Background
Hormone receptor positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer, the most common immunohistochemical subtype, remains the dominant contributor to annual breast cancer deaths worldwide across all racial and ethnic groups. Black women are 41% more likely to die from breast cancer compared to White women, predominantly among women diagnosed ≤ 50 years of age. Yet, Black women remain underrepresented in clinical trials and population-based studies. Thus, it is critical to better characterize tumor molecular features from young Black women to identify factors contributing to the existing racial survival disparity. In the current study, we compared risk of distant recurrence signature, MammaPrint (MP), molecular subtyping signature, BluePrint (BP), and whole transcriptome analysis between young Black women with HR+ HER2- breast cancer compared to matched White controls.

Methods
Patients: This study included 196 Black women aged ≤ 50 with stage III, HR+ HER2- breast cancer of whom, 98 were recruited from 2009-2014 as part of the BEST study (5R01CA204819-04) randomly selected from FLEX and matched by age, tumor stage, nodal status, and receptor status.

Molecular Classification: Tumors were classified through MammaPrint as Low Risk versus High Risk, with Low Risk further stratified into Ultra Low Risk and Low Risk (non-Ultra Low), and High Risk stratified into High Risk 1 and 2. High Risk 2 tumors exhibit superior chemosensitivity as demonstrated in a prior large clinical trial of breast cancer patients (ISPY2).

MammaPrint and BluePrint classified tumors as Luminal A-type (Low Risk), Luminal B-type (High Risk), HER2-type, or Basal-type.

Whole Transcriptome Analysis: Differential gene expression analysis was performed with R packages limma to compare Black and White women and further compare within each molecular subtype. Differentially expressed genes (DEGs) with a false discovery rate ≤ 0.05 were significant.

Table 1. Clinical characteristics of patients
<table>
<thead>
<tr>
<th>Black Women (n = 186)</th>
<th>White Women (n = 186)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean)</strong></td>
<td>42.3 (5.77)</td>
<td>42.3 (5.72)</td>
</tr>
<tr>
<td><strong>N stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>95 (51.1%)</td>
<td>98 (52.7%)</td>
</tr>
<tr>
<td>N1+</td>
<td>76 (40.9%)</td>
<td>78 (41.9%)</td>
</tr>
<tr>
<td>N2</td>
<td>9 (4.8%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>TX</td>
<td>2 (1.1%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>27 (14.5%)</td>
<td>54 (29.0%)</td>
</tr>
<tr>
<td>G2</td>
<td>79 (42.5%)</td>
<td>50 (26.7%)</td>
</tr>
<tr>
<td>G3</td>
<td>39 (21.0%)</td>
<td>32 (17.2%)</td>
</tr>
<tr>
<td><strong>TX</strong></td>
<td>6 (3.2%)</td>
<td>6 (3.2%)</td>
</tr>
</tbody>
</table>

Figure 1. Frequency of MammaPrint risk category (A) and BluePrint molecular subtype (B) among Black and White women

Results

Figure 2. Differential gene expression in breast cancer from Black women compared to White women in each molecular subtype

Figure 3. Kaplan-Meier curves for overall survival (OS).

Conclusion
Among young women with localized HR+ HER2- breast cancer, MammaPrint and BluePrint identify genomic differences in risk and subtype distribution beyond that identified through clinical factors adjusted for age and tumor characteristics. It is important to identify patients with ER+ tumors that reclassify as Basal-type, which occur at a higher frequency in Black compared to White women, and have been reported to have worse outcomes compared to ER+ Luminal-type tumors. The transcriptional differences among Black compared to White women across all BP subtypes provide novel insights about tumor biological features. These findings have tremendous translational potential to identify etiologic underpinnings for racial survival disparities which may guide therapeutic strategies to improve outcomes.

References
1. Richardson et al. 2016. MMWR 65:1765-1775
3. SABCS 2021: P3-14-11

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