Replication of Prostate Cancer Risk Loci in a Japanese Case–Control Association Study
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Background
Two prostate cancer genome-wide scans in populations of European ancestry identified several genetic variants that are strongly associated with prostate cancer risk. The effect of these risk variants and their cumulative effect in other populations are unknown.

Methods
We evaluated the association of 23 risk single-nucleotide polymorphisms (SNPs) with prostate cancer risk and clinical covariates (Gleason score, tumor aggressiveness, and age at diagnosis) in men of Japanese ancestry (311 case subjects and 1035 control subjects) using unconditional logistic regression. We also used logistic regression to test the association between increasing numbers of independently associated risk alleles and the risk of prostate cancer, prostate cancer aggressiveness, and age at diagnosis. All statistical tests were two-sided.

Results
Seven of the 23 SNPs (five independent loci) were associated with prostate cancer risk (P values ranged from .0084 to 2.3 × 10⁻⁸ and effect sizes [estimated as odds ratios, ORs] ranged from 1.35 to 1.82). None of the seven SNPs was associated with Gleason score or aggressive disease. rs6983561 and rs4430796 were associated with age at diagnosis (Ps = .0188 and .0339, respectively). Men with six or more risk alleles (27% of case patients and 11% of control subjects) had a higher risk of prostate cancer than men with two or fewer risk alleles (7% of case patients and 20% of control subjects) (OR = 6.22, P = 1.5 × 10⁻⁸).

Conclusions
These results highlight the critical importance of considering ancestry in understanding how risk alleles influence disease and suggest that risk estimates and variants differ across populations. It is important to perform studies in multiple ancestral populations so that the composite genetic architecture of prostate cancer can be rigorously addressed.


Genome-wide association studies have proven to be a particularly powerful method to discover the genetic variants underlying complex diseases, including prostate cancer. In contrast to linkage scans, which are powered to detect highly penetrant alleles, association studies detect alleles of lower penetrance. Recently, prostate cancer association studies have identified several variants as being strongly associated (P < 10⁻⁶) with prostate cancer risk (1–9). Consistent with other common disease risk alleles, the odds ratios (ORs) for the variants were typically less than 1.3. Most of the studies have been performed in populations of European ancestry. Therefore, the effect of these risk variants in other populations is unknown.

Understanding the consequences of inheriting these variants both within and between populations is extremely important. Prostate cancer, in particular, is a disease that differentially affects populations. For example, in the United States, men of African ancestry have the highest incidence rate of prostate cancer and men of Asian ancestry have the lowest incidence rate. One study suggests that some alleles confer risk across populations but that the magnitude of the risk differs (3). It is also possible that variants confer risk in one population but not in another, as exemplified by Broad11934905, one of the 8q24 risk variants, which was only polymorphic in African Americans in an initial report (3). More data on the association of single-nucleotide polymorphisms (SNPs) with prostate cancer in various populations are required before generalizable conclusions can be made.

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See “Notes” following “References.”

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Subjects and Methods

Study Subjects

DNA samples were obtained from Jikei University Hospital (Tokyo, Japan) and Mitsui Memorial Hospital (Tokyo, Japan). Case subjects in this study were 311 men of Japanese ancestry who were diagnosed with histologically confirmed prostate cancer at Jikei University Hospital between August 1, 2004, and December 31, 2006. Men of Japanese ancestry who were undergoing health screening at Mitsui Memorial Hospital during the same period were asked to participate as control subjects. A total of 1035 control subjects (967 healthy volunteers from Mitsui Memorial Hospital and 68 men without prostate cancer, as indicated by negative prostate biopsy) at Jikei University Hospital were included in the study. Although prostate-specific antigen was most likely measured in control subjects as a screening test, we only had this information for approximately 60% of the control subjects (all nonbiopsy control subjects).

