Characteristics of homologous recombination deficiency (HRD) in paired primary and recurrent high-grade serous ovarian cancer (HGSOC)

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BACKGROUND

- Defects in the homologous recombination (HR) pathway occur in up to 50% of epithelial ovarian cancers1 and have a major impact on treatment response to DNA damaging agents.
- A homologous recombination deficiency (HRD) assay has been developed to assess 3 metrics of genomic instability: TAI (regions of allelic imbalance), LOH (loss of heterozygosity), and LST (large-scale state transitions).
- Previous studies have shown that the HRD score is significantly correlated with progression-free and overall survival in ovarian cancer1,2 and predicts response to DNA-damaging agents in breast cancer.3,4
- Previous studies have been based on the HRD score in the primary, diagnostic tumor specimen.

OBJECTIVE

- Here we assess HRD in paired primary and recurrent HGSOC specimens to better understand possible changes in HRD during tumor recurrence.

METHODS

- Paired primary and recurrent HGSOC samples were obtained for 54 subjects. The majority of patients received platinum-based therapy.
- A total of 116 samples were obtained. Samples from 2 individuals were excluded due to uncertainty regarding the tumor histology.

HRD ANALYSIS

- All tumors were analyzed using the HRD assay, a next generation sequencing assay performed using DNA extracted from FFPE tumor tissue.5,6
- The HRD score is an algorithmic assessment of TAI (regions of allelic imbalance that extend to the subtelomere but do not cross the centromere),7 LOH (number of LOH regions >10 Mb but less than the length of a whole chromosome),8 and LST (breakpoints between regions of imbalance >10Mb after filtering out regions <3 Mb).9,10
- All tumor samples were also tested for LOH (number of alleles lost at the chromosome arm) and LST (breakpoints between regions of imbalance >10Mb after filtering out regions <3 Mb).
- All tumors were scored as either high (≥ 42) or low (< 42) HRD score.

RESULTS

- A homologous recombination deficiency (HRD) assay has been developed to
- The HRD score is an algorithmic assessment of TAI (regions of allelic imbalance that extend to the subtelomere but do not cross the centromere), LOH (number of LOH regions >10 Mb but less than the length of a whole chromosome), and LST (breakpoints between regions of imbalance >10Mb after filtering out regions <3 Mb).
- All tumor samples were also tested for LOH (number of alleles lost at the chromosome arm) and LST (breakpoints between regions of imbalance >10Mb after filtering out regions <3 Mb).
- All tumors were scored as either high (≥ 42) or low (< 42) HRD score.

Table 1. Tumor Characteristics

<table>
<thead>
<tr>
<th>Specimens</th>
<th>Total Tumor Samples</th>
<th>Primary-Recurrence Pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor characteristics</td>
<td>104</td>
<td>54</td>
</tr>
<tr>
<td>Evaluable HRD scores</td>
<td>85% (94/104)</td>
<td>73% (38/52)</td>
</tr>
<tr>
<td>High HRD score (≥ 42)</td>
<td>59% (52/88)</td>
<td>65% (26/40)</td>
</tr>
<tr>
<td>BRCA1 mutation</td>
<td>27% (28/104)</td>
<td>22% (12/52)</td>
</tr>
<tr>
<td>BRCA1 LOH</td>
<td>100% (100/100)</td>
<td>100% (52/52)</td>
</tr>
<tr>
<td>BRCA2 mutation</td>
<td>6% (6/104)</td>
<td>6% (3/52)</td>
</tr>
<tr>
<td>BRCA2 LOH</td>
<td>50% (50/100)</td>
<td>50% (50/100)</td>
</tr>
</tbody>
</table>

- Positive in either the primary and/or recurrent specimen
- LOH could not be determined in both samples of 4 pairs
- Positive in either the primary and/or recurrent specimen
- LOH could not be determined in both samples of 4 pairs

- Table 1.

Figure 1. Correlation between HRD Scores in Primary and Recurrent Tumor Samples.

- 17/52 (33%) primary-recurrent pairs had a mutation in BRCA1 (n=14) or BRCA2 (n=3) (Table 1).
- 10/38 (26%) primary-recurrent pairs had high HRD scores with intact BRCA1/2 (Table 1).
- HRD scores in specimens with BRCA1/2 mutations were highly correlated (p = 0.88) (Figure 1), despite evidence of additional acquired genomic rearrangements (Figure 3).
- HRD scores in specimens with BRCA1/2 mutations were higher in the recurrent than in the primary sample (p=0.064).
- A possible reversion mutation in BRCA1 was observed in one recurrent specimen (Figure 2).
- The original mutation is a 1 bp insertion that puts the transcript out of frame, resulting in a premature truncation of the transcript.
- These results suggest that characterization of HRD in primary or recurrent HGSOC specimens may be beneficial in selecting treatment strategies.

Figure 2. Possible BRCA1 Reversion Mutation

Figure 3. Genomic Profiles of Primary and Recurrent Tumor Samples.

- Examples are shown for tumors with similar (Left) and very divergent (Right) primary and recurrent pairs. The yellow line indicates regions of LOH (allele dosage of 0) and non-LOH (allele dosage of 1). Areas of divergence (red arrows) and similarity (green arrows) are indicated. HRD scores are at the bottom right of each profile.

CONCLUSIONS

- All markers of HRD examined, including mutations in BRCA1 and BRCA2, LOH in BRCA1 and BRCA2, and HRD score, were maintained between the primary and recurrent specimens.
- There was one possible reversion mutation in a recurrent sample; however, both the primary and recurrent tumors had high HRD scores and would be classified as HR deficient.
- High HRD scores (≥42) were observed in all specimens with mutations in BRCA1 or BRCA2, however, high HRD scores were more prevalent than mutations in BRCA1 or BRCA2 (60% versus 34%, respectively).
- These results suggest that characterization of HRD in primary or recurrent HGSOC specimens may be beneficial in selecting treatment strategies.

REFERENCES


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