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Original article

Cancer genetics

Retrospective analysis of the treatment of *BRCA1* and *BRCA2* mutation carriers – the experience of a single-center tertiary institution

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Introduction. Breast cancer gene 1 and 2 (*BRCA1/2*) mutation carriers are at a higher risk of developing breast cancer. There are several established risk-reducing therapies. Our study aimed to characterize the *BRCA1/2* mutation carriers, and to evaluate the implemented treatment methods.

Material and methods. A retrospective analysis of clinical records of 96 female patients hospitalized from October 2019 to December 2022 in the Breast Cancer Unit in Lodz, Poland.

Results. Out of 85 *BRCA1* and 11 *BRCA2* mutation carriers, 96.88% received nipple-sparing or skin-sparing, unilateral or bilateral risk-reducing mastectomies. Out of all the patients, 36 developed 38 breast cancers. One patient was diagnosed with breast cancer 2 years after a bilateral risk-reducing mastectomy. The most common breast cancer subtype was triple-negative breast cancer (73.68%). The patients could receive surgery, chemotherapy, endocrine therapy and radiotherapy. 18 patients had neoadjuvant chemotherapy, in 6 of these patients a complete pathological response (ypT0N0) was achieved.

Conclusions. Oncoplastic bilateral risk-reducing mastectomies are effective and safe procedures.

Key words: breast cancer gene 1/2, breast cancer, risk-reducing mastectomy, hereditary breast cancer, breast cancer unit

Introduction

Breast cancer (BC) is the most commonly diagnosed cancer in the world. It accounted for 24.5% of new oncological cases and 15.5% of cancer-associated deaths in the female population worldwide in 2020 [1]. Several conditions increase the risk of developing BC, they can be divided into modifiable and unmodifiable risk factors. One of the most important genetic factors associated with familial susceptibility is a mutation in the genes: breast cancer gene 1 (*BRCA1*) or breast cancer gene 2 (*BRCA2*) [2, 3]. Women that carry mutations have a lifetime risk of breast cancer development up to 87% for *BRCA1*, and up to 69% for *BRCA2* [4–6].

Early detection of mutations in the above genes enables patients to reduce the incidence of breast malignancies by risk-reducing therapies like risk-reducing mastectomy (RRM) and risk-reducing salpingo-oophorectomy (RRSO), or early detection by means of regular MRI and mammography screening, or chemoprevention with tamoxifen [7–10].

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The aim of our study was to characterize and describe the population of female *BRCA1* or *BRCA2* mutation carriers admitted to the Breast Cancer Unit in Lodz, Poland, and to evaluate treatment methods for breast cancer and susceptibility due to *BRCA1/2* mutations.

Material and methods

The Medical University of Lodz Ethics Committee stated that this study is not a medical experiment and does not require the opinion of the Bioethical Commission (RNN/29/23/KE; 14 February 2023). We retrospectively identified 96 female patients who tested positive for a mutation in the *BRCA1* or *BRCA2* genes. We included women hospitalized from October 2019 to December 2022 in the Breast Cancer Unit, Lodz, Poland. The clinical and histopathological data were obtained from the hospital records. Statistical analysis was performed using Microsoft Excel.

Results

Out of the included patients, 85 (88.54%) were *BRCA1* mutation carriers, and 11 (11.46%) were *BRCA2* mutation carriers. 93 (96.88%) of the patients underwent a risk-reducing mastectomy (n = 82 in *BRCA1*, n = 11 in *BRCA2*). Three women did not receive risk-reducing procedures and at the time of data collection, they were treated due to breast cancer. The median age on the day of the RRM procedure was 40 (25–65) in the *BRCA1* group and 42 (33–48) in the *BRCA2* group. The patients in our study underwent bilateral (mutation carriers) or unilateral risk-reducing procedures (mutation carriers who developed breast cancer in one breast). All these women received oncoplastic and reconstructive techniques – NSM (nipple-sparing mastectomy) or SSM (skin-sparing mastectomy) or SRM (skin-reducing mastectomy). The characteristics of patients in view of the above procedures are shown in table I.

36 (37.5%) women developed 38 breast cancers. 34 patients developed one cancer in one breast (left n = 13, right n = 21), one patient had two independent, non-simultaneous cancers in the left breast and one woman developed bilateral breast cancer. In one patient, a 9 mm cancer of the breast was incidentally found in the left breast specimen after risk-reducing mastectomy, not visualized on preoperative breast MRI. One patient developed breast cancer 2 years after a bilateral risk-reducing mastectomy performed in another institution.

