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BRCA1/BRCA2 MUTATIONS IN BREAST CANCER: CLINICAL SIGNIFICANCE, PROGNOSTAIC VALUE, AND THERAPEUTIC IMPLICATIONS

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ABSTRACT

Objective: The aim of this review article is to present the current state of knowledge regarding BRCA1 and BRCA2 mutations in breast cancer, with particular emphasis on their clinical significance, prognostic value, and therapeutic implications. The paper discusses the biological functions of BRCA genes, the epidemiology of hereditary breast cancer, the role of molecular diagnostics, and contemporary targeted treatment strategies.
Materials and Methods: A narrative review of the scientific literature concerning BRCA1/BRCA2 mutations and breast cancer was conducted. Publications from peer-reviewed medical journals, meta-analyses, clinical guidelines, and clinical trials published between 1998 and 2022 were analyzed. The review included data on epidemiology, molecular biology, prognosis, and modern therapeutic approaches, including PARP inhibitors and platinum-based chemotherapy.
Results: BRCA1 and BRCA2 mutations are among the most significant risk factors for hereditary breast and ovarian cancer. Carriers of BRCA1 mutations more frequently develop triple-negative breast cancer, whereas BRCA2 mutations are more commonly associated with hormone receptor–positive tumors. The presence of these mutations influences the clinical course of the disease, the risk of recurrence, and the selection of therapeutic strategies. The development of PARP inhibitors has significantly improved treatment outcomes in patients with BRCA-mutated breast cancer, both in advanced disease and in early-stage settings. Increasing attention is also being given to prophylactic surgery and treatment individualization.
Conclusions: BRCA1/BRCA2 mutations have substantial prognostic and predictive significance in breast cancer. Advances in molecular diagnostics and targeted therapies enable personalized treatment approaches and improved patient outcomes. Further research is needed to better understand mechanisms of treatment resistance and to identify novel biomarkers predictive of therapeutic response.

KEYWORDS

BRCA1, BRCA2, Breast Cancer, PARP Inhibitors, Targeted Therapy, Molecular Diagnostics, Prognosis

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1. Introduction

Breast cancer remains the most frequently diagnosed malignancy among women worldwide and one of the leading causes of cancer-related mortality [1]. Despite substantial advances in diagnosis and treatment, the disease continues to represent a major public health challenge. Progress in molecular biology and cancer genetics has enabled the identification of numerous mechanisms involved in carcinogenesis, including genes associated with hereditary cancer predisposition.

Particular importance in the pathogenesis of hereditary breast cancer has been attributed to the BRCA1 and BRCA2 genes. These tumor suppressor genes are responsible for maintaining genomic stability through their involvement in DNA damage repair, primarily via the homologous recombination pathway [2,3]. Mutations leading to loss of function of these genes result in increased genomic instability and a significantly elevated risk of malignancy development, especially breast and ovarian cancer [4].

It is estimated that BRCA1 and BRCA2 mutations account for approximately 5–10% of all breast cancer cases and for a substantial proportion of familial breast cancer occurrences [5]. The lifetime risk of developing breast cancer in BRCA1 mutation carriers may reach up to 80%, whereas for BRCA2 carriers it is estimated at approximately 45–70% [8–10]. Hereditary cancers associated with BRCA mutations are characterized by a distinct biological profile, earlier age of onset, and a more aggressive clinical course [15].

In recent years, BRCA mutations have gained considerable importance not only as risk factors for cancer development but also as prognostic and predictive biomarkers. The development of molecularly targeted therapies, particularly poly(ADP-ribose) polymerase (PARP) inhibitors, has led to significant changes in the treatment of patients with hereditary breast cancer [19–24]. Simultaneously, advances in genetic diagnostics have enabled the implementation of more effective preventive strategies and the personalization of therapeutic management.

Another important issue is the impact of BRCA mutations on the prognosis of patients with breast cancer. Findings regarding overall survival and recurrence risk remain partially inconsistent; however, most studies indicate a more aggressive phenotype in BRCA1-associated tumors [11–14]. At the same time, the increased sensitivity of these tumors to DNA damage creates opportunities for the application of specific therapeutic strategies.

The aim of this review article is to comprehensively present the current knowledge regarding BRCA1 and BRCA2 mutations in breast cancer, with particular emphasis on their clinical significance, prognostic implications, and contemporary therapeutic applications.

