EJGO European Journal of Gynaecological Oncology

Multiple primary cancers in BRCA1/2 carriers – A review of literature and our observations

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Summary

An increasing number of patients with diagnosed synchronous or metachronous neoplasms that are gene as well as non-gene dependent which are associated with the development of new oncological treatment, and environmental factors, prompted the authors of this study to conduct an analysis in a narrow group of patients with multiple cancers and simultaneous BRCA1 mutations (confirmed by genetic analysis). BRCA1 mutation, as well as multiple cancers were found in seven patients treated between 2007 and 2013. The patients diagnosed with a second cancer shared a uniquely common trait – a 5382insC mutation. The study describes four patients that did not carry a BRCA1/2 mutation, yet were diagnosed with multiple cancers. A brief review of literature was performed concerning multiple cancers in women.

Key words: Synchronous; Metachronous; BRCA1/2 mutation; Multiple cancers.

Introduction

Multiple cancers are two or more primary cancers detected at various intervals in a single person, which are not an infiltration, a metastasis or a recurrence. If multiple neoplasms are diagnosed in a time period equaling less than six months, then they are referred to as synchronous; whereas if they are diagnosed in a time period greater than six months, then they are referred to as metachronous. Most often, multiple tumors are diagnosed in different organs. If however they are diagnosed in one locus, then the criterion is set to a different histological pattern [1].

According to the U.S. National Cancer Institute statistics (SEER - Surveillance Epidemiology and End Results), it is estimated that the frequency of multiple cancers is 10% to 16% [2-4]. Medical advancement in the field of oncological treatment, with additional endogenous and exogenous factors that increase the risk of cancer incidence, indicate an increase in the occurrence of subsequent tumors.

The review by Wood *et al*. [4] discusses many factors that cause multiple primary cancers, including: genetic susceptibility, prior treatment (e.g. radiotherapy in cervical or prostate cancer, chemotherapy especially with the use of alkylating cytostatics) or the interaction between cancer susceptibility genes and harmful environmental factors. Aside from the increased risk of developing breast and ovarian cancer, BRCA1 and the BRCA2 mutations are associated with the risk of developing multiple primary cancers [4-7].

Noh *et al*. [5] examined breast cancer patients in Korea laden with a number of risk factors such as: diagnosis of cancer at less than 40 years of age, a positive family history, bilateral breast cancer, and male gender - in which 20.6% of patients were positive for the BRCA1/2 mutation. The presence of a second primary cancer, including the most common – gastric cancer (likewise in this part of the Asian population) was statistically significantly higher in BRCA1/2 carriers and was not related to any other risk factors. A second primary cancer in this population was pancreatic cancer.

Shih *et al*. [6] found the BRCA1/2 mutation in 12.1% of women who were diagnosed with breast cancer exclusively, and in 42.9% of women who were diagnosed with breast cancer and a second primary cancer of any location. If the second primary cancer was non-ovarian, then BRCA1/2 mutations were found in 22.7% of women. If however, the second primary tumor was of the ovary, BRCA1/2 mutations were found in as many as 84.4% of women.

Lal *et al*. [7] also confirmed the role of BRCA1 and BRCA2 mutations in the development of second primary tumors among pancreatic cancer patients. Data obtained from a Swedish database of cancer prone families spanning over three generations, confirmed the association between BRCA1/2 mutation and an increased risk of a second primary tumors other than breast cancer, namely: ovarian, pancreatic, prostatic, gastric, and liver cancers [8].

Materials and Methods and Results

Among the women treated at the Oncology Department of Poznań University of Medicine, 36 cases of BRCA1 mutations were diagnosed. The following types of mutations were found: in 31 patients – type 5382insC, in three patients – type 300T/G and in two

Revised manuscript accepted for publication October 19, 2015

patients – type 4153delA. Among seven of the described patients (22.58%) with multiple tumors, the following cancers were diagnosed: in two patients: primary cancer– ovarian cancer diagnosed at age 61 and 49, and secondary cancer– breast cancer diagnosed at age 64 and 59 respectively; in two patients: primary cancer– breast cancer diagnosed at age 43 and 56, and secondary cancer – primary peritoneal cancer diagnosed at age 46 and 56 respectively; in two patients: primary cancer– breast cancer diagnosed at age 61 and 46, and secondary cancer – primary ovarian cancer diagnosed at age 62 and 66 respectively; in one patient: primary cancer – breast cancer diagnosed at age 46, and secondary cancer – fallopian tube cancer diagnosed at age 60. Six cases were diagnosed as metachronous cancers and one (a patient with breast cancer and a primary peritoneal cancer) as a synchronous cancer.

