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Dissertation thesis: Characterisation of hereditary factors in high-risk patients with gynecologic cancers

ABSTRACT

Ovarian cancer (OC) accounts for less than 5% of all cancer-related deaths in women worldwide. More than half of OC patients are diagnosed at an advanced stages with an unfavorable prognosis (with a 5-year survival rate of around 50%). The mean age at diagnosis is around 65 years. Characteristics of OC include a high proportion of hereditary cancers - a germline pathogenic/likely pathogenic variant (GPV) in cancer predisposition genes is identified in more than 20% of cases. However, we can distinguish a specific subgroup of early-onset OC patients (<30 years), in whom an atypically low proportion of hereditary forms is identified with a GPV detection rate in established OC predisposition genes falling below 10%. Thus, the genetic predisposition to early-onset OC remains unclear.

The hereby presented thesis focuses on a comprehensive genetic analysis of early-onset OC patients using whole-exome sequencing at both DNA and RNA levels, complemented by polygenic risk score (PRS) analysis and human leukocyte antigen (HLA) typing. In a cohort of 123 patients diagnosed with early-onset OC (<30 years), we identified only 6 (4.9%) GPV carriers in known OC predisposition genes. Furthermore, we proposed two possible alternative trajectories of inheritance. First, an breast cancer-like inheritance supported by the results of: i) the overrepresentation analysis showing GPV enrichment in breast cancer-associated genes; ii) the increased frequency of GPV carriers in *CHEK2*, a known breast cancer predisposition gene; and iii) the discriminatory ability of the PRS_{313} SNP set to stratify young OC patients from controls, which is commonly used to stratify women according to their breast cancer risk. The second trajectory of possible inheritance points to an immunogenetic cancer predisposition based on the increased frequency of GPV carriers in *LY75-CD302*, a gene involved in immune response and antigen presentation; and the increased frequency of the HLA-DRB1*11:01 allele carriers, previously associated with breast cancer predisposition. The immunogenetic predisposition is also supported by the increased frequency of HLA homozygotes in patients compared to controls impairing the spectrum of presentable antigens. Moreover, an increased germline mutation burden was found in patients with early-onset OC compared to controls. Thus, the hereditary component in high-risk early-onset OC patients does not only follow the

established Mendelian monogenic inheritance, but also extends to polygenic inheritance and immunogenetics.

The hereby presented thesis also includes a survival analysis of OC patients in the Czech Republic combining the results of two studies. We disproved the survival advantage of the rs2185379 carriers in *PRDM1* in Czech patients with advanced OC, that has been previously described in the Japanese population. On the contrary, consistent with previously published studies focusing on the Caucasian population, we confirmed that *BRCA1/2* GPV carriership, younger age at diagnosis and histologic type other than high-grade serous, especially low-grade serous OC, are positive prognostic factors.