2. Methodology

This study was conducted as a narrative review article. Current scientific publications concerning the molecular biology of BRCA1 and BRCA2 genes, the epidemiology of hereditary breast cancer, prognosis, and contemporary therapeutic approaches were analyzed.

The literature search included original articles, meta-analyses, systematic reviews, and clinical guidelines published in scientific journals. The analysis incorporated publications from journals such as *Nature Reviews Cancer*, *The New England Journal of Medicine*, *Journal of Clinical Oncology*, *The Lancet Oncology*, and *Breast Cancer Research and Treatment*.

The review included publications addressing:

- the biological function of BRCA1/BRCA2 genes,
- the epidemiology of hereditary breast cancer,
- the impact of BRCA mutations on clinical course and prognosis,
- the role of molecular diagnostics,
- the use of PARP inhibitors,
- platinum-based chemotherapy,
- prophylactic surgery and genetic counseling.

The analytical process involved identifying the most relevant clinical and experimental studies and synthesizing data regarding contemporary treatment strategies for BRCA-associated breast cancer. Particular attention was given to the OlympiAD, EMBRACA, and OlympiA trials, which played a pivotal role in the development of PARP inhibitor therapy [19,20,23,24].

The manuscript follows the Vancouver citation style in accordance with the standards for biomedical publications.

3. Biological Significance of BRCA1 and BRCA2 Genes

3.1 Structure and Function of BRCA Genes

BRCA1 and BRCA2 belong to the group of tumor suppressor genes responsible for maintaining genomic integrity [3]. The BRCA1 gene is located on chromosome 17q21, whereas BRCA2 is located on chromosome 13q12–13 [2]. Both genes encode proteins involved in DNA damage repair mechanisms, cell cycle control, and maintenance of chromosomal stability.

The BRCA1 protein participates in the cellular response to DNA damage and in the activation of checkpoint mechanisms that arrest the cell cycle [4]. BRCA2 plays a particularly important role in homologous recombination through the regulation of RAD51 protein activity [3]. Defects in these mechanisms lead to the accumulation of genetic mutations and the development of malignant transformation.

Homologous recombination is considered one of the most important pathways for the repair of double-strand DNA breaks. In the absence of functional BRCA proteins, cancer cells become dependent on alternative, less accurate repair mechanisms, resulting in increased genomic instability [30]. This phenomenon constitutes the biological basis for the therapeutic activity of PARP inhibitors.

3.2 Inheritance of BRCA Mutations

BRCA mutations are inherited in an autosomal dominant manner, meaning that inheritance of a single mutated allele significantly increases the risk of cancer development [2]. Mutation carriers exhibit increased susceptibility to breast cancer, ovarian cancer, pancreatic cancer, and several other malignancies.

These mutations may occur as point mutations, deletions, or insertions leading to loss of protein function. In many populations, so-called founder mutations have been identified, occurring with increased frequency within specific ethnic groups [17].

3.3 Epidemiology of BRCA Mutations in Breast Cancer

Hereditary forms of breast cancer account for approximately 5–10% of all breast cancer cases [1]. BRCA1 and BRCA2 mutations have the greatest clinical significance, as they are responsible for the majority of hereditary breast and ovarian cancer cases.

Epidemiological studies have demonstrated that the lifetime risk of breast cancer among BRCA1 mutation carriers is approximately 65–80%, whereas for BRCA2 mutation carriers it is estimated at 45–70% [8–10]. The risk of ovarian cancer is also substantially elevated, reaching 40–60% for BRCA1 and 10–25% for BRCA2 mutation carriers [8].

The EMBRACE study demonstrated that cancer risk depends on both the type of mutation and the patient's age [9]. BRCA1 mutations are more frequently associated with earlier disease onset and a more aggressive clinical course.

The prevalence of BRCA mutations varies among populations. Particularly high frequencies have been observed among Ashkenazi Jewish populations, in whom characteristic founder mutations are common [10]. In Asian populations, the distribution of BRCA mutations demonstrates distinct molecular characteristics [17].

4. Clinical Characteristics of BRCA-Associated Breast Cancer

4.1 Phenotype of BRCA1-Associated Tumors

Breast cancer associated with BRCA1 mutations is characterized by a distinct biological profile. These tumors are typically high-grade malignancies with elevated proliferative activity and lack of expression of estrogen receptors, progesterone receptors, and HER2 [16]. Consequently, most of these tumors are classified as triple-negative breast cancer (TNBC).