In the group of *BRCA1* mutation carriers (fig. 1), 52 (61.18%) did not develop breast cancer, 31 (36.47%) developed one cancer in one breast, one (1.18%) developed 2 cancers in one breast (left breast), and one (1.18%) developed bilateral breast cancer. In the *BRCA2* group, 8 (72.73%) patients did not develop breast cancer, 3 (27.27%) developed breast cancer in one breast (all cancers in the right breast).

The most common molecular subtype of breast cancer in the described group of patients was triple negative; it accounted for 28 (73.68%) cases. Other subtypes included: luminal A (n = 5) and luminal B (HER2-negative) (n = 5). The only histopathological subtype was no special type (NST) (38; 100%). We found grade 3 (G3) in 26 cases (68.42%), G2 in 9, G1 in 1 and GX in 2 tumors. We stated Ki-67 expression ≤20–29% as low and >30% as high. High Ki-67 expression was found in 28 cancers, and in 10 tumor samples it was identified as low. A description of the histological and molecular features of the cancers is shown in table II.

Table I. Risk-reducing mastectomies (RRM) in the described groups of mutation carriers

Procedure	Mutation	
	BRCA1 (n = 82)	*BRCA2* (n = 11)
left RRM	14	3
right RRM	12	0
bilateral RRM	56	8

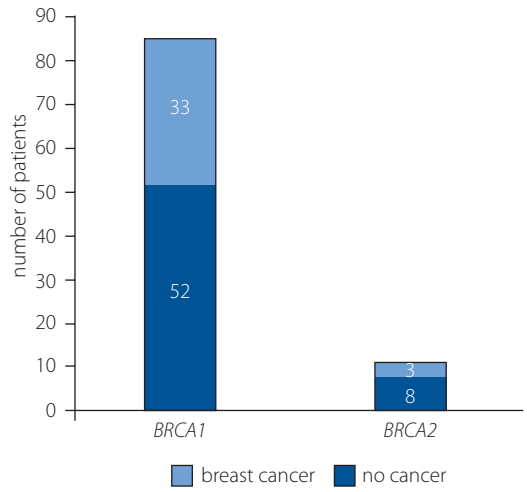

Figure 1. Patients who tested positive for the *BRCA1* or *BRCA2* mutation

Among the patients, tumor sizes T1 (n = 15) and T2 (n = 15) were predominant. Most commonly, in 16 patients, there was no axillary lymph node involvement (N0). Only one woman (*BRCA1*+) developed bone metastases (stage IV), this patient received a mastectomy with delayed breast reconstruction, and postoperative radiotherapy + hormone therapy. The staging of tumors in the characterized group can be seen in table III.

Patients who developed breast cancer could undergo surgery, chemotherapy (neoadjuvant and adjuvant), adjuvant endocrine therapy and postoperative radiotherapy. In relation to surgical cancer treatment, patients received such techniques (n = 37):

- nipple-sparing mastectomy with immediate prepectoral breast reconstruction (n = 13),
- skin-sparing mastectomy with immediate prepectoral breast reconstruction (n = 6),

Table II. Histopathological characteristics of the tumors

Histopathological subtype	Mutation	
	BRCA1 (n = 35)	*BRCA2* (n = 3)
no special type (NST)	35	3
grading		
GX	2	0
G1	0	1
G2	9	0
G3	24	2
Ki-67 expression		
low (≤20–29%)	8	2
high (>30%)	27	1
molecular subtype		
triple-negative (basal-like)	27	1
luminal A	3	2
luminal B (HER2–)	5	0

Table III. Breast cancer staging in the described patients

TNM classification	Mutation	
	BRCA1 (n = 34)	*BRCA2* (n = 3)
primary tumor (T)		
yT0	5	1
T1	14	1
T2	15	0
T3	0	1
regional lymph nodes (N)		
yN0	10	1
N0	15	1
N1	9	1
distant metastases (M)		
M0	33	3
M1	1	0

- breast-conserving therapy (n = 6),
- mastectomy with delayed reconstruction (n = 8),
- mastectomy (n = 4).

