VIA MEDICA

REVIEW ARTICLE

Joanna Kufel-Grabowska[1], Bartosz Wasąg[2]

[1]Department and Clinic of Oncology and Radiotherapy, Medical University of Gdańsk, Poland
[2]Chair and Department of Biology and Medical Genetics, Medical University of Gdańsk, Poland

Diagnosis and treatment of patients with breast cancer and mutation in the *BRCA1/2* genes

Address for correspondence:
Joanna Kufel-Grabowska, MD PhD
Department and Clinic of Oncology and Radiotherapy, Medical University of Gdańsk
ul. Marii Skłodowskiej-Curie 3a,
80–210 Gdańsk, Poland
e-mail: joanna.kufel-grabowska@gumed.edu.pl

Oncology in Clinical Practice
Translation: dr n. med. Dariusz Stencel
DOI: 10.5603/OCP.2023.0035

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Breast cancer is the most common cancer among women in Poland and worldwide, second only to lung cancer in terms of mortality. Germline mutations account for approximately 5–10% of all breast cancer cases, with mutations in the *BRCA1/2* genes being the most frequently identified. The presence of pathogenic variants in the *BRCA1/2* genes is associated with a more than 60% risk of developing breast cancer, a 40–60% risk of ovarian cancer in women with a *BRCA1* mutation, and a 13–30% risk in women with a *BRCA2* variant. Breast cancer is often diagnosed at a younger age in *BRCA1/2* mutation carriers. The prevalence and increased accessibility of genetic testing, especially next-generation sequencing, lead to a higher number of diagnosed individuals and healthy family members. Identifying a pathogenic variant in the *BRCA1/2* genes, analyzing a family history, and genetic counseling enables the development of individual recommendations for further management. This article aims to present the diagnostic and therapeutic approach in breast cancer patients with a pathogenic variant in the *BRCA1/2* genes.
Key words: breast cancer, pathogenic variant, *BRCA1*, *BRCA2*, next-generation sequencing

Oncol Clin Pract

Introduction

Breast cancer is the most common cancer in women in Poland and worldwide and the second cause of cancer-related deaths after lung cancer. In Poland, there is a constant increase in the incidence of breast cancer, which is mainly associated with lifestyle changes and environmental factors. The most important risk factors include sex, older age, presence of mutations in the *BRCA1/2* genes, family history of breast cancer (especially at a young age), early menstruation, late menopause, late birth of the first child, long-term hormone replacement therapy (HRT), mainly based on estrogens and gestagens, long-term contraception (to a small extent), obesity in the postmenopausal period, and radiotherapy to the chest area at a young age. Breast cancers associated with hereditary mutations account for 5–10% of all cases, with most commonly diagnosed mutations in the *BRCA1/2* genes [1].

The presence of pathogenic variants in the *BRCA1* and *BRCA2* genes is associated with greater than 60% risk of breast cancer, as well as 40–60% risk of ovarian cancer in women with a mutation in the *BRCA1* gene and 13–30% risk in women with a variant in the *BRCA2* gene. In addition, there is an increased risk of melanoma, prostate, and pancreatic cancer. Breast cancer is more often diagnosed at a young age. In women with a mutation in the *BRCA1* gene, the greatest risk is noted between 30 and 40 years of age, and in the case of a variant in the *BRCA2* gene — between 40 and 50 years of age; then the risk declines and reaches a plateau until the age of 80. The risk of contralateral breast cancer is higher than in the general population (26% and 40% in women with a mutation in the *BRCA1* and *BRCA2* genes, respectively). In patients with mutations in *BRCA1/2* genes, tumors with a high histological grade (G3) that do not express estrogen (ER) and progesterone receptors (PR) and with no *HER2* gene amplification occur more often than in the general population [2].

Women with mutations in the *BRCA1/2* genes are a special group of patients, due to the presence of the following factors: need for cascade diagnostics in

Received: 05.06.2023 Accepted: 05.06.2023 Early publication date: 25.10.2023

family members, possibility of implementing procedures reducing cancer risk, possibility of appropriate surgical treatment, availability of targeted systemic therapy, applicability of methods securing fertility, which can be used before oncological treatment or before bilateral risk-reducing salpingo-oophorectomy (RRSO) and the use of in vitro fertilization combined with preimplantation genetic diagnosis.