Triple-negative breast cancer is characterized by an aggressive clinical course, increased risk of recurrence, and limited options for hormonal and anti-HER2 therapies [16]. At the same time, these tumors demonstrate greater sensitivity to DNA-damaging chemotherapy.

4.2 Phenotype of BRCA2-Associated Tumors

BRCA2 mutations are more commonly associated with hormone receptor–positive tumors exhibiting estrogen receptor expression [15]. Compared with BRCA1-associated cancers, these tumors generally demonstrate a less aggressive clinical course.

Despite these biological differences, both BRCA1 and BRCA2 mutations are associated with an increased risk of bilateral breast cancer and local recurrence [26–28].

4.3 Prognostic Significance of BRCA Mutations

Assessment of the impact of BRCA1 and BRCA2 mutations on the prognosis of breast cancer patients remains one of the most extensively investigated areas in contemporary molecular oncology. Numerous studies have evaluated the relationship between mutation status and overall survival, disease-free survival, treatment response, and the risk of secondary malignancies [11–14].

Available findings remain partially inconsistent, mainly due to heterogeneity among study populations, differences in breast cancer biological subtypes, and evolving treatment standards. Nevertheless, most analyses indicate that BRCA1 mutations are associated with a more aggressive clinical course [11,12].

Baretta et al. conducted a meta-analysis including multiple studies evaluating the prognostic impact of BRCA mutations in breast cancer. The authors demonstrated that BRCA1 mutation carriers had a higher risk of death and disease recurrence compared with non-carriers [11]. In contrast, the association was less pronounced for BRCA2 mutations.

Similar observations were reported by van den Broek et al., who demonstrated that BRCA1-associated breast cancer more frequently exhibited high histological grade, rapid tumor growth, and increased metastatic potential [12]. However, the authors emphasized that the prognostic impact of BRCA1 mutations may be partially attributable to the predominance of the triple-negative phenotype.

Some studies suggest that differences in survival outcomes may diminish after adjustment for treatment type and biological subtype [13]. In a meta-analysis evaluating survival among patients with BRCA1/2 mutations, Lee et al. demonstrated that prognosis largely depends on systemic treatment strategies and disease stage at diagnosis [13].

In a study involving young women with breast cancer, Copson et al. showed that appropriately selected systemic therapy may improve outcomes in BRCA mutation carriers, particularly in tumors exhibiting high chemosensitivity [18]. These findings suggest that the biological aggressiveness of BRCA-associated tumors may be partially offset by greater responsiveness to specific therapeutic approaches.

Another important prognostic issue is the risk of contralateral breast cancer. BRCA1 and BRCA2 mutation carriers have a substantially higher risk of developing a second primary breast cancer compared with the general population [28]. Metcalfe et al. demonstrated that this increased risk persists for many years following treatment of the primary tumor [28].

Nilsson et al. highlighted the increased risk of local recurrence in BRCA mutation carriers treated with breast-conserving therapy [26]. These observations have important implications for surgical planning and post-treatment surveillance strategies.

In recent years, increasing attention has also been directed toward homologous recombination deficiency as a predictive factor for treatment response. Shao et al. demonstrated that the presence of BRCA mutations and other DNA repair abnormalities may be associated with improved response to PARP inhibitors and platinum-based chemotherapy [14].

In clinical practice, this indicates that BRCA mutations have a dual significance: on one hand, they may be associated with a more aggressive disease course, while on the other hand, they increase tumor sensitivity to specific therapeutic strategies.

4.4 Impact of BRCA Mutations on Tumor Biological Characteristics

Tumors associated with BRCA1 mutations demonstrate a distinct biological profile compared with sporadic breast cancers. In most cases, these tumors are characterized by high histological grade, elevated Ki-67 proliferative index, and absence of hormone receptor expression [16].

Foulkes et al. demonstrated that a substantial proportion of triple-negative breast cancers are associated with BRCA1 dysfunction [16]. This phenotype is linked to an aggressive clinical course, increased recurrence risk, and shorter disease-free survival.

BRCA1-dependent tumors are also characterized by greater genomic instability and a higher degree of aneuploidy. These abnormalities lead to the accumulation of numerous genetic alterations and acceleration of carcinogenesis [3,4].

In the case of BRCA2 mutations, the clinical picture differs somewhat. BRCA2-associated tumors more frequently express estrogen receptors and display a more heterogeneous molecular phenotype [15]. Prognosis in this patient group may be more favorable than in BRCA1-associated cancer, although it still depends on multiple clinical factors.

