High incidence of BRCA1 mutations in patients diagnosed with breast cancer during pregnancy.

Szwiec M[1], Tomiczek-Szwiec J[1], Gełej M[1], Cybulski C[2], Huzarski T[2]
1. Regional Oncology Center, Opole, Poland
2. Department of Genetics and Pathology, International Hereditary Cancer Center, Pomeranian Medical University, Szczecin, Poland

Introduction:

Breast cancer is diagnosed in pregnancy (during and until one year after delivery) with a frequency of from 0,2% to 7,1% [1,2,3,4]. In recent years there have been seeing an increase in the number of breast cancer diagnosed in pregnancy that is associated with later age of first delivery. In Poland the median age of first birth has increased between 2000 and 2012 from 26.1 to 29.0 years. Breast cancers diagnosed during pregnancy tend to have a higher grade (III and IV) of diseases, low level of histopathologic differentiation, negative status of steroid receptors, overexpression of HER2, a high proliferation index Ki-67 and a high frequency of mutations in the BRCA1 and BRCA2 genes [5, 6,7,8]. So far, only in the few papers frequency of mutations in BRCA1 and BRCA2 was rated in patients diagnosed with breast cancer during pregnancy. [7,8] The aim of the study was to evaluate the frequency of recurrence mutations in the BRCA1 and BRCA2 genes in a group of patients consulted in Opole Oncology Centre diagnosed with breast cancer up to the age of 40 and in the group with breast cancer diagnosed during pregnancy in the years 2001-2014 as well as the assessment of clinical and histopathologic features of breast cancers identified in this group

Materials and methods:

The analysis was performed in a group of 191 consecutive patients with breast cancer diagnosed up to the age of 40 consulted in Opole in Oncology Center between 2001 and 2014, who had a genetic consultation and tests to identify recurrent mutations in the BRCA 1 and BRCA2. Each patient gave a written consent for peripheral blood sampling and performing of genetic tests. The genomic DNA was isolated from peripheral blood lymphocytes. During the genetic consultation, we obtained the data on incidence of cancer in relatives of first and second degree. Data related to the incidence of pregnancy, clinical and histopathologic features of diagnosed breast cancers was obtained by retrospective medical chart review. We determined the incidence of breast cancer during pregnancy, clinical and histopathologic features of diagnosed cancers, week of pregnancy at the time of diagnosis, time and manner of termination of pregnancy, birth weight, presence of malformations of newborn and the incidence of recurrent mutations in BRCA1 and BRCA2 within the group of patients and in the group of patients diagnosed with breast cancer during pregnancy.

Results:

Within the group recurrent mutations in the BRCA1 (C61G, 4153delA, 5382insC, 185delAG 3875del4, 3819del5, 5370C> T) and BRCA2 (886delGT, 4075delGT, 5972C> T, 6174delT, 8138del5, 5467insT) was detected in 31 patients representing 16.2% of all (31/191). A mutation in the BRCA1 gene was detected in 29 patients (15.2%) and BRCA2 mutation in 2

patients (1.0%). The following mutations in the BRCA1 were found: 5382insC in 14 patients (7.3%), C61G in 6 patients (3.2%), 3819del5 in 6 patients (3.2%), 185delAG in 2 patients (1.0%) , 5370C>T in 1 patient (0.5%). In the BRCA2 gene there was recognized 8138del5 and 5467insT each in one patient (0.5%). In the group of patients diagnosed with breast cancer in pregnant recurrent mutations in BRCA1 and BRCA2 genes were diagnosed in 5 from 14 patients (35.7%). There were detected only mutations in the BRCA1 gene, respectively C61G in 3 patients, 5382insC in 1 patient and 3819del5 also in one patient. Breast cancer related to pregnancy amounted 7,3% (14/191) of the whole group. The diagnosis during pregnancy was obtained in 8 patients (4.2%), and after delivery in 6 patients (3.1%). The average age of recognized breast cancer was 34.8 years old (28-39). Locally advanced diseases in stage III was observed in 7 patients (50.0%), overexpression of HER2 in 6 patients (42.8%), grade three tumor in 7 patients (50.0%), negative receptor status in 6 patients (42.8%) and in the majority of patients a high Ki-67 (range 20% -100%). Using immunohistochemical surrogates a positive HER2 subtype of breast cancer was observed in 6 patients, basal in 4 patients, luminal B in 3 patients and luminal A in 1 patient. In the case of patients with mutations in the BRCA1 gene we observed luminal B subtype in two patients, basal in two patients and luminal A in one. In 12 patients we evaluate the time from first symptoms to the start of the diagnosis the average was 11.4 weeks (range from 1 to 24 weeks). Delay in diagnosis was caused by the difficulties in clinical breast examination. Multidrug chemotherapy based on anthracycline during pregnancy received 5 patients who gave a birth between 35 and 41 week of gestation children of normal weight and no congenital anomalies. There was observed an increase in the number of patients with diagnosed breast cancer during pregnancy in seven-year intervals. Between 2001 to 2007, there were diagnosed four patients and in one of them mutations in the genes BRCA1 and BRCA2 were detected. Between 2008 to 2014 breast cancer in pregnancy was diagnosed in ten patients, and in four of them recurrent mutations in the BRCA1 gene were found.

Discussion:

Our work confirms the increase in the incidence of breast cancer diagnosed during pregnancy in Opole voivodship between 2001-2014 and an increase in the number of mutations in the BRCA1 and BRCA2 detected in this group. It is expected that more clinicians would be conducting the treatment of patients with recognized breast cancer in pregnancy. The presented results and other literature data suggest that breast cancers diagnosed during pregnancy are locally advanced more often and had unfavorable biological features. In our group locally advanced breast cancer was recognized in half of the patients what may be caused by delayed diagnosis and aggressive phenotype of diagnosed cancers. Evaluation of molecular subtypes based on immunohistochemical studies showed a high percentage of HER2-positive cancers and luminal B. A characteristic feature was the high rate of Ki-67. Changes in the breast during pregnancy and lactation hinder breast self-examination, and in this period patients often refrain from performing imaging studies. At the same time the reason for beginning the diagnosis in all patients had been detected breast tumor, but the delay from first symptoms to beginning of diagnostic amounted 11,4 weeks [5, 6]. In a group of patients with breast cancer during pregnancy we found a high frequency of BRCA1 mutation (35,7%). In two of them were recognized locally advanced diseases. These two patients were

treated by neoadjuvant chemotherapy. In case of women with mutations in BRCA gene, one of the recommended ways to reduce the risk of breast cancer is a long breastfeeding. Taking into consideration the increasing number of patients who carry mutation in BRCA1 and were diagnosed with breast cancers during pregnancy as well as difficulties in self-examination of breast in this period and long breastfeeding in carriers of BRCA mutations, we recommend regular breast self-examination and breast ultrasound during pregnancy and lactation.

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