Most case subjects had undergone both prostate-specific antigen screening and digital rectal examination during routine clinical visits, regardless of whether they had subjective symptoms. Blood samples were collected from 292 (23%) of the 1280 men who underwent needle biopsy and from 87 (42%) of the 208 men who underwent radical prostatectomy. The blood samples were collected during the protocol period before each procedure was performed.

We stored buffy coat immediately after blood collection at −80°C until we isolated DNA for genotyping of all case patients and control subjects. Age at diagnosis, serum prostate-specific antigen levels, Gleason score, and pathological stage were available for case patients. Gleason score was from biopsy reports (72%) or from surgical pathological reports (28%).

One senior pathologist at Jikei University Hospital (Masaaki Suzuki) reviewed the classification of the tumors, which had been characterized according to the Gleason scoring system and the TNM staging. Case patients were divided into low- and high-grade groups. In the low-grade group were those with Gleason scores of 4–6 or 7 (with 3 the most prominent component of differentiation and 4 the second most common). In the high-grade group were those with Gleason scores of 7 (with 4 the most prominent component of differentiation and 3 the second most common) and 8–10. Case patients were also stratified according to age (<66 or ≥66 years, the median age). We defined aggressive and less aggressive disease based on pathological stage and Gleason score. Tumors with a Gleason score of 7 (4 + 3) or higher, pathological stage T3 or higher, spread to lymph nodes, or metastasis (ie, either high-grade or non-organ-confined disease) were defined as aggressive disease; other tumors were defined as less aggressive disease.

Selection of SNPs for Genotyping

We selected 23 SNPs that had been associated with increased risk of prostate cancer using a threshold for statistical significance of \( P < 10^{-6} \) in association studies conducted in populations of European ancestry (1–9). Polymerase chain reaction and extension were performed according to the manufacturer’s instructions, and extended product sizes were determined by mass spectrometry using the iPLEX system (Sequenom Inc, San Diego, CA). The primer information is provided in Supplementary Table 1 (available online). We performed this experiment on the Sequenom genotyping platform (mass spectrometry) in the Center for Cancer Genome Discovery at Dana-Faber Cancer Institute. Genotyping procedures were performed as described in the iPLEX Application Guide (http://128.135.75.36/iPLEXGoldApplicationGuide.pdf).

Briefly, polymerase chain reaction solutions contained 10 ng of genomic DNA, 1.0 U of HotStar Taq polymerase (QIAGEN Inc, Valencia, CA), 9.75 mM MgCl₂, 3.0 mM of each dNTP (Invitrogen, Carlsbad, CA), and 1.0 µM of each primer in a volume of 6 µL. Polymerase chain reaction cycling conditions were 94°C for 15 minutes, followed by 45 cycles of 94°C for 20 seconds, 56°C for 30 seconds, and 72°C for 1 minute. Cycles were followed by a final extension at 72°C for 3 minutes. Shrimp alkaline phosphatase treatments were performed in a volume of 8 µL that contained the entire

Context and Caveats

Prior knowledge

Previously, 23 single-nucleotide polymorphisms were identified as being associated with prostate cancer risk in European populations.

Study design

Genetic association case–control study of the 23 single-nucleotide polymorphisms in a Japanese population; associations between disease aggressiveness and age at diagnosis were included. Associations per allele and of several alleles in combination were studied.

Contributions

A total of seven of the 23 single-nucleotide polymorphisms were associated with increased risk of prostate cancer in this study population, but no associations were found with disease aggressiveness or age at diagnosis. Men with six or more risk alleles had higher risk for prostate cancer than men with two or fewer alleles.

Implications

The findings in the Japanese population were somewhat different from those performed in European populations, although seven of the 23 single-nucleotide polymorphisms that were previously identified in the European population were associated with prostate cancer risk in the Japanese population in this study.

Limitations

Because of the multiple alleles tested, their rare frequency, and the population size, statistical power was limited.

From the Editors

Institutional review boards at both Jikei University School of Medicine and Dana-Farber Cancer Institute approved this study. Written informed consent was obtained from each participant.