Breast-conserving therapy (BCT) was offered to patients who met the criteria to receive this treatment and they were not stated as *BRCA1/2* mutation carriers at the time of breast cancer diagnosis. Because of a strong family history of breast cancer, after the surgery, women consulted with geneticists, and all

Table IV. Treatment (other than surgical excision) received by the patients

Treatment	Mutation	
	BRCA1 (n = 33)	*BRCA2* (n = 3)
HT	4	0
RTH + HT	1	2
preop CHT	10	1
preop CHT + RTH	5	0
preop CHT + RTH + HT	1	0
preop CHT + CHT + RTH	1	0
CHT	8	0
CHT + RTH	2	0
CHT + RTH + HT	1	0

preop CHT – preoperative chemotherapy; CHT – adjuvant chemotherapy; RTH – radiotherapy; HT – hormone therapy

of these patients were proven to carry mutations. 26 patients underwent a sentinel lymph node biopsy, the rest received an axillary lymph node dissection. 18 patients had neoadjuvant chemotherapy, in 6 of these patients (33.33%) a complete pathological response (ypT0N0) was achieved. The description of treatment methods is shown in table IV.

Discussion

With over 2.2 million newly diagnosed cases and over 680,000 deaths recorded in 2020, female breast cancer is considered the most common cancer and the fifth cause of cancer mortality worldwide [1]. Breast cancer may manifest as sporadic (90–95% of all BCs) or hereditary (5–10%) disease [5, 11, 12]. Cases of multiple breast and/or ovarian cancer incidents in families and individuals, those diagnosed at a young age, and male breast cancers may suggest hereditary syndromes [3]. Studies have shown that mutations in several genes can be associated with familial susceptibility to breast cancer development. Commonly mentioned genes include *BRCA1/BRCA2*, *TP53*, *PALB2*, *PTEN*, *CHEK2*, and *ATM* [6, 11–13].

The *BRCA1* (17q21) and *BRCA2* (13q12-q13) genes are tumor suppressors whose main functions are the maintenance of genomic stability and negative regulation of tumor growth. Mutation-carrying individuals, whose gene functions are lost or reduced, are at higher risk of developing breast and ovarian cancer [5, 6, 14]. What is more, abnormal functions of the *BRCA2* gene lead to increased susceptibility to cancers of organs such as the pancreas and prostate [11, 12].

Concerning BC, individuals with a mutation in the *BRCA1* gene most commonly develop TNBC (triple negative breast cancer), where there is no expression of estrogen-receptors, progesterone-receptors, and no overexpression of HER2/*neu* [11, 12]. In our study, the triple-negative subtype was also

the most common molecular type in the *BRCA1* group (n = 27; 77.14%). Due to the lack of drug targets, chemotherapy plays a crucial role in the treatment of TNBC [15]. In the context of the histologic grade of tumors, *BRCA1+* breast cancers are rather considered to be poorly differentiated (G3) [12]. In the described group of patients, out of 35 *BRCA1+* tumors, 24 (68.57%) were stated as high-grade (G3) cancers.

Surgical oncologists' approach to breast cancer surgery and risk-reducing procedures has been transformed from radical mastectomy to conservative mastectomy with immediate reconstruction. Present oncoplastic surgery focuses on providing oncologically safe procedures with possibly the best aesthetic outcomes. Techniques such as NSM, concentrated on preserving the NAC (nipple-areolar complex), and SSM, where NAC is excised with glandular tissue (but may be reconstructed in a subsequent procedure), are considered to achieve the above-mentioned goals [16, 17]. As was reported, the patients involved in our study received various types of surgical operations for breast cancer, including NSM, SSM, BCT, and radical mastectomy with or without delayed reconstruction. Novel surgical techniques, NSM and SSM with immediate prepectoral breast reconstruction, were provided in 19 cases of breast cancer. 8 women received delayed reconstruction after mastectomy.