The multidisciplinary team conducting the treatment of breast cancer consists of a clinical oncologist, surgical oncologist, radiotherapist, gynecologist, reproductive medicine specialist, geneticist, psychologist, and senology nurse. The strategy planned and conducted by the aforementioned team ensures safety and effectiveness of treatment as well as a holistic approach. Dissemination and increasing access to genetic testing — especially next-generation sequencing (NGS) — increases the number of diagnosed patients and healthy family members. Diagnosis of a pathogenic variant in the *BRCA1/2* genes, pedigree analysis, and genetic consultation enable the development of individual recommendations for further management.

This article aims to present diagnostic and therapeutic procedures in breast cancer patients with a pathogenic mutation in the *BRCA1/2* genes.

Mutations in the *BRCA1/2* genes

The relationship between the presence of mutations in the *BRCA1/2* genes and an increased risk of breast and ovarian cancers was described in 1994 [3]. Screening tests to detect mutations in the *BRCA1/2* genes were introduced to clinical practice as early as 1996 [4]. The prevalence of variants in the *BRCA1* and *BRCA2* genes in Western populations ranges from 1 in 400 to 1 in 500 [5]. In addition to *BRCA1/2*, variants in other genes, such as *TP53* (Li Fraumeni syndrome), *PTEN* (Cowden syndrome), *CDH1*, *STK11* (Peutz-Jeghers syndrome), and *MLH1, MSH2, MSH6,* and *PMS2* (Lynch syndrome) are also known to increase the risk of developing breast or ovarian cancer [6].

So far, almost 5000 sequence variants have been described in the *BRCA1/2* genes, most of which are deletions or insertions changing the reading frame and substitutions leading to premature termination of translation and the formation of a shortened protein product [7]. Some abnormalities in the *BRCA1/2* genes may constitute large rearrangements (LRs), whose occurrence varies in individual populations. In the Dutch, Irish, Czech, and German populations, these variants accounted for 27–36%, 11%, 6%, and 3%, respectively [8–11]. In the population of Polish patients with breast and/or ovarian cancer, large *BRCA1/2* gene rearrangements accounted for 2.1–5% [12, 13].

The variable frequency of specific mutations is due to the occurrence of a strong founder effect in some isolated populations or ethnic groups. The clearest relationship concerns the Ashkenazi Jews population, in whom three mutations with a total frequency of 1/40 are identified: c.68_69delAG, c.5266dupC in the *BRCA1* gene and c.5946delT in the *BRCA2* gene [14]. In the Polish population, founder mutations in the *BRCA1* gene are c.5266dupC, c.181T>G, and c.4035del [15]. These variants account for 64–84% of all lesions detected in the Polish population [12, 16, 17].

However, due to the large variety of abnormalities detected in the *BRCA1/2* genes in breast cancer patients, in the case of negative results of the targeted analysis (e.g. no pathogenic variant identified), it is necessary to analyze the entire coding sequence of these genes [6].

The *BRCA1* and *BRCA2* genes play an important role in maintaining the integrity of the genome — when they are disrupted, cells become more sensitive to DNA damaging agents (deoxyribonucleic acid), which causes chromosomal aberrations [18–20]. Both genes are involved in DNA damage repair processes by homologous recombination (HR).

Molecular diagnostics

Currently, only the detection of germline variants in the *BRCA1/2* (*gBRCA1/2*) genes has an impact on the diagnostic and therapeutic management in breast cancer patients. Genetic material isolated from peripheral blood cells should be used in routine molecular tests [21–23]. It is also possible to use fixed tissue material for tests aimed at detecting mutations in the *BRCA1/2* genes. However, there are some limitations regarding use of tissue material [6]. First, if a genetic variant is detected, it is necessary to perform additional analysis using DNA isolated from peripheral blood. This test allows for determining whether the detected variant in the *BRCA1/2* genes is germline and can be the basis for further diagnostic and therapeutic procedures.

Second, performing molecular analysis using DNA isolated from tumor tissue may prevent the detection of approximately 10% of terminal variants (deletions or duplications).

Third, the classification of somatic and germline variants is based on a different methodology. Therefore, it is possible that a lesion that would be considered a germline pathogenic or possibly pathogenic variant based on peripheral blood testing may be classified as a variant of unknown or no clinical significance.

Due to the large variety of variants in the *BRCA1/2* genes, molecular diagnostics in breast cancer patients should be performed using the NGS method [6, 21]. This method should make it possible to detect point variants

and large rearrangements, deletions, and duplications. If the test does not allow for the identification of the above aberrations, it is advisable to perform a supplementary analysis using the multiplex ligation-dependent probe amplification (MLPA).

To summarize, the optimal diagnostic scheme should include the possibility of performing molecular analysis in all breast cancer patients as part of outpatient specialist care. This test should detect all germline *BRCA1/2* variants; therefore, it should be performed using DNA isolated from peripheral blood samples and the NGS technique. Due to the potential impact of the molecular test result on decisions regarding the scope of the surgical procedure, it should be available before treatment.