Selection of SNPs for Genotyping

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polymerase chain reaction mixture and 0.5 U of shrimp alkaline phosphatase, with incubation at 37°C for 40 minutes. The iPLEX extension reactions were performed in a total volume of 10 µL that included the entire shrimp alkaline phosphatase reaction, iPLEX termination mix, iPLEX enzyme, and 5.625 µM of each extension primer. The samples were desalted with 6 mg of clean resin and then dispensed to a microarray chip (SpectroCHIP; Sequenom Inc).

The chips were scanned using the MALDI-TOF MS system, and the genotypes were analyzed by the MassARRAY Typer 3.4 (Sequenom Inc). All assays were performed by investigators who were blinded to the case or control status of the samples. The reactions were performed in 384-well plates with samples from case patients and control subjects interspersed. The average success rate for the 23 SNPs genotyped was greater than 99% (range = 97.2%–99.8%). As an internal control, genotyping was conducted twice in 159 samples (11.8% of total) with 100% concordance.

Statistical Analysis
Fisher exact test was used to test Hardy–Weinberg equilibrium for each SNP separately among control subjects using a cutoff of \( P \) value greater than .01. Genotype frequency differences between case patients and control subjects were tested using unconditional logistic regression. Odds ratios and 95% confidence intervals (CIs) for prostate cancer risk were estimated for men with the risk genotypes compared with the referent genotype under a codominant model, with \( P \) values reported from the additive model. Removal of the 68 biopsy-negative participants from the analysis did not change the effect estimates or the level of statistical significance materially. We used the referent genotype from the original reports (1–9) as the referent in this study. For SNPs in linkage disequilibrium, we only analyzed the SNP that remained in the model after performing logistic regression backward selection.

The five independent SNPs found to be statistically significantly associated with risk of prostate cancer (rs2660753, rs13254738, rs6983561, rs10090154, and rs4430796) were evaluated for association with specific phenotypes of prostate cancer (Gleason score, tumor aggressiveness [as defined above], and age at diagnosis). We tested the cumulative effects of the five statistically significant risk SNPs by counting the number of risk alleles associated with prostate cancer in each subject (categories 0–2, 3, 4, 5, and 6–10).

We then tested for heterogeneity between our statistically significant results and previously reported results in other ethnic groups. We chose to compare our results to the results of Haiman et al. (3) for the 8q24 SNPs because these were reported for multiple ethnic groups; we used the first report (1,8) for the other two SNPs. We generated a DerSimonian and Laird \( Q \) statistic and a \( P \) value using the beta and variance from each study (calculated from the OR and CIs from the previously published results).

Statistical Analysis System version 9.1 (SAS Institute, Cary, NC) was used for statistical analyses. All statistical tests were two-sided, and a \( P \) value less than .05 was considered statistically significant.

Population attributable risk (PAR%) was estimated for SNPs whose association with prostate cancer risk was statistically significant as follows:

\[
\text{PAR}\% = 100 \times \frac{p(OR - 1)}{[\frac{1}{(OR - 1)} + 1]},
\]

where \( p \) is the frequency of the allele associated with prostate cancer among control subjects and the \( OR \) is the odds ratio for allele. The joint PAR was calculated on the basis of the individual PARs of each associated SNP, assuming no multiplicative interaction among the SNPs, with the use of the following equation:

\[
1 - \prod_{i=1}^{n} (1 - \text{PAR}\%_i).
\]

In this equation, \( \text{PAR}\%_i \) is the individual PAR for each associated SNP calculated under the full model (10).

Individual region boundaries within 8q24 were those defined by Haiman et al. (3) as follows: region 1 from 128.54 to 128.62 Mb, region 2 from 128.14 to 128.28 Mb, and region 3 from 128.47 to 129.54 Mb.