4.5 Significance of Age at Diagnosis

One of the characteristic features of hereditary breast cancer is the earlier age of disease onset. BRCA mutation carriers frequently develop breast cancer before the age of 40 years [8–10]. Early onset of the disease is associated with the need to make complex decisions regarding fertility preservation, prophylactic surgery, and systemic treatment.

Young age at diagnosis may influence the clinical course of the disease and increase the likelihood of an aggressive tumor phenotype. At the same time, younger patients are often better able to tolerate intensive systemic therapy, which may partially improve therapeutic outcomes.

4.6 Significance of Molecular Prognostic Biomarkers

Advances in molecular biology have led to the identification of numerous biomarkers associated with homologous recombination defects. Increasing importance has been attributed to the concept of homologous recombination deficiency (HRD), which encompasses not only BRCA mutations but also other abnormalities in DNA repair pathways [30].

Assessment of HRD status may enable the identification of patients who are particularly sensitive to PARP inhibitors and platinum-based chemotherapy. Expanding molecular diagnostics beyond classical BRCA mutations represents one of the most important directions in the development of contemporary precision oncology.

5. Genetic Diagnostics and Counseling

5.1 Indications for Genetic Testing

Advances in molecular diagnostics have significantly increased the importance of genetic testing in oncology. Current NCCN and ASCO guidelines recommend BRCA testing in patients with a family history suggestive of hereditary breast and ovarian cancer syndrome [5,7].

Indications for genetic testing include:

- breast cancer diagnosed before the age of 45 years,
- triple-negative breast cancer,
- bilateral breast cancer,
- coexistence of breast and ovarian cancer,
- positive family history of cancer,
- male breast cancer.

Genetic testing is of considerable importance not only for the patient but also for family members who may be carriers of the mutation.

5.2 Importance of Genetic Counseling

Genetic counseling constitutes an integral component of the management of patients with suspected hereditary breast cancer [6]. It includes assessment of cancer risk, interpretation of genetic testing results, and discussion of available preventive strategies.

An important aspect of counseling is also psychological support for patients diagnosed with BRCA mutations. Awareness of a substantially increased cancer risk may significantly affect quality of life and influence decisions regarding prophylactic surgery.

6. Treatment of BRCA-Associated Breast Cancer

6.1 Surgical Treatment

BRCA mutations influence the selection of surgical strategies. In some patients, bilateral prophylactic mastectomy is considered because of the high risk of contralateral breast cancer [28].

Studies have demonstrated that prophylactic mastectomy may significantly reduce the risk of breast cancer development and improve overall survival [29]. Nevertheless, decisions regarding surgical management should be individualized, taking into account the patient's age, reproductive plans, and psychological preferences.

Pierce et al. compared breast-conserving therapy with mastectomy in BRCA mutation carriers and demonstrated similar overall survival rates, although local recurrence risk was higher following breast-conserving treatment [27].

6.2 Chemotherapy

Tumors associated with BRCA mutations demonstrate increased sensitivity to DNA-damaging chemotherapy. Platinum compounds, such as cisplatin and carboplatin, are of particular importance in this setting [21].

In the TNT Trial, carboplatin showed greater efficacy in BRCA mutation carriers compared with standard chemotherapy [21]. Findings from neoadjuvant studies have also demonstrated high rates of pathological complete response following platinum-containing regimens [25].

Byrski et al. reported very high rates of pathological complete response following cisplatin treatment in young women with BRCA1 mutations [25]. These findings highlight the importance of DNA repair defects in determining treatment response.

6.3 PARP Inhibitors

One of the most significant achievements in modern oncology has been the development of PARP inhibitors. The mechanism of action of these agents is based on the phenomenon of synthetic lethality [22,30].

PARP enzymes participate in the repair of single-strand DNA damage. Inhibition of these enzymes in cells with homologous recombination defects leads to accumulation of DNA damage and subsequent cancer cell death.

6.4 Olaparib

The OlympiAD trial demonstrated that olaparib prolongs progression-free survival in patients with HER2-negative advanced breast cancer carrying BRCA mutations [19]. Treatment was also associated with improved quality of life and lower toxicity compared with conventional chemotherapy.

Another landmark study was the OlympiA trial, which evaluated adjuvant olaparib in patients at high risk of disease recurrence [23]. The study demonstrated significant improvements in both disease-free survival and overall survival [24].