Currently, as part of hospital services, it is possible to order molecular diagnostics in patients diagnosed with breast cancer based on the list of genetic tests in cancer [24]. In this group of patients, advanced genetic tests should be ordered because only within the framework of the aforementioned service is it possible to finance tests using the NGS technique. Tests can be performed using fresh material collected from patients for diagnostic purposes or from archival material. The current rules for ordering advanced genetic testing by the National Health Fund (NHF) indicate that fixed tissue material is used for molecular diagnostics, and in this case, the methodological limitations presented above should be considered.

As part of outpatient specialist care, all patients with breast cancer are entitled to genetic counseling and molecular diagnostics [25]. It should be noted, however, that the tests offered in the first stage allow only the detection of the most common mutations in the Polish population in the *BRCA1* (c.5266dupC; c.181T>G; c.4035delA; c.66_67delAG; c.3700_3704 del GTAAA), *PALB2* (c.509_510 delGA; c. 172_175 del TTGT) and *CHEK2* (1100del C; IVS+1G>A; del 5395; I157T) genes. The diagnostic effectiveness of this test will therefore be limited, and it does not allow excluding of other variants in the *BRCA1/2* genes.

Only at the next stage, it is possible to perform molecular diagnostics for mutations in the *BRCA1/2*, *PALB2,* and *CHEK2* genes using the NGS method in women in whom none of the above mutations were detected and diagnosed with breast cancer, e.g.:

— before the age of 45, regardless of family history;
— with triple-negative receptor status (no expression of estrogen and progesterone receptors, no *HER2* gene amplification);
— simultaneously or sequentially diagnosed with ovarian cancer or bilateral breast cancer;
— and ≥ 1 first- or second-degree relative was diagnosed with breast cancer (male breast cancer), or ≥ 1 first- or second-degree relative was diagnosed with ovarian cancer;
— and ≥ 1 first- or second-degree relative was diagnosed with breast cancer, including at least one diagnosis below 50 years of age;
— and ≥ 2 maternal or paternal first- or second-degree relatives were diagnosed with breast cancer, regardless of age at diagnosis;
— molecular diagnostics for mutations in the *BRCA1/2*, *PALB2,* and *CHEK2* genes using the NGS method can be also used in men diagnosed with breast cancer. Only NGS testing allows for the exclusion of the presence of variants in the *BRCA1/2* genes, provided that the analysis allows the detection of point variants and large rearrangements (deletions and duplications) [5]. This information should be included in the test report.

Cascade diagnostics

In first- or second-degree relatives of a breast cancer patient diagnosed with a germline variant in the *BRCA1/2* genes, it is possible to conduct genetic counseling and perform predictive testing for a known familial mutation (so-called cascade diagnostics) [25]. These tasks are conducted as part of a program of care for families with a high and hereditary risk of breast or ovarian cancer, financed by the NHF. According to the assumptions of this program, genetic counseling and molecular diagnostics may also be performed in relatives of women diagnosed with ovarian cancer. It is possible to perform cascade diagnostics aimed at detecting variants not only in the *BRCA1/2* genes but also *in PALB2* and *CHEK2* genes.

Procedures reducing the risk of developing cancer

In women with a mutation in the *BRCA1/2* genes, breast cancer does not preclude the possibility of developing contralateral breast cancer, ovarian cancer, primary peritoneal cancer, or pancreatic cancer. The implementation of procedures reducing the risk of cancer is, therefore, of particular importance.

Bilateral risk-reducing mastectomy (RRM) reduces the risk of breast cancer by about 90%. Mastectomy in patients already diagnosed with cancer reduces the risk of cancer of the other breast. The impact of these procedures on overall survival (OS) is ambiguous. Young patients diagnosed with early breast cancer (stages I and II) seem to benefit the most. Due to the young age, the risk of developing cancer in the other breast is higher than the risk of recurrence and spread of the primary tumor. Simultaneous reconstruction seems to be a safe procedure, and this prophylactic procedure does not require sentinel node surgery due to the low risk (below 5%) of diagnosis of breast cancer [26].

Risk-reducing salpingo-oophorectomy not only reduces the risk of ovarian cancer by about 90% but also reduces the all-cause mortality and breast/ovarian cancer related deaths in some patients (especially in women with a mutation in the *BRCA1* gene). The protective effect in the case of mutations in the *BRCA2* gene is less certain, which is mainly due to the small patient cohorts in clinical trials [27].

