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Rates of homologous recombination deficiency across different subtypes of ovarian cancer and in pre- and post-neoadjuvant chemotherapy tumor samples

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OBJECTIVES

- Homologous recombination deficiency (HRD) is defined as a pathogenic mutation in *BRCA1/2* and/or a positive Genomic Instability Score (GIS) status (defined as GIS ≥42).
- The GIS assay is a custom hybridization capture panel that targets SNPs distributed across the genome.
- Patients who have ovarian cancer (OC) with HRD may benefit from treatment with therapies that exploit HRD.
- To date, the majority of HRD studies in OC have focused on high-grade serous carcinoma and have not directly compared the subtypes or surgical sample (i.e., biopsy or resection).
- Here, we compared the rate of HRD across chemotherapy response scores (CRS), as well as across different OC subtypes.

METHODS

- Pathology reports were reviewed for a consecutive set of deidentified OC samples analyzed between 9/9/2020 – 1/8/2021.
- *BRCA1/2* mutation analysis captured both sequence variants and large rearrangements. Scores ≥42 were considered GIS-status positive.
- CRS were assigned as follows: 1-no or minimal response, 2-some response, 3-complete or near complete response.
- Tumor DNA percentage was directly determined by an algorithm. Samples with estimated tumor DNA percentage below 30% were considered low tumor DNA. No manual review was performed.
- Descriptive statistics were used for data presentation.

RESULTS

- Of 1351 patients, 1165 were resections, 141 biopsies, and 45 cytology specimens.
- 327 resections were known to be post-neoadjuvant chemotherapy, 274 of which were given a CRS (Table 1).
- Low tumor DNA percentages in resection samples with CRS 2-3 led to a 2- to 3-fold higher inconclusive rate compared to those with CRS 1 ($p=3.5 \times 10^{-4}$), and diagnostic biopsies ($p=4.0 \times 10^{-4}$; Table 1).
- HRD was observed at a higher rate numerically in tumors with CRS 2/3, compared to CRS 1, though this difference was not statistically significant (p=0.18; Figure 1).
- Compared to moderate and low grade endometrioid, low grade serous, clear cell, and mucinous, significantly higher rates of HRD were observed in mixed histology ($p=2.0 \times 10^{-8}$), high grade serous ($p=2.2 \times 10^{-16}$), carcinosarcoma ($p=1.5 \times 10^{-3}$), but not high grade endometrioid (p=0.1; Figure 2).
- High grade tumors had higher rates of HRD compared to moderate and low grade, borderline, and undifferentiated tumors ($p=3.3 \times 10^{-11}$; Figure 3).

Table 1. Relative inconclusive rates for post-neoadjuvant chemotherapy samples.

Sample type	N	Inconclusive rate*	Rate of low tumor DNA
Resections without neoadjuvant therapy	640	1.0	—
Resections with CRS 1	87	1.0	5.7%
Resections with CRS 2	150	3.3	23.3%
Resections with CRS 3	37	3.9	21.6%
Biopsy	141	1.4	—

*Relative to resections without neoadjuvant chemotherapy

Figure 1. HRD results by chemotherapy status and procedure type

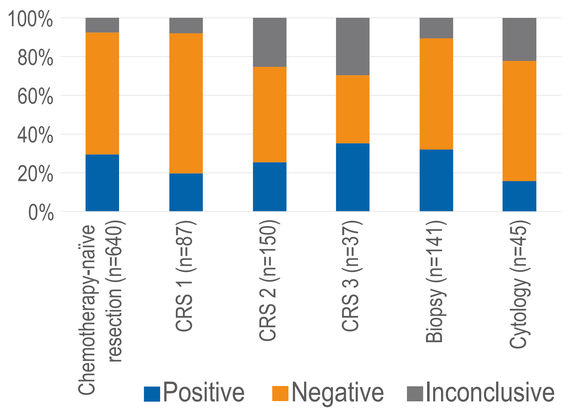


Figure 2. Rate of HRD by histologic subtype

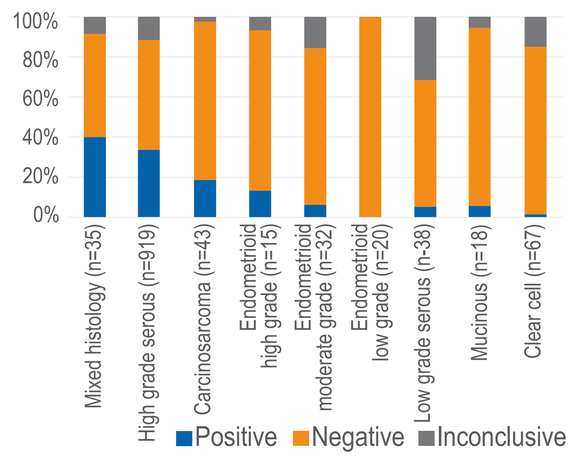
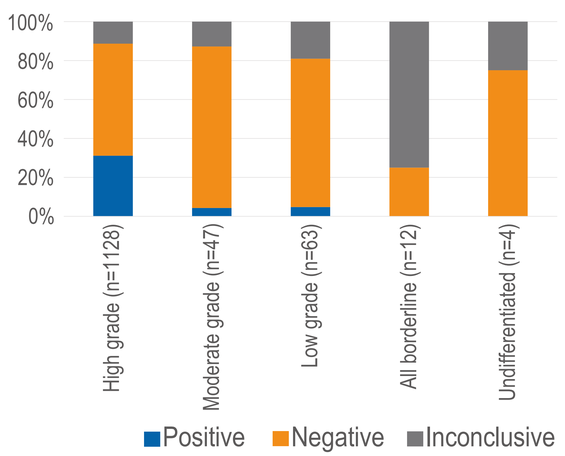


Figure 3. Rate of HRD by tumor grade



Higher inconclusive rates in some tumor subtypes may be due to complete lack of genomic instability in these samples which can make some samples perform as inconclusive. Patients with these sample types may benefit from comprehensive tumor testing that assesses deficiency in non-HR pathways.

CONCLUSIONS

- These data suggest that HRD testing is appropriate for all major ovarian cancer subtypes.
- Patients with certain tumor characteristics (e.g., CRS 2-3, mixed histology, high grade serous carcinoma, and carcinosarcoma) have higher rates of HRD.
- Importantly, due to the relatively low tumor DNA percentage in post-neoadjuvant chemotherapy resections with CRS 2-3, submission of pre-chemotherapy biopsies is optimal.

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