Identifying Homologous Recombination Deficiency in Breast Cancer: Genomic Instability Score Thresholds Differ in Breast Cancer Subtypes

Kirsten M Timms, PhD; Lauren Lenz, MS; Chris Neff, BS; Cara Sollomeno, BS; Darla Flake, PhD; Judy C Boughley, MD; Matthew P Goetz, MD; Andrea L Richardson, MD, PhD; Anna Maria Storniolo, MD; Alexander Gutin, PhD; Reisa M Connolly, MD; Vered Stearns, MD; Jerry S Lanbchury, PhD

1. Myriad Genetics, Inc., Salt Lake City, UT 2. Mayo Clinic, Rochester, MN 3. Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD 4. Indiana University, Indianapolis, IN 5. University College Cork, Ireland

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BACKGROUND

● Patients with homologous recombination (HR) deficient tumors may benefit from treatment with DNA damaging agents.

● Markers of genomic instability can be used to identify HR deficiency, including a 3 biomarker Genomic Instability Score (GIS).

● For patients with ovarian cancer (OC), the FDA-approved GIS threshold for identifying HR deficiency (HRD) is 42, set as the 5th percentile for BRCA deficient tumors.

● Recently, a lower 1st percentile cutoff of ≥ 33 was explored in OC; this threshold was significantly associated with improved outcome after platinum-based treatment.1,2

● Determining an optimal GIS threshold for different types of tumors is crucial, as the GIS distribution may vary between different cancers and even between different cancer subtypes.

● Triple-negative breast (TNBC) and estrogen receptor-negative breast cancer (ER+ BC) have been the primary focus of most breast cancer clinical trials evaluating outcomes based on HRD status. Here, we propose separate GIS thresholds for these subtypes, using the exploratory threshold of ≥ 33 for OC as a comparator.

● A total of 561 OC tumors (190 BRCA deficient), 118 TNBC tumors (46 BRCA deficient), and 406 ER+ BC tumors (76 BRCA deficient) were included across the 5 cohorts (Table 1).

● When score distributions were evaluated for BRCA deficient tumors, the GIS distribution within ER+ BC was significantly different than for OC (p=9.6x10-4) and TNBC (p=2.1x10-4) (Figure 1).

● The 1st percentile of a normal distribution fit in BRCA deficient ER+ BC tumors yielded a threshold of 24 (Figure 2).

RESULTS

Table 1. Cohort Summaries

<table>
<thead>
<tr>
<th>Cohort</th>
<th>BRCA Status</th>
<th>Timms et al</th>
<th>TBCRC008</th>
<th>TCGA</th>
<th>Abkevich et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian</td>
<td>Intact</td>
<td>83</td>
<td>288</td>
<td>23</td>
<td>199</td>
</tr>
<tr>
<td></td>
<td>Deficient</td>
<td>44</td>
<td>146</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Total Patients</td>
<td>127</td>
<td>434</td>
<td>44</td>
<td>213</td>
<td>55</td>
</tr>
</tbody>
</table>

In all cohorts, BRCA2 deficiency was defined as loss of function resulting from a BRCA2 or BRCA2 mutation with LOH in the affected gene. In Abkevich et al., TCGA, and Timms et al., deficiency may also be caused by methylation of the BRCA2 promoter region with LOH of BRCA1.

● Using a threshold of ≥ 33, 64.4% (76/118; 46/46 BRCA deficient) were GIS positive (Figure 3).

● Using the exploratory threshold of ≥ 33, 64.4% (76/118; 46/46 BRCA deficient, 30/72 TBCRC intact) of ER+ BC tumors were GIS positive (Figure 3).

● When compared to OC, the distribution of GIS for BRCA deficient tumors was different for ER+ BC, but not for TNBC. This indicates that different GIS thresholds are appropriate for breast cancer subtypes and that the GIS threshold developed for OC is not appropriate for ER+ BC.

● These findings are consistent with the fact that OC and TNBC are known to have similar molecular signatures.4

● Clinical validity and utility of the more inclusive 1% thresholds evaluated here for breast cancer (24 for ER+ BC and 33 for TNBC) should be examined in future studies to determine whether these cutoffs are associated with a benefit from treatment with DNA-targeting agents, as has been shown previously for the 1% threshold in OC.2

● The threshold difference observed between these cancer subtypes also suggests that cancer or cancer subtype specific thresholds may be needed as evaluations of HR deficiency expands beyond OC to identify candidates for PARP inhibitors.

CONCLUSIONS

● Using a threshold of ≥ 24, 45.1% (183/406; 75/76 BRCA deficient, 108/330 BRCA intact) of ER+ BC tumors were GIS positive (Figure 3).

● In contrast, the GIS distribution for TNBC was not significantly different than for OC (p=0.72) (Figure 3).

● These findings are consistent with the fact that OC and TNBC are known to have similar molecular signatures.8

REFERENCES