ($P = 1.03 \times 10^{-12}$), respectively (P_{het} for race/ethnicity = 0.42).

Discussion

In this GWAS of prostate cancer in Japanese and Latinos, 2 populations that experience the lowest incidence rates of prostate cancer in the United States, we did not identify novel risk variants that reached genome-wide significance. We did observe that the vast majority of the known prostate cancer risk variants were positively associated with risk, which extends our previous findings in these 2 populations (15). Specifically, effect estimates were more than 1 for 79% and 88% of the risk variants tested among Japanese and Latinos, respectively, suggesting that these markers are likely correlated with the biologically functional alleles in these populations. We also determined that, in aggregate, these variants significantly contribute to prostate cancer susceptibility in each population with each additional risk allele associated with a 10% and 7% increased risk of prostate cancer in Japanese and Latinos, respectively.

The inclusion of minorities in previous GWAS of prostate cancer has been notably absent. Of the 16 reports of GWAS of prostate cancer (2–8, 18, 19, 26, 32–36), only 2

Table 4. The association between the total risk score with prostate cancer in Japanese and Latinos

		Index markers from GWAS in Japanese ($n = 56$)	**Index markers from GWAS in Latinos ($n = 56$)**
Mean *N* of risk alleles, (range)		48 (32–67)	51 (35–69)
OR per allele (95% CI)[a]		1.10 (1.08–1.12)	1.07 (1.06–1.09)
P value		2.71×10^{-25}	1.02×10^{-16}
Quartiles of risk alleles[b]			
Q1	*N* (cases/controls)	118/258	135/262
	OR (95% CI)	1.0 (ref.)	1.0 (ref.)
Q2	*N* (cases/controls)	206/254	222/262
	OR (95% CI)	1.77 (1.33–2.36)	1.64 (1.24–2.16)
	P value	8.94×10^{-5}	4.61×10^{-4}
Q3	*N* (cases/controls)	262/264	299/265
	OR (95% CI)	2.16 (1.64–2.86)	2.21 (1.69–2.89)
	P value	5.77×10^{-8}	6.55×10^{-9}
Q4	*N* (cases/controls)	447/266	387/268
	OR (95% CI)	3.68 (2.83–4.82)	2.80 (2.16–3.65)
	P-value	1.17×10^{-21}	1.10×10^{-14}

[a] OR (and 95% CI) adjusted for age and the 1st 10 eigenvalues.
[b] Quartiles based on distribution in controls.

studies have focused on minorities in the discovery stage, 1 of Japanese (19) and the other of African-Americans (18), with the remaining reports limited to men of European ancestry (2–8, 26, 32–36). In the GWAS of prostate cancer in Japanese (cases/controls = 4,584/8,801; ref. 19), 5 novel loci were identified (19). In the GWAS of prostate cancer in African-Americans, a novel risk variant at 17q21-*ZNF652* (18) was identified that is unique to men of African ancestry, suggesting that some prostate cancer risk variants may be population-specific. These findings from GWAS of prostate cancer in non-Europeans emphasize the importance of broadening GWAS to diverse populations to ensure the discovery of the complete spectrum of prostate cancer risk alleles. Although our GWAS of Japanese and Latinos did not identify novel loci for these 2 populations, we recognize that our sample size was smaller than contemporary GWAS; thus, limiting our ability to detect modest association signals. In addition, because of the lack of additional studies of prostate cancer in Latinos, we were unable to replicate our stage I findings in Latino populations and made use of available European data. The Latinos in the MEC are predominantly from Mexico and are highly admixed with Native American (38%), European (59%), and African (3%) ancestry (37). While replication testing of the most significant findings in Europeans allowed for discovery of alleles that are common in European groups, we may have missed alleles that may be important to Latinos. Additional large genetic studies of prostate cancer in Latinos will be needed to search for risk alleles that are more common in Native American populations.