The time of performing RRM and RRSO depends, among others, on the patient's cancer history, family history, procreation plans, and patient's preferences. RRSO is recommended between 35 and 40 years of age in women with a mutation in the *BRCA1* gene and between 40 and 45 years of age in women with a varian in the *BRCA2* gene, which is related to ovarian cancer being delayed by 8–10 years compared to the risk in women with a mutation in the *BRCA1* gene [28].

In a phase II study in women with a mutation in the *BRCA1/2* genes who underwent treatment for breast cancer, irradiation of the other breast reduced the risk of developing cancer; however, the procedure is not generally recommended [29].

Systemic treatment

BRCA1/2 genes are involved in the repair of DNA strand breaks based on the homologous recombination mechanism. In the presence of mutations, alternative pathways protect the cell from irreversible double helix damage. Poly-ADP-ribose polymerase (PARP) is a great target for PARP inhibitors (PARPi) leading to irreversible damage to cancer cells.

The effectiveness of PARPi was first proven in patients with advanced disease in the first and subsequent treatment lines. The OlympiAD and EMBRACA trials showed a benefit in terms of extending the time to cancer progression and improving the quality of life compared to systemic treatment of investigator's choice [7.0 *versus* 4.2 months; hazard ratio (HR) = 0.58; 95% confidence interval (CI) 0.43–0.8; $p < 0.001$] and (8.6 *vs*. 5.6 months; HR = 0.4; 95% CI 0.41–0.71; $p < 0.001$), respectively. No increase in overall survival was observed [30–31].

In patients with early breast cancer with high recurrence risk, any intervention that improves prognosis is of great importance. The OlympiA study compared one-year therapy with olaparib in combination with hormone therapy and zoledronic acid with placebo in patients after surgery and completion of perioperative treatment (chemotherapy, radiotherapy). There was a statistically significant reduction in the risk of death of approximately 30% (HR = 0.68; 98.5% CI 0.47–0.97; $p = 0.009$), an improvement in the 4-year invasive disease-free survival rate [82.7% *vs.* 75.4% (Δ 7.3%; 95 % CI 3.0–11.5%)] and the 4-year metastasis-free survival rate [86.5% *vs.* 79.1% (Δ 7.4%; 95% CI 3.6–11.3%)] [32].

Platinum derivatives in combination with chemotherapy based on anthracyclines and taxanes in HER2-negative breast cancer patients in stages II and III and with mutations in *BRCA1/2* genes are the standard of care in neoadjuvant treatment, regardless of the mutation status in these genes. Achieving a complete response confirmed by pathomorphological examination was associated with a reduction in recurrence risk, also regardless of the patient's genetic burden [33].

The effectiveness of platinum derivatives in patients with advanced breast cancer is similar to that of docetaxel, which is one of the most active drugs in breast cancer. The results of the TNT study confirm that women with mutations in the *BRCA1/2* genes are particularly platinum-sensitive, with an objective response rate (ORR) 2-fold higher than with docetaxel (68% *vs*. 33%; $p = 0.01$). The time to cancer progression was also longer in patients receiving carboplatin (6.8 *versus* 4.4 months; $p = 0.002$) but without OS prolongation [34].

Contraception

Family planning is one of the elements of care for women with a mutation in the *BRCA1/2* genes and applies to healthy people and those diagnosed with cancer. Removal of the ovaries should be planned after the pedigree analysis, but also after the completion of procreation plans. Patients with ovarian cancer at a young age should consider early motherhood, and cooperation among a gynecologist, oncologist, geneticist, and reproductive medicine specialist is extremely important in their case [35].

Hormonal contraception reduces the risk of ovarian cancer, but its protective effect is not comparable to the effect of RRSO. Data on the impact of hormonal contraception on breast cancer risk are ambiguous – it seems that this risk be higher if it is used before the age of 20 or if the patient develops cancer at a young age [36].

In women with mutations in the *BRCA1/2* genes who developed breast cancer, hormonal contraception is not recommended regardless of cancer biological subtype, which also applies to patients diagnosed with triple-negative breast cancer. A safe option is hormone-free or barrier contraception (condom, cervical cap, hormone-free intrauterine device) used during treatment and for a certain period after treatment (depending on the therapy used, e.g. for 12 months after chemotherapy, 7 months after trastuzumab, 3 months after hormone therapy, and 5 months after immunotherapy).

Fertility protection

Pregnancy after breast cancer treatment is possible and safe, regardless of the biological subtype of cancer or presence of mutations in the *BRCA1/2* genes. In cancer

patients, however, it requires appropriate planning in relation to the treatment, the risk of cancer recurrence, and the patient's age and preferences. Some reports indicate a better prognosis for patients who become pregnant after anti-cancer treatment; this has been called the "healthy mother effect" [37].

