Introduction

The availability of inherited cancer (IC) panel genetic testing has expanded the diagnosis of hereditary cancer syndromes and the identification of at-risk individuals. For some genes, like BRCA1/BRCA2, pathogenic variant rates in women with breast cancer of varying ethnic backgrounds have been reported. Some pathogenic variants that are more common in certain ethnic backgrounds (e.g. BRCA1/BRCA2 Ashkenazi Jewish founder variants) have been well-described and have directed the establishment of practice guidelines that include appropriate testing algorithms. Little is known about the differences in pathogenic/likely pathogenic (P/LP) variant frequency between ethnic backgrounds in genes other than BRCA1/BRCA2. Understanding of such differences may aid in the identification of genes and/or variants that are more common in certain populations, thus leading to more appropriate and cost-effective testing.

Results

- A total of 498 women were identified to have a P/LP variant in a gene other than BRCA1/BRCA2 (5.8%). Eight Caucasian women and 1 African American woman also carried a P/LP variant in BRCA1/BRCA2, while 7 Caucasian women were found to have 2 P/LP variants in non-BRCA1/BRCA2 genes. Stratified by ethnicity, 6.5% (437/6730) of Caucasian women, 3.3% (13/400) of Asian women, 3.5% (81/2391) of African American women, and 3.1% (17/542) of Hispanic women were found to have a P/LP variant (compared to BRCA1/BRCA2) with yields of 2.8%, 6.0%, 4.5% and 8.1%, respectively. (Table 1) When subdividing Ashkenazi Jewish women from the larger Caucasian population, there was a similar rate of P/LP variants (18/288, 6.3%).
- Among Caucasian women, 22.1% (1484/6730) had a Variant of Uncertain Significance (VUS) as the highest reportable result compared to 39.5% (158/400, p=0.0001) of Asian women, 30.3% (267/881, p=.0001) of African American women and 24.9% (135/542, p=0.1328) of Hispanic women. (Table 1)
- Women reporting only a Caucasian background were significantly more likely to carry a P/LP variant than women who reported only African American (p=0.0003), Hispanic (p=0.0012) or Asian (p=0.0078) background, (Table 1) There was no significant difference in the frequency of multiple primary tumors in Caucasian women versus the other ethnic groups. Caucasian women were not more likely to report a family history of breast, colon, endometrial, pancreatic, ovarian or stomach cancer when compared to other ethnic backgrounds.
- When stratified by category of gene in which the P/LP variants were identified (moderate risk, newly described, Lynch-associated, high risk), there were no significant differences between the groups. (Figure 1)

Table 1. Pathogenic/Likely Pathogenic (P/LP) and Variant of Uncertain Significance (VUS) Rates by Ethnicity

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Women with breast cancer</th>
<th>Women with 1 or more P/LP Variant</th>
<th>P/LP variant rate</th>
<th>p value</th>
<th>Women with overall VUS result</th>
<th>VUS rate</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>6730</td>
<td>437</td>
<td>6.5%</td>
<td>--</td>
<td>1484</td>
<td>22.1%</td>
<td>--</td>
</tr>
<tr>
<td>African American</td>
<td>881</td>
<td>31</td>
<td>3.5%</td>
<td>0.0003</td>
<td>267</td>
<td>30.3%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Asian</td>
<td>400</td>
<td>13</td>
<td>3.3%</td>
<td>0.0078</td>
<td>158</td>
<td>39.5%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hispanic</td>
<td>542</td>
<td>17</td>
<td>3.1%</td>
<td>0.0012</td>
<td>135</td>
<td>24.9%</td>
<td>0.1328</td>
</tr>
<tr>
<td>Total</td>
<td>8553</td>
<td>498</td>
<td>5.8%</td>
<td></td>
<td>2044</td>
<td>23.9%</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

- In a cohort of 8,553 women with breast cancer, those who reported only a Caucasian ethnicity had a higher P/LP variant frequency when compared to women of Asian, African American or Hispanic descent.
- The difference in P/LP variant frequency was not due to a higher frequency of multiple primary tumors in these women nor was it due to a reported family history of cancer. A possible explanation for the differences in variant rates between ethnicities may be the amount of literature available on variants identified in each background; fewer studies on variants found in non-Caucasian populations, for example, may contribute to a higher VUS rate.
- An understanding of the differences in variant frequency between ethnicities may lead to the identification of certain founder variants and allow for better clinical care and more appropriate IC testing in the future.

References


Figure 1. Breakdown of P/LP Variants Observed in Each Ethnic Background

Entry for Table 1. Pathogenic/Likely Pathogenic (P/LP) and Variant of Uncertain Significance (VUS) Rates by Ethnicity