Replication and Heritability of Prostate Cancer Risk Variants: Impact of Population-Specific Factors

Victor Virlogeux,1,2 Rebecca E. Graff,3 Thomas J. Hoffmann,1,3 and John S. Witte,1,3,4,5

Abstract

Background: Prostate cancer incidence and mortality rates vary across populations, with African American men exhibiting the highest rates. To date, genome-wide association studies have identified 104 SNPs independently associated with prostate cancer in men of European ancestry.

Methods: We investigated whether the ability to replicate findings for these 104 SNPs in African American, Asian, and Latino populations depends on variation in risk allele frequencies (RAF), strength of associations, and/or patterns of linkage disequilibrium (LD) at the associated loci. We extracted estimates of effect from the literature, and determined RAF and LD information across the populations from the 1000 Genomes Project.

Results: Risk variants were largely replicated across populations. Relative to Europeans, 83% had smaller effect sizes among African Americans and 73% demonstrated smaller effect sizes among Latinos. Among Asians, however, 56% showed larger effect sizes than among Europeans. The largest difference in RAFs was observed between European and African ancestry populations, but this difference did not impact our ability to replicate. The extent of LD within 250 kb of risk loci in Asian ancestry populations was suggestively lower for variants that did not replicate (P = 0.013).

Conclusions: Despite substantial overlap in prostate cancer risk SNPs across populations, the variation in prostate cancer incidence among different populations may still in part reflect unique underlying genetic architectures.

Impact: Studying different ancestral populations is crucial for deciphering the genetic basis of prostate cancer. Cancer Epidemiol Biomarkers Prev; 24(6): 938–43. ©2015 AACR.

Introduction

Prostate cancer is the second most commonly diagnosed cancer among men globally and the sixth most common cause of cancer death (1, 2). Prostate cancer incidence and mortality rates vary substantially across regions of the world. Rates are highest in developed countries and lowest in developing areas of Asia and Africa (2, 3). In the United States, African Americans have an incidence rate 1.6 times higher and a mortality rate 2.5 times higher than that in men of European Ancestry (4). This variation may reflect a number of factors, including distinctive screening practices, environment, and genetics (5–9).

Genetics are especially important given that prostate cancer is the most heritable common cancer, with a recent twin study estimating a heritability of 58% (95% confidence intervals, 52%–63%; ref. 10). Moreover, risk increases between 2- and 4-fold for first-degree male relatives of affected individuals (11). Genome-wide association studies (GWAS) have identified over 100 SNPs that are associated with risk of prostate cancer (12). Although a majority of these GWAS have been conducted among men of European ancestry, many of the SNPs that they have identified are also associated with prostate cancer risk among men of other ancestries (13, 14). Still, some SNPs have not replicated and the strength of associations for those that have is often variable across populations. Risk allele frequencies (RAF) of prostate cancer-associated SNPs also show substantial variation across populations. These disparities may drive population differences in heritability and may in part explain the epidemiologic variations in disease risk (15).

In this study, we evaluated whether the risk SNPs identified from previous GWAS help explain the race/ethnicity patterns of prostate cancer by analyzing data from existing studies of European, African American, Asian, and Latino populations. We compared these populations with respect to risk SNP allele frequencies, strength of associations, linkage disequilibrium (LD) patterns, and heritability. We aimed to help clarify whether SNPs identified are also associated with prostate cancer risk among men of other ancestries (13, 14). Still, some SNPs have not replicated and the strength of associations for those that have is often variable across populations. Risk allele frequencies (RAF) of prostate cancer-associated SNPs also show substantial variation across populations. These disparities may drive population differences in heritability and may in part explain the epidemiologic variations in disease risk (15).

Materials and Methods

Replication of risk SNPs

We evaluated 104 SNPs that were previously identified as significantly associated with an increased risk of developing...
prostate cancer in men of European ancestry (12, 14, 16–30). We determined the corresponding odds ratios (ORs) for each SNP from the literature for European, African American, Asian, and Latino populations (13, 16–28, 30–41). For African Americans, the ORs were obtained from two recent studies that evaluated the risk of prostate cancer for 82 and 21 SNPs, respectively (one SNP had no available data for African Americans from either study; refs. 13, 14). For Asians and Latinos, only a subset of the SNPs was available from the literature: 75 of 104 SNPs for Asians and 71 of 104 SNPs for Latinos (13, 14, 16–20, 22–28, 30–41). When several studies for one SNP were available for these two populations, an inverse variance weighted average of the ORs was calculated.