6.5 Talazoparib

Talazoparib is another PARP inhibitor used in the treatment of BRCA-associated breast cancer. The EMBRACA trial demonstrated a significant prolongation of progression-free survival compared with standard chemotherapy [20].

The results of clinical trials have confirmed the efficacy of PARP inhibitors as a new standard of care for patients with germline BRCA mutations.

7. Prevention Strategies in BRCA Mutation Carriers

7.1 Prophylactic Surgery

BRCA mutation carriers are at a substantially increased risk of developing both breast and ovarian cancer. For this reason, prophylactic mastectomy and prophylactic salpingo-oophorectomy are considered in selected patients [29].

Prophylactic mastectomy may reduce the risk of breast cancer by more than 90%. However, the procedure is associated with significant psychological and aesthetic consequences and therefore requires appropriate patient preparation and counseling.

Prophylactic removal of the ovaries and fallopian tubes reduces the risk of ovarian cancer and partially decreases breast cancer risk through reduction of hormonal exposure.

7.2 Surveillance Programs

Women carrying BRCA mutations are recommended to undergo intensive oncological surveillance, including:

- regular breast magnetic resonance imaging (MRI),
- mammography,
- ultrasonographic examinations,
- oncological and genetic consultations.

Early detection of malignant lesions improves treatment efficacy and increases patient survival.

7.3 Significance of the "BRCAness" Concept

In recent years, increasing attention has been directed toward the concept of "BRCAness," which refers to tumors demonstrating homologous recombination defects similar to those observed in BRCA-mutated cancers despite the absence of detectable BRCA mutations [30].

Tumors exhibiting a "BRCAness" phenotype may demonstrate increased sensitivity to PARP inhibitors and platinum-based chemotherapy. Identification of such tumors represents one of the most important directions in the development of personalized medicine.

Further advances in the study of homologous recombination deficiency (HRD) may enable the expansion of targeted therapies to additional groups of patients.

8. Discussion

BRCA1 and BRCA2 mutations play a pivotal role in the pathogenesis of hereditary breast cancer and constitute one of the best-characterized examples of the relationship between genetic alterations and malignant transformation. Advances in molecular biology and cancer genomics have substantially expanded the understanding of the biological functions of these genes and their clinical significance. Contemporary breast cancer management increasingly relies on personalized medicine, in which identification of BRCA mutations directly influences therapeutic decision-making.

Numerous studies have demonstrated that BRCA1-associated tumors exhibit a more aggressive clinical course than sporadic breast cancers [11–16]. These tumors more frequently display a triple-negative phenotype, high proliferative index, and higher histological grade. Such biological characteristics are associated with an increased risk of recurrence and poorer prognosis, particularly during the first years following diagnosis.

At the same time, tumors associated with BRCA dysfunction exhibit increased sensitivity to DNA-damaging therapies. This mechanism results from homologous recombination defects, which impair the ability of cancer cells to repair genetic damage effectively [3,4]. In clinical practice, this translates into greater efficacy of platinum-based chemotherapy and PARP inhibitors.

The introduction of PARP inhibitors is considered one of the major breakthroughs in modern oncology. The mechanism of action of these agents is based on the phenomenon of synthetic lethality, in which simultaneous disruption of two DNA repair pathways results in cancer cell death [22,30]. Cells harboring BRCA mutations are unable to perform efficient homologous recombination; therefore, inhibition of PARP activity leads to accumulation of DNA damage and apoptosis.

The OlympiAD and EMBRACA trials confirmed the efficacy of PARP inhibitors in the treatment of advanced HER2-negative breast cancer with germline BRCA mutations [19,20]. Treatment with olaparib and talazoparib resulted in prolonged progression-free survival and improved quality of life compared with conventional chemotherapy.

Particularly important were the findings of the OlympiA trial, which demonstrated the efficacy of adjuvant olaparib in patients with early-stage breast cancer at high risk of recurrence [23,24]. These results contributed to changes in treatment standards and expanded the use of PARP inhibitors to earlier stages of disease.

Despite significant therapeutic advances, many clinical challenges remain unresolved. One of the most important issues is the development of resistance to PARP inhibitors. Mechanisms of resistance include secondary mutations restoring BRCA function, activation of alternative DNA repair pathways, and alterations in the expression of proteins involved in drug transport [22].

In recent years, growing attention has also been devoted to the concept of "BRCAness," referring to tumors that exhibit homologous recombination defects despite the absence of classical BRCA mutations [30]. Identification of such tumors may allow expansion of indications for PARP inhibitor therapy to a broader patient population.

