

Polygenic inheritance and the risk of ovarian carcinoma

Ewa Grzybowska

Center for Translational Research and Molecular biology of Cancer, Maria Skłodowska-Curie National Research Institute of Oncology, Gliwice branch

High penetrance mutations in BRCA1 and BRCA2 explain around 25% of the observed familial relative risk and further 10% is explained by moderate risk mutations in MLH1, MSH2, MSH6, RAD51C, RAD51D and B RIP1. Genome-wide association studies (GWAS) have identified ~30 common low-risk SNPs that are associated with ovarian cancer, accounting for approximately 6.5% of the FRR. Their inclusion in ovarian carcinoma risk prediction models may improve risk precision. Providing refined personalized cancer risks can result in better risk stratification and hence help in improving early cancer detection and prevention.

In this study we genotyped 225 ovarian cancer patients, 64 breast and ovarian cancer patients and 348 healthy controls. In total, 12 polymorphic variants and 2 deletions in PGR, ABCB1, ABCG2, GSTT1, GSTM1, GSTP1, ATM, TP53 and ATP7B genes were analyzed using ASA-PCR, RFLP-PCR, multiplex-PCR and sequencing. Ten genetic polymorphisms were significantly associated with the risk of developing ovarian carcinoma in at least one of the groups under study. Impact of PGR gene polymorphisms on ovarian cancer risk was specific only for the group of the BRCA1 mutation carriers (in presence of p.Val660Leu variant- OR 2,82; $p = 0,010$), which confirms the difference in modulation of ovarian cancer risk between sporadic and hereditary malignancies, including the breast-ovarian cancer group (as a cancer-prone group). The analyses showed also the importance of ATP7B gene in ovarian carcinogenesis, both studied variants of which significantly modulated the ovarian cancer risk in all groups excluding the group with BRCA1 mutation. Cumulative risk analysis revealed 3 unfavorable variants that increased significantly the risk of developing ovarian cancer (p.Ile1145 ABCB1+ p.Asp1853Asn ATM+ p.Ser406Ala ATP7B-OR 7,47; $p = 0,002$) and significantly modified the progression free survival (PFS) of the patients, and also two favorable genotypes which protected against ovarian cancer (p.Arg952LysATP7B+ p.Arg72Pro TP53- OR 0,50; $p = 0,008$). PFS analysis for carriers of favorable versus unfavorable genotypes emphasized the impact of the regulation of cell cycle (p.Asp1853AsnATM) and active transport of xenobiotics (p.Ser894Ala/ThrABCB1) on the risk of disease progression (HR 3,81; $p = 0,010$) after paclitaxel/cisplatin chemotherapy. The unfavorable genetic variants could facilitate carcinogenic process and once their carriers developed malignancy, their chances of survival were smaller. Our analyses also showed a strong gene-dosage effect with the decrease of progression-free survival for the carriers of two unfavorable genetic factors.