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Metachronic cancers in women with breast cancer and detected *BRCA1* gene mutation

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ABSTRACT

Introduction. Breast cancer is the most common malignancy in women, both worldwide and in Poland. Mutation in the *BRCA1* gene is responsible for approximately 6% of all breast cancers in Poland diagnosed in patients under the age of 50 years. *BRCA1*-dependent cancers occur early and are frequently bilateral. The purpose of this thesis was to evaluate the frequency of metachronic cancers in a population of 42 patients with breast cancer with detected *BRCA1* gene mutation.

Materials and methods. We analysed the health records of 196 patients with confirmed mutation in the *BRCA1* gene, consulted between years 2005 and 2016 in the Genetics Outpatients Unit of the Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Division in Cracow. Medical histories of 42 consecutive patients with breast cancer were selected for further analysis for metachronic cancers.

Results. During the observation period (median 10 years) 21 (50%) neoplasms metachronic to primary breast cancer were diagnosed. The most common was breast cancer of the contralateral breast, detected in 16 (38%) cases. Additionally, two synchronous breast cancers occurred, and in three other cases breast cancer was diagnosed as a metachronic neoplastic disease.

Conclusions. Taking into consideration the results of our study, we should improve awareness, in the medical community, of the scale of the problem of metachronic cancers in patients with diagnosed *BRCA1* mutation. We should also consider intensifying the surveillance of female carriers of the *BRCA1* gene mutation, who were treated for breast cancer in order to detect secondary neoplasms. Another important issue is to offer to each woman being a carrier of a *BRCA1* gene mutation and previously treated for breast cancer a prophylactic mastectomy and a bilateral adnexectomy.

Key words: breast cancer, *BRCA1* mutation, metachronic cancers

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Introduction

Breast cancer is the most common malignant neoplasm in women. The prevalence of breast cancer reaches 1.7 million and the death rate 0.5 million per year, worldwide [1]. Also in Poland breast cancer constitutes the most common cancer in women — the annual morbidity rate reaches more than 16 thousand, and the mortality rate is five thousand [2]. A continuous upward tendency of morbidity of breast cancer across

all age groups is estimated for the years 2010–2025 [3]. The therapy has an interdisciplinary character, and according to the recommendations of the European Society of Breast Cancer Specialists (EUSOMA), should be conducted in a specialised oncological unites (so called breast units), dedicated to diagnosing and to treating only this disease entity [4]. The acknowledged factors increasing the risk of breast cancer are: older age, occurrence of breast cancer in the family, mutations of the *BRCA1* and/or *BRCA2* gene, some benign

proliferative diseases of the breast, exposure to ionising radiation, prior prevalence of breast cancer, late age of first childbirth, early first period and late menopause, long-term hormone replacement therapy, and obesity in postmenopausal women [5]. *BRCA1* is an extensive gene encoding a protein composed of 1836 amino acids. A potential spectrum of possible mutations is huge; however, de novo mutations rarely occur in this gene. This feature is probably responsible for the so-called 'founder effect' [6]. The most common mutations detected in the Polish population are 5382insC, C61G, and 4153delA [7–9], a fact which renders the genetic diagnostics of breast cancer patients and their relatives much easier. The real incidence of the *BRCA1* gene mutation in the Polish population is difficult to evaluate. Genetic background concerns probably 6% of breast cancer patients diagnosed under 50 years of age [10]. *BRCA1* gene mutation-dependant breast cancers occur early (42–45 years old) and in 18–32% of patients are bilateral [10–13]. The presence of the *BRCA1* gene mutation is related with a 50–80% risk of breast cancer development and with 40% [14, 15] risk of ovarian cancer occurrence, depending on the mutation type [15–17].

The aim of this thesis was to evaluate the incidence of the metachronic cancers in the population of breast cancer patients with a diagnosed mutation in the *BRCA1* gene.

Materials and methods

We analysed the health records of 196 patients consulted in the Genetics Outpatients Unit of the M. Curie-Skłodowska Memorial Cancer Centre and Institute in Cracow in the years 2005–2016, in order to identify breast cancer patients with detected *BRCA1* gene mutation. The medical records of 42 consecutive patients who had been diagnosed with a breast cancer were included in the further analysis. In all patients, *BRCA1* gene mutations were detected after the diagnosis of a breast cancer, results were confirmed in two independent blood samples, and the presence of the mutation was appropriately documented by the treating physician in the health record of each patient. The health records of these patients were analysed for occurrence of metachronic cancers, defined as a malignancy occurring over six months after the primary diagnosis of breast cancer [18]. Data concerning synchronic cancers and other neoplastic diseases that had occurred prior to the breast cancer diagnosis were additionally collected.