Another important issue is the accessibility of genetic diagnostics. Current NCCN and ASCO guidelines emphasize the necessity of BRCA testing in patients meeting specific clinical criteria [5,7]. In practice, however, access to molecular testing remains limited in many countries, particularly in regions with lower healthcare expenditures.

Limited access to genetic diagnostics may lead to delayed identification of hereditary breast and ovarian cancer syndromes and reduce opportunities for implementing personalized therapies. This issue is especially significant in developing countries, where the number of specialized genetic centers remains insufficient [39].

An important component of contemporary management is also prevention in BRCA mutation carriers. Prophylactic mastectomy and prophylactic salpingo-oophorectomy substantially reduce the risk of breast and ovarian cancer [29]. However, decisions regarding preventive surgery are complex and require an individualized approach.

BRCA mutation carriers often face difficult decisions regarding surgical treatment, family planning, and quality of life. Consequently, genetic counseling and psychological support play a crucial role in patient care.

Modern management of BRCA-associated breast cancer requires close collaboration within a multidisciplinary team involving medical oncologists, surgeons, radiation oncologists, clinical geneticists, psychologists, and reproductive medicine specialists.

Current evidence also highlights the need for further development of molecular biomarkers. The presence of a BRCA mutation alone does not always allow comprehensive assessment of tumor biology or accurate prediction of treatment response. Increasing importance is attributed to the evaluation of homologous recombination deficiency (HRD), expression of DNA repair proteins, and genomic profiling of tumors.

The development of next-generation sequencing (NGS) technologies enables increasingly detailed analysis of genetic alterations associated with hereditary cancers. In the future, these technologies may facilitate even more precise personalization of therapy.

Another important research direction is the evaluation of combinations of PARP inhibitors with immunotherapy. Preliminary findings suggest that tumors with DNA repair deficiencies may exhibit greater immunogenicity, creating potential opportunities for combination treatment strategies.

Increasing interest has also been directed toward the use of PARP inhibitors in other BRCA-associated malignancies, including ovarian cancer, prostate cancer, and pancreatic cancer. Findings from these studies underscore the broad importance of homologous recombination defects in oncology.

The psychosocial impact of BRCA mutation detection should also be emphasized. Information regarding mutation status may cause substantial psychological distress and influence decisions related to treatment and family life. Many patients experience anxiety related to cancer risk, concerns regarding the health of their children, and difficulties in making decisions about prophylactic surgery.

Contemporary oncology increasingly recognizes the importance of comprehensive patient care, encompassing not only cancer treatment but also psychological support, rehabilitation, and health education.

Attention should also be given to the economic aspects of diagnostics and treatment of BRCA-associated breast cancer. Targeted therapies, including PARP inhibitors, are associated with high treatment costs. At the same time, early identification of mutation carriers and implementation of preventive measures may reduce the costs associated with treatment of advanced-stage disease.

Economic analyses suggest that expanding genetic testing programs may be beneficial from both clinical and economic perspectives. Identification of mutations in young women with triple-negative breast cancer appears to be of particular importance.

Further development of molecularly targeted therapies can be expected in the future. Novel PARP inhibitors, agents targeting DNA repair mechanisms, and combination therapies are currently under intensive investigation.

One potential direction of future development is the application of artificial intelligence and bioinformatics in genomic data analysis. These technologies may enable faster mutation identification and more precise prediction of treatment response.

In summary, BRCA1 and BRCA2 mutations have substantial clinical and therapeutic significance in breast cancer. Advances in molecular diagnostics and targeted therapies have profoundly changed the management of patients with hereditary cancer predisposition. Further research into the biological mechanisms of carcinogenesis and treatment resistance may contribute to even more effective personalization of therapy.

9. Conclusions

BRCA1 and BRCA2 mutations represent some of the best-characterized genetic factors predisposing individuals to the development of breast and ovarian cancer. Contemporary research clearly demonstrates that the presence of these mutations influences not only cancer risk but also the biological characteristics of tumors, the clinical course of disease, treatment response, and long-term patient prognosis [2–4].

The findings of the analyzed studies confirm that BRCA1-associated breast cancer is characterized by a particularly aggressive molecular phenotype. These tumors frequently exhibit features of triple-negative breast cancer, a high proliferative index, and increased genomic instability [15,16]. Such characteristics are associated with an increased risk of recurrence and poorer prognosis, especially during the first years following diagnosis [11–14].

