The application of ctDNA based tests in ovarian cancer diagnostic and research.

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Introduction

Ovarian carcinoma (OC) is one of the most common gynecological malignancy and accounts for approximately 239,000 new cases and 152,000 deaths worldwide annually. Because of non-specific symptoms and the lack of effective screening tests, most of the individuals are diagnosed with an advance disease (stage III or IV) with the 5-year survival rate below 30%. The overall frequency of germline and somatic variants is estimated at 15-20% and 3-10% respectively, with the majority of mutations being diagnosed in *BRCA1/2* genes. Circulating tumor DNA (ctDNA) is a valuable material and an important source of information on the OC molecular pathogenesis and is expected to be a diagnostic and prognostic marker in OC patients.

The aim of this study was to establish the prevalence and spectrum of pathogenic and likely pathogenic variants in the 93 cancer-related genes that may play a role in the development and progression of OC.

Material and methods

The study comprises 121 unselected OC patients who were referred to the University Hospital in Gdansk and the Red Cross Hospital in Gdynia between 2012 and 2013. The ctDNA was extracted using cfDNA Sample Preparation Kit, Roche Diagnostic, and mutation screening was performed using the BRCA Tumor MASTR Plus assay (Agilent) followed by Human Breast Cancer Panel (Qiagen, GmbH).

Results

In the studied group 24.8% of patients (n=30/121) were diagnosed with *BRCA1/2* pathogenic variants, including 22 and seven individuals with exclusively germline or somatic mutations, respectively and a patient with variants of both origins. Within this cohort, seven patients had more than one pathogenic variant.

Consequently, patients that were found to be negative for *BRCA1/2* pathogenic variants were eligible to further screening using Human Breast Cancer Panel. So far, the analysis was successfully completed in 50 patients. Within this group the most representative were pathogenic alterations in *TP53* gene, followed by pathogenic or likely pathogenic variants in

CSMD1, *KRAS*, *NF1*, *PIK3CA* and *SMARC4A*. Interestingly, the analysis revealed the presence of additional *BRCA1/2* mutations that had not been previously identified.

Conclusions

Our findings demonstrated that detection of both germline and somatic alterations is feasible and might be helpful as a complementary tool for identification of somatic alterations when the standard diagnostic procedures utilizing FFPE samples are insufficient.

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