We evaluated whether the risk SNPs had similar estimates of association with prostate cancer across ancestral populations, comparing the European ancestry population with each other population. We also stratified these comparisons by whether the ORs were nominally significantly associated with prostate cancer in the non-European populations (P < 0.05). We then assessed whether the distribution of risk SNP association P values in the African American, Asian, and Latino populations was uniform. This was done by writing a Python script to look at the distribution of log ORs for risk SNPs, assuming that the overall lifetime risk of developing prostate cancer is 15% (based on the literature) and that the sibling recurrence risk (λs) is 3.14 (44, 48). Here, we used the INDI-V tool (http://cns.genomics.com/software; ref. 49). All other statistical analyses were performed with R version 3.1.1 (R Development Core Team).

Results

Figure 1 plots the logarithms of the ORs (logOR) for the associations of the 104 risk SNPs with prostate cancer, comparing the European ancestry population to the African American, Asian, and Latino populations (details for each risk SNP are given in Supplementary Table S1 and Supplementary Fig. S1). Overall, most of the logORs were larger in the European ancestry population, as expected since this is the population in which they were discovered (Fig. 1). LogORs for risk SNPs nominally associated with prostate cancer (P < 0.05, blue in Fig. 1) in the non-European populations were generally larger than those not associated with disease (P > 0.05, red in Fig. 1). Relative to the African American population, 83% of the logORs (85/103) were larger in the European population; nevertheless, 41% (41/103) of these SNPs had P < 0.05 (blue, Fig. 1) and 68% (28/41) of these nominally significant SNPs had a higher RAf in the African Americans (P = 0.008). In contrast, relative to Asians, only 44% of the logORs (32/75) were larger in the European population, 56% (42/75) of the SNPs were replicated (P < 0.05, blue, Fig. 1), and 52% (22/42) of these nominally significant SNPs had a higher RAf in the Asians (P = 0.89). Relative to Latinos, 73% of the logORs (52/71) were larger in the European population, 31% (22/71) of these SNPs had P < 0.05 (blue, Fig. 1), and 59% (13/22) of these nominally significant SNPs had a higher RAf in the Latinos (P = 0.23).

For the replicated SNPs (P < 0.05), fitting a linear regression to the logORs gave correlations of r² = 0.51 (P = 6.8 x 10⁻⁴), r² = 0.64 (P = 5.3 x 10⁻⁶), and r² = 0.23 (P = 0.30) between the European ancestry population and the African American, Asian, and Latino populations, respectively (blue dashed lines in Fig. 1). When repeating this analysis for the nonreplicated SNPs, there was no correlation for the African American or Asian populations (P = 0.90 and P = 0.81, respectively), but there was for the Latino population: r² = 0.45 (P = 0.001). The difference in results for the Latino population likely reflects the small number of replicated SNPs (15); the slopes of the lines for the replicated (blue) and nonreplicated (red) SNPs were very similar when comparing the European ancestry to Latino populations. These lines suggest that the Latino population had a suggestive trend toward replication of all of the risk SNPs.

To further evaluate potential replication, we plotted the association P values for each of the three non-European ethnic groups (Fig. 2). Doing so showed a clear clustering of small P values, with the remaining P values uniformly distributed.

As expected based on evolutionary history, we found that the largest difference in RAf was between the European and African American populations. The overall mean RAf was slightly higher among African Americans (2.5%) but not significantly different (P = 0.46). The mean difference in RAf between the two populations was higher (6.7%) when evaluating only the SNPs significantly associated with prostate cancer in the African American population (P < 0.05). The Asian and Latino populations had slightly higher (albeit nonsignificant) mean RAf than the European population when comparing the SNPs significantly associated with prostate cancer in these populations (0.4% and 2.2%, respectively).

To investigate patterns of LD around the risk SNPs, we looked at pairwise r² within 500 kb windows, and compared the mean
Genetic effects of SNPs nominally associated with prostate cancer \((P < 0.05)\) in each of the three non-European ancestral populations (Table 1; note that the European population means of \(r^2\) values differed slightly depending on what SNP association information was available for a given comparison population; hence they were lower in the Asian and Latino populations). As expected, the African American population had the lowest mean \(LD\) around the risk loci (Table 1). However, this \(LD\) did not differ based on whether the risk SNPs were replicated in African Americans \((P = 0.37)\). In addition, no significant difference in \(LD\) among Europeans was observed between these replicated and nonreplicated SNPs \((P = 0.19)\). However, we did observe a trend \((P = 0.087)\) toward such an \(LD\) difference with a smaller window size (200 kb instead of 500 kb). This suggests that among African Americans, the similarity between the \(LD\) for the replicated and nonreplicated SNPs may simply reflect lower overall \(LD\) in this population. In contrast, a higher mean \(r^2\) value was observed for replicated versus nonreplicated SNPs in the Asian population \((P = 0.013)\), whereas no difference in the \(LD\) among Europeans was observed between these replicated and nonreplicated SNPs \((P = 0.60)\). Slightly weaker but similar results were observed in the Latino population with a higher mean \(r^2\) value for replicated versus nonreplicated SNPs \((P = 0.054)\), whereas no such difference in the \(LD\) among Europeans was observed \((P = 0.15)\). These results for the Asian and Latino comparisons were essentially unchanged when using a smaller window (200 kb total; note that the GWAS arrays generally used for these studies have higher coverage in European than in other ancestral populations).