Results
For case patients, the median age at diagnosis was 66.7 years (range = 47–85 years) and the median prostate-specific antigen value at diagnosis was 9.1 ng/mL (Table 1). Most (81.1%) case subjects had a Gleason score of 7 or lower. A subset of patients \( (n = 87) \) underwent radical prostatectomy with systemic lymph nodes dissection; 31 (35.6%) case subjects had pathological stage T3 and/or N+

Twenty-three SNPs representing 17 distinct loci were genotyped; nine SNPs mapped to 8q, three SNPs to 10q, two SNPs each to 11q and 17q, and one each to 2p, 3p, 6q, 7p, 7q, 19q, and Xp. One SNP was monomorphic (Broad11934905); the others did not deviate from Hardy–Weinberg equilibrium in control subjects using a threshold of \( P \) value greater than .01. Allele frequencies in case patients and control subjects for the 22 polymorphic SNPs were calculated (Table 2). All reference allele frequencies among control subjects (ranged from .89% to 63.8%) were similar to those of Japanese population from Tokyo based on the International HapMap project (National Center for Biotechnology Information genome, build 36) (data not shown).

<table>
<thead>
<tr>
<th>Case subject characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), y</td>
<td>66.7 (47.0–85.0)</td>
</tr>
<tr>
<td>PSA at diagnosis, ng/mL</td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td>19.5 (1.9–97.8)</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>9.1 (6.4, 14.0)</td>
</tr>
<tr>
<td>Gleason score, No. (%)</td>
<td></td>
</tr>
<tr>
<td>4–6</td>
<td>113 (36.3)</td>
</tr>
<tr>
<td>7 = 3+4</td>
<td>93 (29.9)</td>
</tr>
<tr>
<td>7 = 4+3</td>
<td>46 (14.8)</td>
</tr>
<tr>
<td>8</td>
<td>30 (9.6)</td>
</tr>
<tr>
<td>9–10</td>
<td>29 (9.3)</td>
</tr>
<tr>
<td>Pathological stage, No. (%)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>56 (64.4)</td>
</tr>
<tr>
<td>T3</td>
<td>27 (31.0)</td>
</tr>
<tr>
<td>Any T and N+</td>
<td>4 (4.6)</td>
</tr>
<tr>
<td>Any T and M+</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* Distributions for complete set of case patients except pathological stage, which was determined for 87 case subjects. M = metastasis; N = lymph nodes; PSA = prostate-specific antigen; T = tumor.
Seven risk SNPs located on previously identified regions at 8q24, 17q12, and 3p12 were statistically significantly associated with prostate cancer risk; 15 SNPs did not achieve statistical significance (Table 2). Two of the seven SNPs associated with prostate cancer risk SNPs, rs16901979 and rs1447295, were in strong linkage disequilibrium with rs6983561 and rs10090154, respectively ($D^2 = 1.0$ and $r^2 = 0.892$ and $r^2 = .576$, respectively). Therefore, we only included rs6983561 and rs10090154 because the other two SNPs did not independently contribute to risk; the following analyses evaluated five independent risk variants.

At 8q24, three risk SNPs were statistically significantly associated with prostate cancer across three independent regions [individual region boundaries within 8q24 are those defined by Haiman et al. (3); see “Methods”]. Two SNPs in 8q24 region 2 (rs13254738 and rs6983561) were statistically significantly associated with prostate cancer risk in this study with large effect sizes (additive OR = 1.59, 95% CI = 1.30 to 1.94, $P = 5.3 	imes 10^{-6}$ and OR = 1.81, 95% CI = 1.46 to 2.24, $P = 4.9 	imes 10^{-8}$, respectively). In 8q24 region 1, one SNP (rs10090154) was statistically significantly associated with prostate cancer risk in this Japanese population (OR = 1.41, 95% CI = 1.12 to 1.78, $P = .0038$).