Results

In the analysed group of patients, the median of age at the breast cancer diagnosis was 45 years (range:

26–79). The first symptoms of neoplastic disease were detected by breast self-exam in 22 patients, by physical exam by a physician in 12 patients, and by the control imaging exams (ultrasonography [US] or mammography) in eight patients. The performance status at the time of the diagnosis was defined as very good or good in all patients (according to the World Health Organisation PS 0 in 37 patients and PS 1 in another five). All patients underwent radical treatment. The median observation time was 10 years (range: 1–32). A metachronic cancer occurred in 21 (50%) patients: in 16 a cancer of the second breast, two cases of the ovary cancer, one case of the sarcoma of the uterus, one case of the Kaposi sarcoma, and one case of the clear-cell renal cancer. Moreover, in two patients a bilateral synchronic breast cancer was diagnosed, and in two patients the breast cancer was a metachronic neoplasm (in both cases ovary cancer had been diagnosed 2 and 3 years prior to the diagnosis of the breast cancer). In one case, before the diagnosis of the breast cancer, a cervical cancer had been diagnosed (17 years earlier). In 26 (62%) breast cancer patients with a detected *BRCA1* gene mutation a secondary, independent cancer occurred [median observation time was 10 years (range: 1–32)]; metachronic, synchronic or neoplastic disease reported in the health records before the diagnosis of the breast cancer. In the subgroup of 21 patients in whom a neoplasm metachronic to primary breast cancer had been diagnosed, the median of time was 5.5 years (range: 1–17) from the date of the start of the therapy of the first breast cancer. During the observation time, in 17 patients a prophylactic hysterectomy and bilateral adnexectomy were performed. No patient had a prophylactic mastectomy. The results are presented in Table 1.

Discussion

In the general population, the risk of breast cancer occurrence is significantly higher in women who have already had breast cancer in the past. This risk equals 10–15% for a 55-year-old woman with a history of breast cancer compared to a 2.5% risk for a healthy 55-year-old women over a 15-year observation time [19]. We estimate that metachronic breast cancer may occur in 1% of the general population of patients previously treated for breast cancer, and the risk increases with time from the primary diagnosis [20, 21]. The risk of development of bilateral breast cancer in carriers of the *BRCA1* gene mutation is significantly higher compared to the general population. In the analysed group a metachronic cancer was observed in 50% of patients and in 38% it was a cancer of the second breast. A relatively low incidence of ovarian cancer in the analysed population should be acknowledged — only two cases of metachronic cancer

Table 1. Independent malignant neoplasms in patients with breast cancer and *BRCA1* mutation

Number of patients (n)	42
Median observation time (years)	10 (1–32)
Metachronic neoplasms (n/%)	21/50%
Median time to diagnosis of metachronic neoplasm (years)	5.5 (1–17)
Type of metachronic neoplasm (n):	
— cancer of the second breast	16
— ovary cancer	2
— sarcoma of the uterus	1
— Kaposi sarcoma	1
— renal carcinoma	1
Synchronic, bilateral breast cancers (n)	2
Malignant neoplasms diagnosed before the breast cancer; type of neoplasm (n):	
— ovarian cancer	2
— cervical cancer	1
Independent malignant neoplasms inclusively (n/%)	26/62%

and two cases diagnosed prior the diagnosis of breast cancer (together 9.5%) compared to a 40% risk of ovarian cancer defined in patients with detected *BRCA1* gene mutation, as reported in the literature [14, 15]. This phenomenon may be partially explained by the fact that in 17 patients (40%) a prophylactic hysterectomy with bilateral adnexectomy was performed, as well as by a limited observation time.

The therapy of breast cancer is becoming more and more effective. The five-year overall survival rate for Polish patients diagnosed in the years 1995–1999 equals 73.8% [22], and in Europe 79% (ranging from 69% in the Czech Republic to 86% in Sweden) [23]. The prognosis in the case of a bilateral breast cancer changes with the time from the primary diagnosis of the neoplasm with a longer time of overall survival in the process of time [24]. A paper by Gozdz et al. reported a 60.1% chance of five-year overall survival for patients with a metachronic cancer and 54% chance for those with a synchronic neoplastic disease [25].

Considering the prevalence of breast cancer and the significant population of patients who have undergone a radical therapy for breast cancer as well as relatively simple diagnostics for the presence of the *BRCA1* gene mutation, we may expect that the number of patients post breast cancer therapy and with detected mutation will increase. The authors of this thesis, based on the presented result, postulate consideration of the following:

- to improve in the medical community the awareness of the scale of metachronic neoplasms in patients with detected *BRCA1* gene mutation;

- to intensify the surveillance for secondary neoplasms in *BRCA1* gene mutation female carriers who were previously treated for breast cancer;
- to offer to each person previously treated for breast cancer, who is a carrier of the *BRCA1* gene mutation, mastectomy and bilateral adnexectomy.

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