To assess how much heritability is explained by the risk SNPs and how it differs by ethnic group, we estimated the total proportion of heritability explained by the set of SNPs available for each population. The total heritability proportion for the 103 SNPs was 0.20 for Europeans and 0.10 for African Americans. The total heritability proportion for the 75 SNPs available for the Asian population was 0.17 for Europeans and 0.28 for Asians. The total heritability proportion for the 71 SNPs available for the Latino population was 0.14 for Europeans and 0.11 for Latinos.

**Discussion**

We found that most ORs for the prostate cancer risk SNPs were larger in Europeans than in African Americans or Latinos, but were similar between Europeans and Asians. We also observed that, for SNPs that replicated, the effect sizes in the European population
European GWAS in the different ethnic groups. Indeed, 60% of risk SNPs in populations of European ancestry. Moreover, a winner’s curse effect could have contributed to the differences observed regarding the strength of associations across the populations (50).

Our observation that regions exhibiting higher LD were more likely to replicate across populations may reflect better tagging of the potential causal variants by the GWAS arrays in high LD regions. This result supports the hypothesis that the most conserved regions between different ancestral populations (high LD) may be more associated with prostate cancer than the regions in which the LD is lower (e.g., if the potential causal variants are not necessarily shared across populations). Thus, when attempting to replicate results across different ancestral populations, one may need to fine map a broad region surrounding the index association finding.

Recent work has explored whether extensive fine mapping of prostate cancer risk loci in nondiscovery ethnic groups can improve replication (13). When fine mapping each European prostate cancer locus in search of more strongly associated risk SNPs in African Americans, the number of replicated SNPs (P < 0.05) increased from 30 of 82 (37%) to 44 of 82 (54%), and two of the 14 newly replicated variants in high LD with the index SNP (defined as r² > 0.80) may have actually been specific to African Americans (13). These results highlight the value of trans-ethnic fine mapping of GWAS loci to help identify causal variants that may vary across ethnic populations.

The differences in associations of SNPs with prostate cancer across the ancestral populations could also be related in part to the flip-flop phenomenon, which occurs when independent studies show associations between a SNP and trait for different alleles. This phenomenon may be attributable to varying LD architectures across populations (51). Another potential issue here is that although the 1000 Genomes Project includes many ethnic subgroups and tries to be representative of all ancestral populations, our findings depend on the accuracy of its information.

Concerning heritability, many previous studies have focused on the heritability of prostate cancer in family cohort and twin studies. The recent Nordic Twin Study of Cancer cohort (10) estimated that additive genetic effects account for 58% of the heritability of liability of developing prostate cancer, currently the highest estimate of heritability for any common cancer (52). Another recent study, based on 77 of the GWAS risk SNPs, estimated that these variants explain approximately 30% of familial risk (16). In contrast, we estimated the total heritability of prostate cancer attributed to a larger set of 103 SNPs to be 20% in the European population. This highlights the difference between estimating familiarity and heritability, although some may incorrectly interpret these estimates as exchangeable (53).

For the Asian population, we estimated an even higher total heritability proportion due to the prostate cancer risk variants (28%). Taken together, our findings confirm that further studies are needed to determine more accurate effect estimates across the different populations.

Heritability was calculated for each risk SNP, and provides no information about the actions of and interactions between individual genes. (53) Moreover, although our evaluation of LD gives

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**Figure 2.** Enrichment for small P values among SNPs that are significantly associated in European GWAS in the different ethnic groups.

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were correlated with effect sizes in the African American and Asian populations. The extent of LD in Asians and Latinos was lower in SNPs that did not replicate in these populations. A slight trend of lower LD was seen comparing the European with African American populations with a smaller window size. The prostate cancer risk SNPs appear to explain twice as much heritability in Europeans than African Americans (20% vs. 10%). In contrast, a higher estimated heritability was found in Asians than Europeans (28% vs. 17%; 75 risk SNPs) and no clear difference was observed between Europeans and Latinos (71 risk SNPs).