The other two markers that demonstrated a statistically significant association were located on chromosomes 17q12 and 3p12. In the 17q region, two SNPs (rs4430796 at 17q12 and rs1859962 at 17q24.3) were previously reported to be associated with prostate cancer risk (2,8). In this Japanese population, however, only rs4430796 was associated with risk ($P = 4.9 	imes 10^{-5}$). Rs2660753, a variant located in a gene-poor region on chromosome 3, was also statistically significantly associated with prostate cancer risk ($P = .0005$).

The five SNPs that were associated with prostate cancer risk were evaluated for association with three specific clinical characteristics of prostate cancer: Gleason score, tumor aggressiveness, and age at diagnosis. No associations were found between SNPs and Gleason score or aggressive disease (Supplementary Table 2, A and B, available online). Rs6983561 and rs4430796 were associated with a younger (<66 years) age at diagnosis among case subjects ($P = .0188$ and .0339, respectively) (Supplementary Table 2, C, available online).

The cumulative effects of the alleles on risk and clinical variables were examined. Overall, men who carried six or more risk alleles (27% of case patients and 11% of control subjects) had a sixfold increased risk of developing prostate cancer compared with men who carried two or fewer of the risk alleles (7% of case subjects and 20% of control subjects) (OR = 6.22, 95% CI = 3.74 to 10.33, $P = 1.5 	imes 10^{-13}$) (Table 3). No statistically significant results were observed for total number of risk alleles and Gleason score or aggressiveness of prostate cancer (Supplementary Table 3, A and B,
Table 3. Association of total number risk allele with prostate cancer risk*

<table>
<thead>
<tr>
<th>Total number of risk alleles</th>
<th>Case patients (N = 307), n (%)</th>
<th>Control subjects (N = 1006), n (%)</th>
<th>OR (95% CI)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>24 (7.8)</td>
<td>202 (20.1)</td>
<td>1.00 (referent)</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>54 (17.6)</td>
<td>247 (24.6)</td>
<td>1.84 (1.10 to 3.08)</td>
<td>.0205</td>
</tr>
<tr>
<td>4</td>
<td>73 (23.8)</td>
<td>269 (26.7)</td>
<td>2.28 (1.39 to 3.75)</td>
<td>.0011</td>
</tr>
<tr>
<td>5</td>
<td>71 (23.1)</td>
<td>173 (17.2)</td>
<td>3.45 (2.08 to 5.73)</td>
<td>.1608</td>
</tr>
<tr>
<td>6–10</td>
<td>85 (27.7)</td>
<td>115 (11.4)</td>
<td>6.22 (3.74 to 10.33)</td>
<td>.1608</td>
</tr>
</tbody>
</table>

* Numbers of case patients and control subjects vary because of missing genotype data. CI = confidence interval; N = number of subjects.
† From two-sided Wald test from logistic regression.

available online). Compared with men who carried two or fewer risk alleles, however, men who carried six or more risk alleles had an increased risk of developing prostate cancer at a younger age (OR = 4.50, 95% CI = 1.62 to 12.49, P = .0039) (Supplementary Table 3, C, available online). On average, the age at diagnosis of prostate cancer decreased by 0.68 years for each additional risk allele (P = .004).

Two of the variants demonstrated statistically significant differences in effect size between populations. The effect of rs6983561 was statistically significantly stronger in this study than initially reported in European Americans and African Americans (Phet heterogeneity = .019 and .0186, respectively). Rs4430796 in this study compared with a previous study of European Americans (8) showed borderline statistically significant heterogeneity (Phet heterogeneity = .049). Heterogeneity of effect size was not observed for the remaining statistically significant risk variants (Table 4).

Discussion

Although many prostate cancer risk variants have now been identified, most initial scans and replication studies have been performed in European American populations. Because the prevalence of prostate cancer and the allele frequencies differ across populations, it is important to understand the effect of these markers in other people of other ethnicities. We therefore comprehensively examined the association between 23 previously identified risk SNPs and prostate cancer risk and clinical covariates in a hospital-based Japanese population from Tokyo and its environs. Seven SNPs from chromosomes 8q24, 17q12, and 3p12 were statistically significantly associated with prostate cancer risk (P values ranged from 0.0084 to 2.3 × 10−4), including some with large effect sizes (eg, rs6983561 additive OR = 1.81, 95% CI = 1.46 to 2.24). Although an additive odds ratio for rs6983561 may seem large in the context of many previous genome-wide association study findings, this result was similar to what was reported for Japanese Americans in the study by Haiman et al. (3) (OR = 1.78, 95% CI = 1.47 to 2.15).

