

The genetic risk of thyroid cancer among breast cancer patients

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Introduction. Coincidence of breast cancer with thyroid cancer has been demonstrated in literature previously. It has been recognized that breast cancer survivors have almost twofold increased risk of developing thyroid cancer and the risk is higher than the risk of breast cancer in thyroid cancer survivors. Several factors have been indicated to be involved in both thyroid and breast cancer development. Two genes were identified to be connected with coexisting breast and thyroid cancer: CHEK2 and PARP4. To our knowledge, no study has examined the risk of developing metachronous thyroid cancer in breast cancer patients with mutation in CHEK2 or other genes.

The aim of study. The aim of this study is to identify the genes of high risk of thyroid cancer among breast cancer patients.

Patients. We recruited 10 869 breast cancer patients. The available information included the age of breast cancer diagnosis, deaths, year of breast cancer surgery, the treatment oncology center, lymph node status, tumor size, histopathology, estrogen-receptor status, progesterone-receptor status, HER2 status, multicentricity, bilaterality, previous treatment (chemotherapy, radiotherapy, hormonotherapy), adnexectomy, other concomitant cancers in probands and family history. Two cohorts were selected: 6755 women with breast cancer diagnosed at age below 51 and 4114 women with breast cancer diagnosed at age above 50. Among 10 869 breast cancer patients, 93 patients (0,9%) developed thyroid cancer in probands. 93 patients with both breast and thyroid cancer were called “research group” and 10 776 patients with breast cancer without thyroid cancer were called “control group”.

Methods. The DNA of peripheral blood lymphocytes of patients was examined for the presence of selected germline mutations in two phases. First one was focused on identification of hereditary mutations (including founder mutations) in BRCA1, BRCA2, CHEK2, NBN, RECQL, NOD2, PALB2 and CDKN2A using PCR methods. Then, DNA of 51 patients were examined using NGS (next-generation sequencing) to recognize mutation in 19 selected genes: APC, ATM, BRCA1, BRCA2, CDH1, CDKN2A, CHEK2, MLH1, MUTYH, MSH2, MSH6, NBS1, PALB2, PTEN, PMS2, RAD51C, RAD51D, STK11 and TP53.

Results. In the group of patients with breast cancer diagnosed at age below 51 and above 50, the results of BRCA1/2, NOD2, CDKN2A, NBN, PALB2 and RECQL mutation were not statistically significant. The frequency of CHEK2 mutation was studied separately. In the group of 6755 patients with breast cancer diagnosed at age below 51, CHEK2 mutations were present in 10 of 52 (19,2%) breast-thyroid cancer patients and in 585 of 6703 (8,7%) breast cancer patients (OR 2.49; P = 0.01). Missense mutations were seen in 7 of 52 (13,5%) patients from research group and in 417 of 6703 (6,2%) controls (OR 2.34; P = 0.04). Similar tendency was found in the group of protein-truncating mutations (5,8% vs 2,6%), but the results were not statistically significant. In the group of 4114 patients with breast cancer diagnosed at age above 50, CHEK2 mutations were present in 8 of 41 (19,5%) breast-thyroid cancer patients and in 324 of 4073 (8,0%) breast cancer patients (OR 2.81; P = 0.01). The missense mutations were seen in 6 of 41 (14,6%) patients from the research group and in 247 of 4073 (6,1%) controls (OR 2.66; P = 0.03). 2 protein-truncating mutations were detected in research group and 79 mutations in control group (OR 2.59; P = 0.19). Among 51 breast-thyroid cancer patients, 15 mutations were detected using NGS method including 3 new

pathogenic or likely pathogenic mutations in genes - TP53 (c.1024C>T), ATM (c.6095G>A) and PTEN (c.852dupA). Among breast cancer patients, 53 thyroid cancers (0,49%) were diagnosed after breast cancer diagnosis (SIR 4.4). In the group of 919 CHEK2 mutation carriers, 10 patients developed thyroid cancer (SIR 9.6). Median time to thyroid cancer diagnosis after breast cancer diagnosis was 5 years. Among 104 breast cancer patients with thyroid cancer in relatives, the frequency of CHEK2 mutation was higher than in the group of breast cancer patients without thyroid cancer in probands or relatives (11,5% vs 8,5%). Breast cancers in women with coexisting thyroid cancer and CHEK2 mutation had tendency to express different histopathological and clinical features – tumors had more often positive estrogen and progesterone receptor status (especially in the group of breast cancer diagnosed below 51 years), were more often multifocal, none was bilateral nor had HER2 overexpression.

Conclusions.

1. Breast cancer patients have 1,5-fold increased risk of thyroid cancer, especially during 6 years after breast cancer diagnosis (SIR 4.4).
2. Breast cancer patients with CHEK2 mutations have 2-3-fold increased risk of thyroid cancer. The risk is independent on the age of breast cancer diagnosis, type of CHEK2 mutation and is the highest during 5 years after breast cancer diagnosis (SIR 9.6).
3. Next-generation sequencing (NGS) enable to detect new germline mutations among breast-thyroid cancer patients.
4. Screening for thyroid cancer should be considered among breast cancer patients with CHEK2 mutation.