The first data from the POSITIVE trial indicate the safety of discontinuing adjuvant hormone therapy to realize maternity plans. Most of the patients participating in the study were diagnosed with early-stage breast cancer (I–II). Patients who gave birth within a planned interval had a lower risk of recurrence than those who did not become pregnant. The treatment interruption itself, which was a maximum of 2 years, did not reduce the effectiveness of therapy. Some patients benefited from assisted reproductive methods. Observations are certainly promising, but patients require further follow-up [38].

It should be remembered that cancer treatment may lead to permanent or reversible infertility. The gonadotoxic effect of chemotherapy depends on the treatment used, patient's age, and initial ovarian reserve. In patients with estrogen-dependent cancer, adjuvant hormone therapy is used for 5–10 years. Treatment alone does not increase the risk of premature ovarian failure, but it postpones the possibility of becoming pregnant, which in some patients over 30 years of age may preclude motherhood. In the treatment of patients with early triple-negative breast cancer in certain stages, in addition to chemotherapy, perioperative immunotherapy is also used. Immune checkpoint inhibitors can lead to primary or secondary hypogonadism and infertility. Some patients may experience late effects of immunotherapy. Currently, there are no known factors that would allow oncologists to select a group of patients who will develop infertility caused by immunotherapy.

Some studies indicate worse ovarian reserve at baseline in women with mutations in the *BRCA1/2* genes, which is an additional argument for the need to consult patients with a reproductive medicine specialist before starting anticancer treatment. Fertility protection gives patients a chance for motherhood after treatment completion [39].

The basic method of fertility preservation in women with mutations in the *BRCA1/2* genes is cryopreservation of oocytes or embryos, which requires hormonal stimulation. The whole process lasts from 2 to 3 weeks, which slightly postpones the start of anti-cancer treatment. During the stimulation, tamoxifen or an aromatase inhibitor is used, effectively lowering the level of endogenous estrogens. If the patient has a partner, it is possible to fertilize eggs with sperm and then cryopreserve embryos. Preimplantation diagnostic techniques allow for the examination of embryos before implantation into the uterine cavity and selecting only those that are free of mutations in *BRCA1/2* genes. The availability of this procedure in Poland is very limited, but the test itself is an important option for women with mutations in the *BRCA1/2* genes [40].

Another fertility preservation procedure is excision of ovarian tissue and its freezing, followed by ortho- or heterotopic reimplantation after treatment. The advantage of this method is the possibility of natural pregnancy and return of hormonal activity. Cryopreservation of ovarian tissue is rarely chosen in women with *BRCA1/2* gene mutations who are at high risk of developing ovarian cancer. Despite performing appropriate diagnostic tests before tissue freezing, there is a risk of reimplantation of cancer cells with ovarian tissue. Therefore, the method can be considered when it is not possible to use the freezing of oocytes or embryos [41].

An important option to supplement the basic methods of fertility preservation is using gonadoliberin analogs during perioperative chemotherapy, which reduces the risk of premature ovarian failure and increases the chance of pregnancy after treatment [42].

Conclusions

In the population of Polish breast cancer patients, mutations in the *BRCA1/2* genes are most often germline variants. Genetic diagnosis at an early stage of cancer is of great importance for the patient and her family. The implementation of an appropriate surgical treatment, which most often consists of bilateral mastectomy with or without reconstruction and systemic therapy in the case of early or advanced disease, is associated with an improvement in patients' prognosis. Appropriate treatment, procedures reducing the risk of cancer, planning children, and contraception require proper preparation of several specialists engaged in the care of a patient with a mutation in the *BRCA1/2* genes, regardless of her previous cancer history. It is essential to conduct molecular diagnostics in strictly defined populations of patients, in whom the risk of mutations in *BRCA1/2* genes is relatively high. Appropriate methodology used for molecular tests, correct qualification of genetic variants detected in *BRCA1/2* genes, as well as consultation with a clinical geneticist while deciding further procedures are equally important.

Article Information and Declarations

Author contributions

The authors equally contributed to the article.

Financing

AstraZeneca commissioned the article.

Acknowledgments

None.

Conflict of interest

J.K.-G.: lectures and trips to conferences financed by Roche, AstraZeneca, Pfizer, Ely Lilly, Novartis, Accord, Teva, and Gilead.
B.W.: fees for attending advisory meetings or lectures from AstraZeneca, Novartis, and Pfizer.

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