To understand the cumulative effects of these variants on prostate cancer risk, we created a combined score of the total number of risk alleles from the five SNPs that were independently associated (ie, in linkage equilibrium) with risk. Men who carried at least six risk alleles had a sixfold increased risk of developing prostate cancer compared with men who carried two or fewer risk alleles. Because a large proportion of participants carried six or more risk alleles (27% of case patients and 11% of control subjects), the cumulative effects of these SNPs on prostate cancer incidence in Japan are substantial. Although we calculated the combined PAR% (Supplementary Table 4, available online) for these five SNPs (59.4%), we found the cumulative number of risk alleles to be a more intuitive measure for these nonmodifiable risk factors, given that the PAR% is often misinterpreted or overinterpreted (11).

A recent study on a Japanese population of 507 prostate cancer case patients (286 aggressive and 221 nonaggressive) and 511 control subjects examined the association of two SNPs at 8q24 with prostate cancer risk (12). The authors found that rs1447295 was associated (P = .041) with overall risk but more strongly associated with aggressive disease (P = .013), whereas rs6983267 was only associated with the risk of less aggressive disease (P = .0068).

Table 4. Heterogeneity of associations between Japanese population and Japanese American, European American, and African American populations*

<table>
<thead>
<tr>
<th>SNP, chromosome (region)</th>
<th>OR (95% CI), risk allele frequency in control subjects</th>
<th>Phet heterogeneity with current study†</th>
<th>Model, first author (reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs13254738, 8q24 (region 2)</td>
<td>1.59 (1.30 to 1.94), 64%</td>
<td>.454</td>
<td>Additive, Haiman (3)</td>
</tr>
<tr>
<td>rs6983561, 8q24 (region 2)</td>
<td>1.81 (1.46 to 2.24), 62%</td>
<td>.078</td>
<td>Additive, Eeles (1)</td>
</tr>
<tr>
<td>rs10090154, 8q24 (region 1)</td>
<td>1.41 (1.12 to 1.78), 16%</td>
<td>.049</td>
<td>Additive, Gudmundsson (8)</td>
</tr>
<tr>
<td>rs2660753, 3p12.1</td>
<td>1.42 (1.17 to 1.72), 15%</td>
<td>.078</td>
<td>Additive, Haiman (3)</td>
</tr>
<tr>
<td>rs4430796, 17q12</td>
<td>1.51 (1.24 to 1.85), 63%</td>
<td>.3452</td>
<td>Additive, Eeles (1)</td>
</tr>
</tbody>
</table>

* Each cell of the table gives ORs (and 95% CIs) and risk allele frequency in control subjects or Phet heterogeneity. AA = African Americans; CI = confidence interval; EA = European Americans; JA = Japanese Americans; OR = odds ratio; SNP = single-nucleotide polymorphism.
† Testing for heterogeneity of allele effects with the risk allele frequency in control.
Although the allele frequency for these SNPs was similar in our study and the study by Terada et al. (12) (0.34 and 0.17 compared with 0.38 and 0.18 for rs6983267 and rs1447295, respectively), we found limited evidence to suggest that rs1447295 and rs6983267, or any other risk SNPs, were associated with aggressive prostate cancer as defined by Gleason score and pathological stage. However, this could be because of limited power in these subgroup analyses. Rs6983561 and rs4430796 were statistically significantly associated with younger age at diagnosis ($P_s = 0.0188$ and 0.0339, respectively). In addition, using the “risk allele score,” men who carried six or more risk alleles had an increased risk of being diagnosed below the median age (66 years) compared with men who carried two or fewer risk alleles (OR = 4.50, 95% CI = 1.62 to 12.49, $P = 0.0039$). On average, the age at diagnosis of prostate cancer decreased by 0.68 years for each additional risk allele ($P = 0.004$); the average age at diagnosis for men with two or fewer risk alleles was 69.4, whereas it was 65.0 for men with six or more risk alleles.

