Short Communication

Evaluation of 11 Breast Cancer Susceptibility Loci in African-American Women

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Abstract

Recent genome-wide association studies (GWAS) have identified multiple common genetic risk variants for breast cancer among women of Asian and European ancestry. Investigating these genetic susceptibility loci in other populations would be helpful to evaluate the generalizability of the findings and identify the causal variants for breast cancer. We evaluated 11 GWAS-identified genetic susceptibility loci for breast cancer in a study including 2,594 African-American women (810 cases and 1,784 controls). Two single-nucleotide polymorphisms, rs13387042 (2q35) and rs1219648 (FGFR2 gene), were found to be associated with breast cancer risk. Risk increased nearly linearly with the number of affected risk alleles, with a 2-fold elevated risk for women homozygous for the risk alleles in both single-nucleotide polymorphisms. No additional significant associations, however, were identified for the other nine loci evaluated in the study. The results from this study extend some of the recent GWAS findings to African-Americans and may guide future efforts to identify the causal variants for breast cancer.

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Introduction

Recent genome-wide association studies (GWAS) conducted among Chinese women (1) or women of European ancestry have identified multiple single-nucleotide polymorphisms (SNP) associated with breast cancer risk (2–6). It is unclear, however, whether these genetic variants may also be associated with breast cancer risk among African-American women whose genetic architecture differs considerably from other ethnic groups. In this review, we evaluated 11 GWAS-identified loci in relation to breast cancer risk in African-American women using data from two ongoing studies, the Southern Community Cohort Study (SCCS) and the Nashville Breast Health Study (NBHS).

Materials and Methods

The SCCS is a prospective cohort study initiated in 2002 focusing on investigating racial disparities in cancer risk (7). Included in the current project were 527 women that reported having a prior breast cancer diagnosis and provided a blood or buccal cell sample at the baseline interview. Controls (n = 1,054) were selected randomly from those who were cancer-free at baseline and frequency-matched to cases in a 2:1 ratio on age at enrollment (±1 y), recruitment method, and sample type (blood/buccal cell). The NBHS, a population-based case-control study (1), provided additional subjects to the current project. Incident breast cancer cases were identified through the Tennessee State Cancer Registry and a network of major hospitals that provide medical care for patients with breast cancer. Controls were identified via random digit dialing of households in the same geographic area as cases and frequency-matched to cases on age (5-y group). Included in the current project were 291 cases and 178 controls that provided buccal cell samples. To increase the statistical power of the study, additional controls (n = 564) were randomly selected from cancer-free SCCS participants and frequency-matched to NBHS cases by age (±1 y), family income, and education. In total, 810 cases and 1,784 controls from the SCCS and NBHS were included in the current study after excluding subjects whose DNA samples were limited.

In addition to the 12 SNPs initially reported from GWAS (Table 1), 20 additional SNPs were selected to tag all common SNPs (minor allele frequency, ≥5%) in a ±50 kb region flanking each of the initially reported SNPs. These common SNPs were identified from the HapMap data (release 24) that are in high linkage disequilibrium (r2 ≥ 0.8) with each of the initially reported SNPs in Chinese (for rs2046210) or European descendants (for all other SNPs) but not in Africans (r2 < 0.8). For the FGFR2
gene, two additional SNPs (rs2981578 and rs7895676) were considered, as these SNPs were reported to be potentially functional (8). SNP rs7895676, however, was found to be nonpolymorphic and was excluded from the analysis. No tagging SNPs were found for 5p12/MRPS30, 11p15.5/LSP1, and 16q24.1/unknown (1). A genetic score was constructed by counting the number of risk alleles each woman carries. A dose-response association was observed between the number of risk alleles and risk of breast cancer (P for trend, 0.004), with a 1.2-fold increase per risk allele and a 2-fold elevated risk observed for women homozygous for the risk alleles in both SNPs (Table 3). Having one or more risk alleles of these two SNPs was associated with a population-attributable risk of 37.9%.

To our knowledge, this is the first study in African-Americans that has systematically evaluated breast cancer susceptibility loci recently identified through GWAS. Results from our study are helpful to assess the generalizability of previously identified associations and guide fine-mapping efforts to search for causal variants. Of the 33 SNPs evaluated, 12 SNPs reported from previous GWAS and 21 tagging SNPs, only 2, in two different loci, were found to be significantly associated with breast cancer risk. This finding perhaps is not surprising, given the large difference in genetic architecture between African-Americans and European descent (10). On the other hand, rs803662 at 16q12.1 was not found to be associated with breast cancer risk in our study, whereas a significant association was identified in the study by Stacey et al involving 442 cases and 447 controls of African-Americans with an association in the opposite direction of that seen in other ethnic groups (6). The reasons for this inconsistency are unknown, and the sample sizes for both studies were small. In an attempt to explore the region surrounding previously reported susceptibility loci, for each locus, we