A common feature of patients who were characterized by the occurrence of a second cancer was that it was only found in women with the 5382insC mutation. The mean age at diagnosis of the first primary cancer in patients with BRCA1 mutation was 51 years (min.43 y/o, max. 61 y/o), while the mean interval between metachronous cancers being 8.5 years (minimum one year, max. 20 years).

Discussion

An analysis of over 200 Polish families was published in 2004 (100 families with three or more cases of breast cancer and 100 families with at least one case of breast cancer, as well as one case of ovarian cancer) showed that the most common BRCA1 mutations were: 5382insC, C61G, and 4153delA [9]. BRCA1/2 mutations were present in 66% of breast cancer associated families and in 63% of breast-ovarian cancer associated families. Among the 129 diagnosed mutations, 122 (94.6%) were found in the BRCA1 gene, whereas seven (5.4%) in the BRCA2 gene. The authors of the study suggested to implement the identification of the three most common mutations in the BRCA1 gene for the same spectrum of gene defects, both in families with or without ovarian cancer, with an 86% sensitivity in comparison to the more costly analysis of both BRCA1 and BRCA2 genes. In the analyzed group of patients of the Department of Oncology in Poznan, it was found that most often patients were diagnosed with the 5382insC mutation in the BRCA1 gene. In view of the fact that a significant percentage of patients developed multiple cancers (seven patients, 22.6% of the 31 patients with a 5381insC mutation in BRCA1), one should consider genetic testing in every case of breast and/or ovarian cancer.

It was proven, also by the results obtained in the group analyzed at the Oncology Department of Poznan University of Medicine, that BRCA1/2 mutations increases the risk of ovarian and breast cancer. Epidemiological studies of BRCA1 carriers by Antoniou *et al*. [10] estimated a 66% risk for ovarian cancer and a 45% risk for breast cancer by the age of 70. A meta-analysis of 22 studies from a number of research centers across the world analyzed 8,139 patients with a diagnosed breast and ovarian cancer (86% female patients with breast cancer, 2% male patients with breast cancer, 12% female patients with ovarian cancer), BRCA1 or BRCA2 mutations were found in 500 patients. The average risk for BRCA1-mutation by age 70 was 65% for breast cancer (95% confidence interval, 44%–78%) and 39% for ovarian cancer (18%–54%). The estimate for the BRCA2-mutation group was 45% (31%–56%) and 11% (2.4%–19%), respectively. [11]

A report by the German HNPCC Consortium of Families with Lynch Syndrome (HNPCC- Hereditary Non Polyposis Colon Cancer) states that MLH1- and MSH2 mutation carriers also develop a second primary cancer. Rectal and gastric cancers occurred substantially more frequently. In addition, in carriers of the MSH2 mutation, prostate cancer was the second primary cancer.[12]

A Greek study by Ladopoulou *et al*. [13] analyzed the BRCA1 and the BRCA2 gene in 85 patients with at least one first or second degree relative affected by breast and/or ovarian cancer. The study found that among 14 families with a disease-associated defect, 11 were in the BRCA1 gene and three in the BRCA2 gene. The 5382insC mutation was found in seven unrelated families. Other mutations identified in the BRCA1 gene were: non-sense R1751X mutation and a variant 5586G>A, while in BRCA2: 2024del5, 3034del4, and 6631del5 were found. Nine out of 14 families of Greek heritage had a history of three or more cases of breast and/or ovarian cancer. The authors suggested that the 5382insC mutation found in the BRCA1 gene is the most common gene defect in the Greek population. Other studies among Italian [14], Yugoslavian [15], Turkish [16], and Russian populations confirm that this type of mutation is most frequently described, while Szabo *et al*. concluded that this is the most common type of mutation among those of European descent [17].

It seems probable that the presence of mutations not related to BRCA1/BRCA2 may also be associated with mutations in other genes: TP53 – Li-Fraumeni syndrome associated with an increased risk of soft tissue sarcomas, osteosarcomas and breast cancers, brain cancers, adrenocortical carcinomas, and leukemias [18]. PTEN – Cowden syndrome associated with hamartomatous lesions (benign), mammary, endometrial and thyroid cancers [19]. LKB1 (also known as STK11) – Peutz-Jeghers syndrome, associated with hamartomatous polyps in the gastrointestinal tract, skin, and mucosal lentigines, as well as colorectal, gastric, pancreatic, breast, and ovarian cancers, and sex cord tumors with annular tubules [20, 21].

In conclusion, patients with a diagnosed BRCA1 mutation, especially with the 5382insC type of mutation, must be carefully monitored for signs of multiple cancers, both metachronous as well as synchronous, especially those occurring within the breast and the ovary.

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