A Breast Cancer Risk Model Incorporating Tyrer-Cuzick Version 8 and a Polygenic Risk Score for Diverse Ancestries

Elisha Hughes, PhD; Braden Probst, MStat; Holly J. Pederson, MD; Timothy Simmons, MStat; Brian Morris, BS; Susan M. Domchek, MD; Charis Eng, MD, PhD; Monique Gaye, MD; Ora Gordon, MD; Jennifer R. Klemp, PhD, MPH; Semanti Mukherjee, PhD; Kenneth Offitt, MD; Olufunmilayo Olopade, MD; Mark E. Robson, MD; Joseph Vijai, PhD; Pat W. Whitlatch, MD, FACS, FSSO; Susanne Wagner, PhD; Jerry S. Lanchbury, PhD; Thomas P. Slavin, MD; Alexander Gutin, PhD

BACKGROUND

- Breast cancer (BC) risk assessment is important for guiding personalized screening and preventive interventions.
- In clinical practice, Tyrer-Cuzick Version 8 (TCv8) is used to estimate BC risk based on age, breast density, family cancer history, and other clinical factors.
- Accuracy may be improved by combining TCv8 with a polygenic risk score (PRS).
- We recently developed and validated a PRS for diverse ancestries based on 149 common genetic variants (PRS-149).
- PRS-149 incorporates 56 ancestry-informative and 93 BC-associated variants.
- Here, we describe a BC risk model that combines PRS-149 with TCv8 (CRS).

METHODS

- Study subjects were referred for hereditary cancer testing and negative for pathogenic variants in BC susceptibility genes.
- A development cohort of 12,363 women with Breast Imaging Reporting and Data System (BI-RADS) breast density measurements was used to test the extent to which breast density and PRS-149 improve BC risk stratification over family history and other clinical factors.
- Even though PRS-149 uses ancestry-specific SNPs to guide the reported risk, subsamples herein were grouped for analyses based on self-reported ethnicity.
- We used multivariable logistic regression to test breast density and PRS-49 for association with risk of BC.
- An independent test cohort of 6,030 women with BI-RADS assessment was used to evaluate risk stratification.
- Relative contributions of family history, breast density, other clinical factors in TCv8, and PRS-149 were examined by adding terms sequentially to an ANOVA model.
- We compared differences in classiﬁcations of women as high (≥20%) versus low/moderate (<20%) remaining lifetime risk according to TCv8 versus CRS.

RESULTS

- In the development cohort, increased breast density was significantly associated with higher risk of BC (p=2.4x10^-6) with an effect size consistent with its weighting in TCv8.
- PRS-149 improved BC risk stratification over age, breast density, and family history (OR per unit standard deviation: 1.40, 95% CI: 1.36–1.45; p: 3.7x10^-6).
- PRS-149 was weakly but signiﬁcantly correlated with both family history (r=0.08) and breast density (r=0.01).
- After adjusting for multiple testing, no other factors were signiﬁcantly correlated with CRS.
- For family history, breast density, and other clinical factors (Figure 1).
- Adding PRS-149 to TCv8 signiﬁcantly altered risk estimates for women of all ancestries, with 16.3% of patients classiﬁed differently by CRS versus TCv8 in the independent test cohort (Table 2).
- Among patients who were classiﬁed as high-risk by TCv8 in the independent test cohort, 25.1% were downgraded by CRS and, among patients classiﬁed as low/moderate by TCv8, 10.9% were upgraded by CRS (Figure 2).

CONCLUSIONS

- This is the ﬁrst BC risk model that includes breast density, family history, and a PRS based on genetically determined ancestry that is validated for diverse populations.
- The addition of PRS-149 substantially improved risk stratification over TCv8 alone and may therefore lead to enhanced BC risk reduction and early detection strategies such as preventive medications and increased surveillance, respectively.

Table 1. Patient Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N = 12,363)</th>
<th>BC Unaffected (N = 11,555)</th>
<th>BC Unaffected (N = 6,030)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-Degree Relative(s) with BC</td>
<td>N (%)</td>
<td>5,029 (48.6%)</td>
<td>4,812 (42.1%)</td>
</tr>
<tr>
<td>Age at Testing (years)</td>
<td>Range</td>
<td>18-84</td>
<td>18-84</td>
</tr>
<tr>
<td>Self-Reported Ancestry</td>
<td>Asian</td>
<td>254 (2.05%)</td>
<td>228 (1.97%)</td>
</tr>
<tr>
<td></td>
<td>Black/African</td>
<td>856 (6.92%)</td>
<td>782 (6.77%)</td>
</tr>
<tr>
<td></td>
<td>European*</td>
<td>9,481 (76.69%)</td>
<td>8,920 (77.20%)</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>806 (6.52%)</td>
<td>746 (6.46%)</td>
</tr>
<tr>
<td></td>
<td>All Others</td>
<td>968 (7.81%)</td>
<td>878 (7.60%)</td>
</tr>
</tbody>
</table>

Table 2. Risk Reclassification by Ancestry

<table>
<thead>
<tr>
<th>Ancestry</th>
<th>CRS</th>
<th>Low</th>
<th>High</th>
<th>TCv8</th>
<th>CRS</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>46</td>
<td>6</td>
<td>117</td>
<td>23</td>
<td>60</td>
<td>32</td>
<td>1,349</td>
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<tr>
<td>Black/African</td>
<td>19</td>
<td>261</td>
<td>332</td>
<td>2,475</td>
<td>16</td>
<td>251</td>
<td>332</td>
</tr>
</tbody>
</table>

*Includes White/Non-Hispanic, and/or Ashkenazi Jewish

Figure 1. Relative Contributions of Risk Factors to CRS

Figure 2. Risk Reclassification