BRCA2-associated tumors demonstrate greater biological heterogeneity and more frequently retain hormone receptor expression. Nevertheless, patients in this group also exhibit a significantly elevated risk of cancer development and secondary malignancies [8–10].

One of the most important conclusions derived from the literature analysis is the critical role of genetic diagnostics in modern oncology. Identification of BRCA mutations enables recognition of individuals at high risk of cancer development before the onset of malignancy. This makes it possible to implement oncological surveillance programs, preventive measures, and appropriately timed therapeutic interventions [5–7].

Current clinical guidelines emphasize the necessity of genetic testing in patients with positive family history, early age at diagnosis, bilateral breast cancer, and triple-negative tumor phenotype [5,7]. Expanding access to genetic testing may facilitate earlier identification of hereditary cancer syndromes and improve treatment outcomes.

Particularly important is the fact that BRCA mutations currently constitute one of the most significant predictive biomarkers of treatment response. The development of targeted therapies has fundamentally changed the management of patients with hereditary breast cancer [19–24].

The introduction of PARP inhibitors should be regarded as one of the greatest breakthroughs in contemporary molecular oncology. Agents such as olaparib and talazoparib have demonstrated high efficacy in both advanced and early-stage BRCA-mutated breast cancer [19,20,23,24]. These therapies exploit the phenomenon of synthetic lethality, leading to selective destruction of cancer cells with homologous recombination defects [22,30].

Clinical studies have shown that PARP inhibitors prolong progression-free survival and improve patients' quality of life. Some studies have also demonstrated beneficial effects on overall survival [19,24,35]. These findings underscore the importance of treatment personalization based on the molecular profile of the tumor.

Another therapeutically significant feature is the increased sensitivity of BRCA-associated tumors to platinum-based chemotherapy. Defects in DNA repair mechanisms render cancer cells more susceptible to agents inducing genetic damage [21,25].

Results from neoadjuvant treatment studies indicate that patients with BRCA mutations may achieve high rates of pathological complete response following appropriately selected chemotherapy regimens [25]. Achievement of pathological complete response is associated with improved prognosis and reduced recurrence risk.

The literature analysis also confirms the importance of prophylactic surgery in BRCA mutation carriers. Bilateral prophylactic mastectomy and salpingo-oophorectomy significantly reduce the risk of breast and ovarian cancer [29]. However, decisions regarding prophylactic surgery should take into account the patient's individual needs, age, reproductive plans, and psychological factors.

Genetic counseling remains an essential component of care for BRCA mutation carriers. Information regarding mutation status may substantially affect psychological well-being, family relationships, and therapeutic decision-making [6,37]. Consequently, appropriate psychological support and health education are necessary.

Contemporary management of hereditary breast cancer requires a multidisciplinary approach. Effective treatment and prevention depend on cooperation among medical oncologists, surgeons, geneticists, radiation oncologists, psycho-oncologists, and reproductive medicine specialists [5–7].

Current evidence also indicates the growing importance of homologous recombination deficiency (HRD). Homologous recombination defects may occur not only in patients with classical BRCA mutations but also in other tumors exhibiting genomic instability [14,30]. Expanding diagnostics to include HRD assessment may facilitate identification of additional patient groups likely to benefit from PARP inhibitor therapy.

Another important conclusion from the literature review is the need for further development of prognostic and predictive biomarkers. The presence of a BRCA mutation alone does not always provide a comprehensive assessment of tumor biology or reliably predict treatment response. Increasing importance is therefore attributed to comprehensive genomic profiling of tumors [14,30,38].

Advances in next-generation sequencing (NGS) technologies enable increasingly precise identification of molecular alterations responsible for hereditary cancers [37,38]. In the future, these technologies may become the foundation of routine oncological diagnostics and facilitate even more precise personalization of therapy.

An important clinical challenge remains the development of resistance to PARP inhibitors. Resistance mechanisms include secondary mutations restoring BRCA function, activation of alternative DNA repair pathways, and alterations in the expression of transport proteins [22,36]. Understanding these processes may enable the development of novel therapeutic strategies.

Growing attention is also being directed toward combination therapies. Preliminary findings suggest the possibility of synergistic effects between PARP inhibitors and immunotherapy. DNA repair defects may increase tumor immunogenicity, potentially enhancing the efficacy of immune checkpoint inhibitors [22,35,36].

The analyzed publications also emphasized the economic aspects of diagnostics and treatment of BRCA-associated breast cancer. Targeted therapies are expensive; however, early identification of mutation carriers and effective preventive strategies may reduce the costs associated with treatment of advanced-stage disease [6,39].