Only a small number of studies have investigated the known prostate cancer risk variants among Asians and Latinos (1, 13, 14, 18, 19, 38). For Asians, only 2 small Japanese studies have examined risk variants of prostate cancer (14, 39) separate from the MEC's previous smaller reports (in sample size and number of SNPs), whereas a larger study of Chinese men has recently been conducted (15, 18, 40). Yamada and colleagues observed 1 variant at 3p12 (rs2660753) and 6 variants at chromosome 8q24 (rs13254738, rs6983561, rs16901979, rs1447295, rs10090154, and rs4430796) were associated with prostate cancer risk in 311 Japanese prostate cancer cases and 1,035 controls (14). Terada and colleagues reported an association between rs6983267 at 8q24 among 507 Japanese prostate cancer cases and 511 controls (39). Of the 5 novel risk loci (rs13385191, rs12653946, rs1983891, rs339331, and rs9600079) identified by the GWAS of prostate cancer in Japanese (19), we observed positive associations with all 5 variants and replicated significant associations with 3 of the risk variants (rs12653946, rs339331, and rs9600079). For the association at 3p12 (rs2660753) reported by Yamada and colleagues (14), we observed a nonsignificant positive association with the risk allele of rs2660753 among Japanese (OR = 1.14; $P = 0.084$) and a significant association in Latinos (OR = 1.23; $P = 7.2 \times 10^{-3}$). Of the previous 8q24 associations in these Japanese studies (14, 39), our findings in this larger MEC study confirm that there are multiple association signals at 8q24 (1, 41). Wang and colleagues in a study of Chinese men (40) examined the 5 prostate cancer risk variants identified in the Japanese GWAS of prostate cancer (19). Three of these risk variants (rs12653946, rs339331, and rs9600079) were associated with prostate cancer in Chinese men, providing evidence that some risk loci found in Japanese generalize to Chinese men (40). For Latinos, only 1 additional study outside the MEC has reported the effects of prostate cancer risk variants (42). In this study of 196 Latino prostate cancer cases and 472 controls, 12 SNPs at 8q24 were associated with prostate cancer risk (42). Overall, aside from our reduced power to detect the originally reported effect estimates of small magnitude (Supplementary Table S6), our study was able to show positive associations for the majority of risk variants (> ~80%) among Japanese and Latinos. Moreover, our study not only corroborates previous reports (14, 19, 39, 42) but also provides the largest and most comprehensive evaluation to date of known prostate cancer risk variants and their cumulative genetic effect among Japanese and Latinos.

Given adequate statistical power, there are many questions directed toward understanding the reproducibility of risk variants across populations. There are 3 possible scenarios to consider. First, the disease locus identified by GWAS of European populations may not be relevant in other populations because the functional allele is limited to Europeans. Second, the locus is important in other populations; however, a different variant (not the index SNP) is better in capturing risk in specific racial/ethnic populations, as patterns of LD may vary between the index variant and functional allele across ancestral groups. Thus, fine-mapping of risk loci in different racial/ethnic groups could identify the most appropriate variant for a particular population. Finally, the index risk variant identified in GWAS of Europeans is similarly associated with risk in other racial/ethnic groups. Directional consistency of an association for a given index signal across populations implies a shared functional common variant in each region and provides little support for the "synthetic association" model (43), which suggests that GWAS signals with common alleles are due to rare alleles, many of which are likely to be ethnically distinct. For the majority of the risk loci examined in this study, our observations support the existence of a common functional variant that is shared across populations.

As more prostate cancer risk variants are identified, the cumulative effects of these variants may have important clinical implications. With the 56 risk variants we examined, both Japanese and Latinos at the top quartile of the risk distribution had a highly significant approximately 3-fold increased risk of prostate cancer in comparison with those at the lowest quartile. In the absence of an established risk model of prostate cancer analogous to the Gail model for breast cancer (44), as more risk variants are identified, a SNP-based risk model for prostate cancer may serve as a useful tool to define high-risk populations for targeted screening regimens and may better inform clinical decision making. Such models in development incorporate SNPs and family history in predicting prostate cancer risk (45). For individuals not at the high end of a genetic risk score, the clinical usefulness of such genetic information is unclear. Given the potential risks and costs associated with prostate cancer screening (46), these men may be less inclined to seek screening.

In summary, we did not identify novel genome-wide significant prostate cancer loci for Japanese and Latino men. However, we established that known risk variants for prostate cancer contribute to prostate cancer susceptibility in these populations. The challenge remains to conduct large well-powered genome-wide scans and follow-up studies in diverse populations to further dissect the complete array of risk alleles that may contribute to prostate cancer risk across populations.

Disclosure of Potential Conflicts of Interest

F.C. Hamdy is employed by the University of Oxford as a head of the department. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health of England. No potential conflicts of interest were disclosed by the other authors.

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