Abstract

In my dissertation, I studied the genetic predisposition of selected types of cancer that have not been systematically studied in the Czech Republic.

We used next-generation panel sequencing to identify germline pathogenic variants. Analysis of 1333 patients with ovarian cancer, 527 patients with endometrial cancer, and 334 patients with hepatocellular carcinoma included sequencing using the CZECANCA panel. A specific CZMELAC panel was prepared for the analysis of 264 melanoma patients. We focused on the identification of pathogenic variants in known predisposition genes. We also evaluated candidate genes and phenotypic characteristics in carriers of pathogenic variants.

Analysis of high-risk melanoma patients revealed pathogenic variants in melanoma associated genes in 9/264 (3.4%) patients, and an additional 22 (8.3%) patients carried a pathogenic variant in one of the other predisposition genes. The odds of carrying a pathogenic variant were increased in probands with multiple melanomas and in the presence of melanoma in relatives. The incidence of germline pathogenic variants was highest in ovarian cancer, where pathogenic variants were found in 427/1332 (32.0%) patients, with a predominance of mutations in *BRCA1*, *BRCA2*, followed by alterations in other ovarian predisposition genes. Breast and ovarian cancer tumor duplicity and the presence of a family history of ovarian cancer were the strongest factors indicating the presence of a pathogenic variant, but we also detected 20% of pathogenic variants in patients without a positive family history. In a study of patients with endometrial cancer, carriers of pathogenic variants were identified in 60/527 (11.4%) cases, divided approximately equally between carriers of alterations in genes associated with breast and ovarian cancer and carriers of pathogenic variants in Lynch syndrome genes, which have a significantly higher risk of endometrial cancer at a significantly younger age. The presence of any cancer in the family was associated with an increased probability to carry a pathogenic variant. Analysis of patients with hepatocellular carcinoma detected the presence of a pathogenic variants in hepatocellular carcinoma associated genes in only 7/334 (2.1%) patients, indicating that analysis of tumor predisposition is not clinically informative in this diagnosis.

The results of this work contributed to the mapping of tumor predisposition in the studied cancers in the Czech Republic and the identification of phenotypic characteristics of high-risk patients, which may contribute to their improved diagnostics and prevention.

Key words: hereditary cancer predisposition, melanoma, endometrial cancer, ovarian cancer, hepatocellular cancer, panel sequencing, next generation sequencing, germline variants