Detection of homologous recombination deficiency using cell-free DNA whole-genome sequencing profile in ovarian cancer

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Background: Ovarian cancer is a gynecological malignancy with the highest mortality rate. The primary type of ovarian cancer is high-grade serous carcinoma (HGSC), with 50 % of cases exhibiting homologous recombination deficiency (HRD). HRD-positive tumors respond favorably to platinum-based chemotherapy and poly (ADP-ribose) polymerase (PARP) inhibitors. Currently, determining HRD status necessitates expensive and time-consuming genomic profiling from tissue samples. Therefore, the development of new, broadly applicable methods is of paramount importance.

Objectives: The objective of this study is to investigate the potential of shallow whole-genome sequencing (sWGS) on cell-free DNA (cfDNA) for therapy optimization in ovarian cancer.

Methods: The study included 17 HGSC patients and 8 control patients. cfDNA was isolated from their plasma samples and sWGS was performed with 1-1.5x coverage. Downstream analyses, including fragment size examination and identification of copy number variations using the ichorCNA method, were conducted using the sequencing data. Large genomic alterations (LGA) are indicators of the HRD phenotype, and their quantitative determination allows for the assessment of HRD status.

Results: It is well-established that the concentration of cfDNA is elevated in cancer patients, a fact that our examination of samples also confirmed. Our results also showed that the average length of cfDNA reads is typically longer than the size of tumor-derived fragments. Specifically, we found significant differences between cfDNA fragments from control and HGSC samples. Using the inchorCNA method, we identified 7 HGSC samples with more than 20 LGA variants (which we defined as a cut-off value) and considered them HRD-positive.

Conclusion: In summary, cell-free DNA sWGS is a cost-effective method that can aid in the selection of personalized therapy for ovarian cancer patients based on their HRD status. Further investigations are planned on a larger patient cohort.