Fifteen previously identified risk SNPs were not associated with prostate cancer in this population (P values ranged from 0.09 to 0.94). In the initial report, the Broad11934905 SNP was only polymorphic in African Americans (3); it was monomorphic in this Japanese population as well. A number of reasons exist as to why the variants did not replicate. First, it could be that the current study had insufficient power to detect the modest effect sizes. Second, the risk allele may affect both populations, but the magnitude of the effect differs because of gene–gene or gene–environment interactions. Finally, perhaps some of the variants only confer risk in one population and not another.

For the majority of these SNPs, limited power was most likely the issue (Supplementary Figure 1, A, available online). However, this study was well powered to detect the effect of one of the SNPs recently reported in African American men. Thus, there was substantial power (95%) to detect the large effect previously reported for rs7008482 (OR = 1.80) (13), but a statistically significant result was not observed. The frequency of the risk allele is more than twice as large in Japanese as in African Americans (39% vs 17%, respectively). Of note, we also observed no statistically significant association in a population of European ancestry (unpublished data).

We chose to use the two-sided $P$ values to determine statistical significance, which is conservative. Although this is in some sense a replication study, with the exception of the 8q24 SNPs, these associations have only been reported in European or European American populations. If we used a one-sided test, the statistical power improves (Supplementary Figure 1, B, available online); if a one-sided test was implemented, rs2735839 on chromosome 19q13 would also reach statistical significance at a 0.05 level.

Heterogeneity of effect size for the SNPs that were statistically significantly associated with prostate cancer risk was present for two variants. The effect of rs6983561 was much stronger here in the Japanese than initially reported in European Americans and African Americans (3) ($P_{heterogeneity} = 0.019$ and 0.0186, respectively), whereas the effect of rs4430796 was marginally stronger here than in European Americans (8) ($P_{heterogeneity} = 0.049$) (Table 4). European American and Japanese populations have different baseline risks for prostate cancer. One might assume, however, that the relative risk for a factor associated with a disease in one population would have a similar relative risk in another population. The heterogeneity we observe across ethnicities therefore could be because of a modification by other risk factors, such as gene–environment or gene–gene interactions. Future studies should investigate SNPs that are heterogeneous across populations to specifically address interactions, which may lead to an improved understanding of the differences in disease prevalence.

As previously mentioned, one limitation of this study to discuss is the power. Given the sample size and the low minor allele frequency of several of the SNPs, it is possible that we are missing true associations. In addition, the differences in effect size and the lack of statistically significant association with some of the SNPs studied and prostate cancer risk in this population could be because of differences in linkage disequilibrium patterns. The effect of the causal SNP could be the same across populations, but strength of the correlation between the marker we typed and the true causal SNP may be different in Japanese and European Americans. We would then observe differences in the strength of the association in this population. Also, because of varying strengths of linkage disequilibrium, the power to observe an association could be decreased in our study, which may explain why all SNPs did not reach statistical significance.

The results from this study highlight the critical importance of considering ancestry in understanding how risk alleles influence disease across populations. This study supports previous evidence showing that risk estimates differ across populations and that the actual variants may differ between populations (3,5,14). Examining variants (and their interactions with other variables) within and between populations will likely provide insight into the dramatically different incidence rates of prostate cancer. Additionally, given the number of recently identified risk SNPs, prostate cancer risk assessment tests are being discussed and marketed. Before applying those tests to men, it is important to understand ethnic differences so that the appropriate level of risk is applied to an individual.

References


Notes

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