The results observed here regarding the strength of associations and extent of heritability are in part due to the discovery of the 104 risk SNPs in populations of European ancestry. Indeed, 60% of variants for African Americans, 44% of variants for Asians, and 69% of variants for Latinos were not replicated at P < 0.05, which suggests that either these variants are not adequately correlated with the underlying biologically relevant variant (8) or that further studies with larger sample sizes are required to have sufficient power to detect associations with these specific variants.
an idea of the global dynamic architecture of the genomic regions included in this study, it may also be interesting to conduct an evaluation of SNP–SNP interactions in the different populations in an attempt to better explain risk patterns across race/ethnicity groups. Indeed, Lin and colleagues studied the SNP–SNP interaction network in angiogenesis genes associated with prostate cancer aggressiveness and observed an association between five SNP–SNP interactions in three gene pairs and more aggressive prostate cancer (54). This approach is also supported by the genomic repartition of the SNPs associated with prostate cancer with some "hotspot" regions such as 8q24, where the heritability explained seems to be higher than in other genomic regions (Supplementary Fig. S3).

This study evaluates the LD and heritability across multiple populations for a set of SNPs associated with prostate cancer. Combining results from several studies with genomic data from the 1000 Genomes Project may help limit potential biases arising from individual GWAS (55). Although only some of the risk SNPs replicated across populations, the variation in associations across populations does not appear to explain the ethnic variation in prostate cancer risk. This situation is not unique to prostate cancer; difficulties replicating results across ethnic groups have been observed for other cancers (e.g., breast) as well as traits such as body mass index (56). Larger scale studies of ethnically diverse populations should help us further clarify these issues. Moreover, efforts are still needed to detect risk SNPs that are of particular importance and potentially unique to men of African and other ancestries, such as some of those at loci on chromosomal regions 8q24 and 17q21 (9, 26).

### Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

### Authors’ Contributions
Conception and design: V. Virlogeux, J.S. Witte
Development of methodology: V. Virlogeux, J.S. Witte
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): V. Virlogeux
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): V. Virlogeux, T.J. Hoffmann, J.S. Witte
Writing, review, and/or revision of the manuscript: V. Virlogeux, R.E. Graff, T.J. Hoffmann, J.S. Witte
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): V. Virlogeux
Study supervision: V. Virlogeux

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### References

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### Table 1. Comparison of LD at prostate cancer risk loci detected in European ancestry populations that were replicated versus not replicated in other ancestral populations

<table>
<thead>
<tr>
<th>Test population</th>
<th>Replicated SNPs</th>
<th>Not replicated</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>African Americans</td>
<td>Number of SNPs</td>
<td>41</td>
<td>60</td>
</tr>
<tr>
<td>AFR</td>
<td>0.13 ± 0.06</td>
<td>0.12 ± 0.05</td>
<td>0.99</td>
</tr>
<tr>
<td>EUR</td>
<td>0.21 ± 0.10</td>
<td>0.18 ± 0.09</td>
<td>0.01</td>
</tr>
<tr>
<td>Asian</td>
<td>Number of SNPs</td>
<td>42</td>
<td>32</td>
</tr>
<tr>
<td>ASN</td>
<td>0.24 ± 0.12</td>
<td>0.23 ± 0.09</td>
<td>0.05</td>
</tr>
<tr>
<td>EUR</td>
<td>0.21 ± 0.09</td>
<td>0.21 ± 0.08</td>
<td>0.05</td>
</tr>
<tr>
<td>Latino</td>
<td>Number of SNPs</td>
<td>22</td>
<td>49</td>
</tr>
<tr>
<td>LAT</td>
<td>0.21 ± 0.09</td>
<td>0.19 ± 0.08</td>
<td>0.05</td>
</tr>
<tr>
<td>EUR</td>
<td>0.22 ± 0.10</td>
<td>0.19 ± 0.09</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Note: LD is measured by the correlation coefficient (r2) between the index SNP reported as associated with prostate cancer in a European ancestry population and all other SNPs within a 500-kb window (250 kb on either side of the index SNP). For each index SNP in the different comparisons, a pair of mean r2 (one for each population) is calculated using all the r2 corresponding to the same pair’s index SNP in both populations. For each pair SNP/index SNP with both r2 were under 0.05 in both populations, the pair was excluded from the analysis. LD is based on data from the 1000 Genomes Project; further details are given in Supplementary Table S2.

Data for each mean of each index SNP are reported in Supplementary Table S2.

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