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chr/Gene</th>
<th>Position*</th>
<th>Allele†</th>
<th>Tested allele frequency (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>Reference‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs13387042</td>
<td>2q35/unknown</td>
<td>217614077</td>
<td>A/G</td>
<td>0.562</td>
<td>1.11 (1.03-1.20)</td>
<td>4.5 × 10^-15</td>
<td>Stacey et al. (5)</td>
</tr>
<tr>
<td>rs1041679</td>
<td>5p12/MRPS30</td>
<td>44742255</td>
<td>A/G</td>
<td>0.245</td>
<td>1.27 (1.19-1.35)</td>
<td>2.5 × 10^-12</td>
<td>Stacey et al. (6)</td>
</tr>
<tr>
<td>rs889312</td>
<td>5q11.2/MAP3K1</td>
<td>56067641</td>
<td>A/G</td>
<td>0.308</td>
<td>1.13 (0.99-1.29)</td>
<td>7.0 × 10^-10</td>
<td>Easton et al. (2)</td>
</tr>
<tr>
<td>rs2180341</td>
<td>6q23.3/ECHDC1</td>
<td>127642323</td>
<td>G/A</td>
<td>0.257</td>
<td>1.41 (1.25-1.59)</td>
<td>2.9 × 10^-8</td>
<td>Gold et al. (4)</td>
</tr>
<tr>
<td>rs2046210</td>
<td>8q21.1/unknown</td>
<td>151990599</td>
<td>A/G</td>
<td>0.351</td>
<td>1.36 (1.24-1.49)</td>
<td>2.0 × 10^-12</td>
<td>Zheng et al. (1)</td>
</tr>
<tr>
<td>rs15281615</td>
<td>8q24.1/unknown</td>
<td>128424800</td>
<td>A/G</td>
<td>0.458</td>
<td>1.06 (1.01-1.11)</td>
<td>5.0 × 10^-10</td>
<td>Easton et al. (2)</td>
</tr>
<tr>
<td>rs1219648</td>
<td>10q26.13/FGFR2</td>
<td>123336180</td>
<td>G/A</td>
<td>0.465</td>
<td>1.00 (1.0-1.02)</td>
<td>1.1 × 10^-10</td>
<td>Hunter et al. (3)</td>
</tr>
<tr>
<td>rs2981582</td>
<td>10q26.13/FGFR2</td>
<td>123342307</td>
<td>A/G</td>
<td>0.456</td>
<td>1.23 (1.18-1.28)</td>
<td>2.0 × 10^-19</td>
<td>Easton et al. (2)</td>
</tr>
<tr>
<td>rs3817198</td>
<td>11p15.5/LSP1</td>
<td>1865582</td>
<td>C/T</td>
<td>0.327</td>
<td>1.06 (1.02-1.11)</td>
<td>3.0 × 10^-9</td>
<td>Easton et al. (2)</td>
</tr>
<tr>
<td>rs8051542</td>
<td>12q12.1/TOX3**</td>
<td>51091668</td>
<td>C/T</td>
<td>0.451</td>
<td>1.27 (1.18-1.29)</td>
<td>1.0 × 10^-12</td>
<td>Easton et al. (2)</td>
</tr>
<tr>
<td>rs12443621</td>
<td>16q12.1/TOX3</td>
<td>51105538</td>
<td>A/G</td>
<td>0.458</td>
<td>1.10 (1.05-1.16)</td>
<td>1.1 × 10^-12</td>
<td>Easton et al. (2)</td>
</tr>
<tr>
<td>rs3803662</td>
<td>16q12.1/TOX3</td>
<td>51143842</td>
<td>A/G</td>
<td>0.248</td>
<td>1.23 (1.18-1.29)</td>
<td>1.0 × 10^-12</td>
<td>Easton et al. (2)</td>
</tr>
</tbody>
</table>

NOTE: ORs and P values presented in the table are from those published in the original articles.

*The position is based on the National Center for Biotechnology information database, Build 36.
†Tested allele/reference allele initially reported (based on forward strand).
‡Author (year) of the initial report.
§With the exception of rs2046210, data for Caucasians are provided.
¶From HapMap phase III (120 Caucasians, 90 Chinese, and 120 Africans), all others from HapMap phase II (60 Caucasians, 45 Chinese, and 60 Africans).
**Also known as the TNRC9 gene as reported initially.

Results and Discussion

Of the 33 SNPs, only rs13281615 (8q24.21) and rs12598982 (16q12.1) were found to deviate from the Hardy-Weinberg equilibrium at P ≤ 0.05. Significant associations (P < 0.05) with breast cancer risk were found for rs13387042 (2q35, P = 0.02) and rs1219648 (FGFR2 gene, P = 0.004; Table 2).

The pattern of the association for these two SNPs tended to be consistent in the SCCS and NBHS, although some of the study-specific point estimates were not statistically significant (Table 3). To evaluate the combined effect of these two SNPs, a genetic score was constructed by counting the number of risk alleles each woman carries. A dose-response association was observed between the number of risk alleles and risk of breast cancer (P for trend, 0.004), with a 1.2-fold increase per risk allele and a 2-fold elevated risk observed for women homozygous for the risk alleles in both SNPs (Table 3). Having one or more risk alleles of these two SNPs was associated with a population-attributable risk of 37.9%.

