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

Authors: Grzegorz J. Stępień, Thomas Wow, Agnieszka Kołacińska-Wow

DOI: 10.5603/njo.96294
Article type: Research paper (original)
Submitted: 2023-07-02

Accepted: 2023-08-01
Published online: 2023-08-21

This article has been peer reviewed and published immediately upon acceptance. It is an open access article, which means that it can be downloaded, printed, and distributed freely, provided the work is properly cited.
Retrospective analysis of the treatment of BRCA1 and BRCA2 mutation carriers – the experience of a single-center tertiary institution

Grzegorz J. Stępień1, 0000-0003-1585-3877, Thomas Wow2, 0000-0003-0055-3273, Agnieszka Kołacińska-Wow1, 3, 0000-0001-8707-0877

1. Department of Oncological Physiotherapy, Medical University of Lodz, Lodz, Poland
2. Department of Surgical Oncology and Breast Diseases, Polish Mother’s Memorial Hospital – Research Institute, Lodz, Poland
3. Breast Unit Cancer Center, Copernicus Memorial Hospital, Lodz, Poland

Introduction. 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. 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 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: BRCA1/2, 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 BRCA1 (breast cancer gene 1) or BRCA2 (breast cancer gene 2) [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 RRM (risk-reducing mastectomy) and RRSO (risk-reducing salpingo-oophorectomy), or early detection by means of regular MRI and mammography screening, or chemoprevention with tamoxifen [7–10].

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 ninety-six female patients who tested positive for a mutation in the genes BRCA1 or BRCA2. 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 all patients underwent 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 9 mm breast cancer 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 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 group of BRCA2 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 Ki67 expression ≤20–29% as low and >30% as high. High Ki67 expression was found in 28 cancers, in 10 tumor samples it was identified as low. A description of histological and molecular features of cancers is shown in table II.

Tumor sizes T1 and T2 were predominant, they were found in the same numbers of patients – each 15. 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 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),
- 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 diagnosis of breast cancer. Because of a strong family history of breast cancer, after the surgery, women were consulted with geneticists, and all of these patients were proven to carry mutations. 26 patients underwent sentinel lymph node biopsy, the rest received 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 to be 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].

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
for developing breast and ovarian cancer [5, 6, 14]. What is more, abnormal functions of the 
BRCA2 gene lead to increased susceptibility to cancers of such organs 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 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 transforming 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 it was reported, 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.

In regard to 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, and decreased breast cancer incidence rate [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 insure 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 not-satisfying aesthetic results [17, 22, 23]. There is also a chance that after RRM a patient would have to undergo revisional surgery [19]. Even after the procedure there still remains a low risk of cancer development, due to the possibility of leaving a portion of glandular tissue during the surgery. 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 the study of 105 female patients, found that NAC represents a tiny fraction (1.3%) of 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% 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

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. 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, 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.

**Funding**
None declared

**Conflict of interest**
None declared

**Grzegorz J. Stępień**

*Medical University of Lodz*

*Department of Oncological Physiotherapy*

*ul. Paderewskiego 4*

*93-509 Łódź, Poland*

*e-mail: grzegorz.stepien@stud.umed.lodz.pl*

**Received:** 2 Jul 2023

**Accepted:** 1 Aug 2023

**References**


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

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Mutation</th>
<th>BRCA1 (n = 82)</th>
<th>BRCA2 (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>left RRM</td>
<td>14</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>right RRM</td>
<td>12</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>bilateral RRM</td>
<td>56</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

### Table II. Histopathological characteristics of the tumors
### Table III. Breast cancer staging in the described patients

<table>
<thead>
<tr>
<th></th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histopathological subtype</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no special type (NST)</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td><strong>Grading</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GX</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>G1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>G2</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>G3</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td><strong>Ki-67 expression</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>low (≤20–29%)</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>high (&gt;30%)</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td><strong>Molecular subtype</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>triple-negative (basal-like)</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>luminal A</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>luminal B (HER2–)</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td><strong>TNM classification</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary tumor (T)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yT0</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>yT0</strong></td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>T1</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>T2</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>T3</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>regional lymph nodes (N)</th>
<th>n = 34</th>
<th>n = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>yN0</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>N0</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>N1</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>N2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>distant metastases (M)</th>
<th>n = 34</th>
<th>n = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td>M1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA1/2 mutation carriers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HT</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>RTH + HT</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>preop CHT</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>preop CHT + RTH</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>
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

Figure 1. Patients tested positive for BRCA1 or BRCA2 mutation