As regards the risk-reducing mastectomy, studies have proven that it offers >90% breast cancer risk reduction [18, 19]. Several research papers, regarding the effects of RRM, described such positive outcomes as a gain in life expectancy, decreased all-cause and breast cancer-specific mortality rates, and decreased breast cancer incidence rate, compared to surveillance [8, 20, 21]. In the study of Heemskerk-Gerritsen et al., BRRM (bilateral risk-reducing mastectomy), compared with surveillance (mammography + clinical-and self-examination), was proven to have higher ten-year breast cancer-free survival (100% *vs.* 74%) and higher ten-year overall survival (99% *vs.* 96%) [8]. Besides, the proactive surgical approach can ensure psychological well-being by mitigating cancer-related anxiety [19]. Like any other surgical procedure, oncoplastic risk-reducing mastectomies with immediate reconstruction entail the risk of complications. These include nipple-areola or mastectomy skin flap necrosis, wound infection, breast asymmetry, BIA-ALCL (breast implant-associated anaplastic large cell lymphoma), and unsatisfying aesthetic results [17, 22, 23]. There is also a chance after RRM that a patient might have to undergo revisional surgery [19]. Even after the NSM procedure there still remains a low risk of cancer development, due to the possibility of remaining a portion of glandular tissue in the NAC. In our analyzed group, we documented a case of a woman who was treated for breast cancer that developed after bilateral RRM. In contraposition to our evaluation, in the study of Jakub et al., after 548 risk-reducing NSMs in 346 *BRCA1/2* mutation carriers, there was no case of primary breast cancer on both sides after the bilateral procedure, or ipsilateral side after the unilateral risk-reducing procedure [24]. Surgeons' doubts about glandular breast tissue that can be left in the NAC after NSM and the associated risk of cancer were partly resolved. Baltzer et al., in a study of 105 female patients, found that NAC represents a tiny fraction (1.3%) of the entire breast tissue. With an extremely small chance of breast cancer development, this study supports the safety of the described procedure [25].

Women carrying *BRCA1/2* mutations, who were diagnosed with a primary cancer of one of the breasts, are still vulnerable to the next malignancy incidence. They have a higher risk of contralateral breast cancer compared to the general population [22, 26].

In the study of Kuchenbaecker et al., the cumulative risk for ovarian cancer development in *BRCA1* and *BRCA2* patients was estimated at 44% (95% confidence interval [CI], 36–53%) and 17% (95% CI, 11–25%) respectively [4]. There is scientific evidence that risk-reducing salpingo-oophorectomy is effective in decreasing ovarian cancer incidence and mortality [27]. In regard to breast cancer, besides RRM, the mutation carriers may also opt for RRSO. In patients without previous breast cancer diagnosis, it was shown that risk-reducing salpingo-oophorectomy can reduce all-cause mortality, breast cancer-specific mortality, ovarian cancer-specific mortality, and risk of breast cancer development [9].

For the good of women, it seems important to spread public awareness of hereditary syndromes related to breast and ovarian cancer, and ways to handle them. Evans, D Gareth et al., showed increased genetic consultations uptake in the United Kingdom after the famous decision of the actress Angelina Jolie who, in May 2013, chose to undergo BRRM because of being a *BRCA1* mutation carrier [28].

It is believed that the best quality of care for breast cancer patients can be accessible in breast cancer units (BCU). These centers, organized in one location, provide highly qualified specialists and services that focus particularly on breast cancer detection and its treatment. Units consist of a multidisciplinary team involving geneticists, radiologists, pathologists, surgeons, oncologists, radiation oncologists and psychologists [29, 30].

There are limitations to our study. A relatively small number of mutation carriers were involved in the analysis. There is a need for further research in the field of *BRCA*-mutation carriers treatment and its associated outcomes.

Conclusions

The *BRCA1* and *BRCA2* mutations are related to a higher risk of breast cancer development, especially triple-negative subtypes. Knowledge of being a mutation carrier enables the patients to take steps to minimize the risk of malignancy occurrence. A bilateral risk-reducing mastectomy, performed with oncoplastic techniques, remains an effective oncological procedure for women who test positive for *BRCA1* or *BRCA2* mutations. Due to the possibility of finding malignant tissue not visualized on preoperative imaging

scans, a proper histological examination of post-RRM specimens is essential.

Surgical oncologists must clearly inform the patients about various risk-reducing approaches and potential post-surgical complications, changes in body image and self-perception after the surgery.

Article information and declarations

Data availability statement

The data presented in this study are available on request from the corresponding author.

Ethics statement

The Medical University of Lodz Ethics Committee stated that this study is not a medical experiment and does not require the opinion of the Bioethical Commission (RNN/29/23/KE; 14 February 2023).

Author contributions

Grzegorz Stępień – writing, original draft preparation, data collection.

Thomas Wow – supervision, review.

Agnieszka Kołacińska-Wow – data collection, supervision, conceptualization, review.

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Conflict of interest

None declared

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