To our knowledge, this is the first study in African-Americans that has systematically evaluated breast cancer susceptibility loci recently identified through GWAS. Results from our study are helpful to assess the generalizability of previously identified associations and guide fine-mapping efforts to search for causal variants. Of the 33 SNPs evaluated, 12 SNPs reported from previous GWAS and 21 tagging SNPs, only 2, in two different loci, were found to be significantly associated with breast cancer risk. This finding perhaps is not surprising, given the large difference in genetic architecture between African-Americans and women of Chinese or European descent.

Similar to our study, a significant association between SNPs in the FGFR2 gene and breast cancer risk was also reported from a recent study conducted in 1,250 cases and 1,245 controls of African descent (10). On the other hand, rs803662 at 16q12.1 was not found to be associated with breast cancer risk in our study, whereas a significant association was identified in the study by Stacey et al involving 442 cases and 447 controls of African-Americans with an association in the opposite direction of that seen in other ethnic groups (6). The reasons for this inconsistency are unknown, and the sample sizes for both studies were small.

In an attempt to explore the region surrounding previously reported susceptibility loci, for each locus, we
evaluated all SNPs in a 100 kb region that are in strong linkage disequilibrium with the initially reported SNPs in subjects of Chinese (for rs2046210) or European descent (for all other SNPs), but not in Africans. None of these SNPs, however, were found to be associated with breast cancer in African-American women, indicating that these SNPs are neither causal variants nor in linkage disequilibrium with causal variants in African-Americans.

Table 3. Breast cancer risk associated with two SNPs in African-American women by study and by number of risk alleles

<table>
<thead>
<tr>
<th>SNP (locus)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR (95% CI)*</th>
<th>OR (95% CI)* per risk allele</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs13387042 (2q35)</td>
<td>810</td>
<td>1,784</td>
<td>1.23 (0.81-1.86)</td>
<td>1.45 (0.96-2.19)</td>
<td>1.20 (1.03-1.39)</td>
</tr>
<tr>
<td>ComBined</td>
<td>810</td>
<td>1,784</td>
<td>1.23 (0.81-1.86)</td>
<td>1.45 (0.96-2.19)</td>
<td>1.20 (1.03-1.39)</td>
</tr>
<tr>
<td>SCCS</td>
<td>519</td>
<td>1,607</td>
<td>1.04 (0.66-1.66)</td>
<td>1.14 (0.72-1.78)</td>
<td>1.08 (0.90-1.28)</td>
</tr>
<tr>
<td>NBHS</td>
<td>291</td>
<td>177</td>
<td>2.32 (0.90-6.01)</td>
<td>3.19 (1.24-8.19)</td>
<td>1.92 (1.10-3.31)</td>
</tr>
<tr>
<td>rs1219648 (10q26.13/FGR2)</td>
<td>812</td>
<td>1,783</td>
<td>1.14 (0.93-1.41)</td>
<td>1.47 (1.14-1.91)</td>
<td>1.21 (1.06-1.37)</td>
</tr>
<tr>
<td>ComBined</td>
<td>812</td>
<td>1,783</td>
<td>1.14 (0.93-1.41)</td>
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</tr>
<tr>
<td>SCCS</td>
<td>522</td>
<td>1,607</td>
<td>1.11 (0.87-1.42)</td>
<td>1.59 (1.17-2.14)</td>
<td>1.24 (1.07-1.45)</td>
</tr>
<tr>
<td>NBHS</td>
<td>290</td>
<td>176</td>
<td>1.30 (0.85-2.00)</td>
<td>1.15 (0.67-1.99)</td>
<td>1.10 (0.84-1.44)</td>
</tr>
</tbody>
</table>

*Adjusted for age, education, and population structure. In the combined analyses, the study (SCCS or NBHS) structure was also adjusted.
Additional fine-mapping work in a larger region with more extensive coverage is needed to identify SNPs in these loci for breast cancer risk in African-American women.

The sample size of the study was not large. With the exception of a few SNPs, most of the SNPs evaluated in the study had a minor allele frequency of 0.2 or higher. It is estimated that the study had 80% statistical power to identify SNPs with a minor allele frequency of ≥20% and an allelic OR of ≥1.22 at a significance level of 0.05. Therefore, it is possible that some of the null associations observed in this study could be due to the inadequate statistical power to identify a weak association. Another possible limitation of the study is that patients with prevalent cancer were included in the SCCS. As reported recently, however, these variants were not associated with breast cancer survival (11), and thus, including prevalent cases is unlikely to introduce bias. Indeed, the results from the SCCS (prevalent cases) and NBHS (incident cases) were generally consistent.

The results from this study show the complexity of uniformly applying GWAS findings across ancestral groups. Large-scale studies are needed to identify genetic risk variants for breast cancer in this understudied African-American population.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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References

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