Abstract

Pancreatic adenocarcinoma (PDAC) has one of the worst prognoses out of all cancers worldwide. Endometrial carcinoma (EC) is the most common gynecological cancer. Genetic background of tumors is highly heterogenous and differs among populations.

We have analyzed DNA of 226 PDAC patients and 527 EC patients using panel next-generation sequencing. Targeted genes were divided into main predisposition genes (11 for PDAC, 19 for EC) and other candidate genes. EC patients were categorized based on meeting the indication criteria for germline genetic testing. Two sets of population-matched controls were used (controls with negative cancer history, and general population controls).

Germline pathogenic variants (PV) in main predisposition genes were identified in 18 (8.0%) PDAC patients. The most mutated gene was *BRCA2* (50% of carriers). PDAC risk was significantly elevated in carriers of PV in *BRCA1* (OR = 10.4, p = 0.04), *BRCA2* (OR = 6.4, p = 0.0009), and *CHEK2* (OR = 17.5, p = 0.003). Germline mutations in genes participating in homologous recombination processes were associated with improved overall survival of patients. Among EC patients there were 60 (11.4%) carriers of PV in main predisposition genes. Carriers of PV in Lynch syndrome (LS) genes had markedly elevated risk of developing EC (OR = 22.4, p = 1.8×10^{-17}). Other genes associated with higher EC risk were *BRCA1* (OR = 3.9, p = 0.001), *BRCA2* (OR = 7.4, p = 0.002), and *CHEK2* (OR = 3.2, p = 0.04). Carriers of LS gene mutations had lower age of EC onset than non-carriers (51.0 *vs.* 61.4 years, p = 0,01). 28.3 % of PV carriers in clinically relevant genes did not meet any indication criteria for germline genetic testing.

The results of this thesis emphasize the importance of genetic testing of patients suffering from oncological disease.

Key words: hereditary predisposition to cancer, pancreatic ductal adenocarcinoma, endometrial cancer, next-generation sequencing, panel sequencing, germline mutation