Expansion of genetic testing programs may therefore be beneficial from both clinical and economic perspectives. Identification of mutations in young women with triple-negative breast cancer and positive family history is of particular importance [5,15,16].

Another significant issue is the unequal access to molecular diagnostics and targeted therapies across different regions of the world [39]. In countries with limited healthcare resources, access to modern genetic testing and PARP inhibitors may be restricted. This challenge highlights the need for further development of global strategies aimed at improving treatment accessibility.

Contemporary oncology increasingly recognizes quality-of-life considerations in patient care. Management of BRCA-associated breast cancer involves not only anticancer treatment but also psychological support, rehabilitation, and assistance in decision-making regarding prophylactic surgery and family planning [6,37].

Public education regarding hereditary breast and ovarian cancer syndromes is also becoming increasingly important. Raising public awareness may contribute to earlier participation in diagnostic programs and more effective prevention.

Further advances in precision medicine can be expected in the future. Novel DNA repair inhibitors, combination therapies, and the application of artificial intelligence in genomic data analysis are currently under intensive investigation [22,36–38].

Analysis of large-scale molecular datasets may facilitate the identification of novel biomarkers and enable more precise prediction of treatment response. The development of bioinformatics and digital technologies will likely become one of the most important directions in the future evolution of oncology.

In summary, BRCA1 and BRCA2 mutations have fundamental significance in the pathogenesis, diagnosis, and treatment of breast cancer. Advances in molecular biology and targeted therapies have substantially improved therapeutic options for patients with hereditary breast cancer and opened new perspectives for personalized medicine [19–24,30].

Early identification of mutation carriers, appropriately implemented preventive strategies, individualized treatment, and the development of molecularly targeted therapies currently constitute the foundation of modern oncological management [5–7].

Despite remarkable progress, further research is still needed regarding mechanisms of treatment resistance, novel biomarkers, and broader accessibility of molecular diagnostics. Continued development of precision medicine may contribute to even more effective treatment of patients with BRCA mutations and further improvement in their quality of life [22,36–39].

10. Future Research Perspectives

The dynamic development of molecular biology and genomic sequencing technologies has established BRCA1 and BRCA2 mutations as one of the most intensively investigated topics in contemporary oncology. In recent years, particular attention has been focused on the possibility of further personalizing treatment strategies for patients with homologous recombination defects.

One of the principal directions of current research is the identification of mechanisms responsible for the development of resistance to PARP inhibitors. Despite the initially high efficacy of these therapies, some patients develop acquired resistance leading to disease progression [22,35,36]. Proposed mechanisms include secondary mutations restoring BRCA function, increased activity of alternative DNA repair pathways, and alterations in the tumor microenvironment.

Increasing importance is also being attributed to the analysis of homologous recombination deficiency (HRD). Defects in homologous recombination may occur not only in patients with detectable BRCA1/2 mutations but also in other tumors characterized by impaired DNA repair mechanisms [14,30]. Expanding molecular diagnostics to include HRD assessment may enable identification of additional patient groups likely to benefit from PARP inhibitor therapy.

Combination treatment strategies also represent an important area of ongoing development. Studies are currently investigating the combination of PARP inhibitors with immunotherapy, immune checkpoint inhibitors, and antiangiogenic agents [22,35]. Preliminary findings suggest the possibility of synergistic effects between these therapeutic approaches.

Significant progress has also been observed in the field of next-generation sequencing (NGS) technologies. Advances in high-throughput sequencing methods enable increasingly precise analysis of molecular alterations associated with hereditary breast cancer [37,38]. In the future, these technologies may become the foundation of routine oncological diagnostics.

Artificial intelligence and bioinformatics are also playing an increasingly important role. Analysis of large genomic datasets may facilitate the identification of novel prognostic and predictive biomarkers and enable more accurate matching of therapy to the individual molecular profile of each patient.

Another important direction for future research is the assessment of quality of life in BRCA mutation carriers. Increasing attention is being paid to psychosocial aspects, the impact of prophylactic treatment on women's functioning, and the importance of psychological support [6,37].

Further development of molecularly targeted therapies, novel DNA repair inhibitors, and more advanced diagnostic methods can be expected in the future. Expansion of genetic testing programs and improved accessibility of molecular diagnostics may contribute to earlier cancer detection and improved treatment outcomes.

11. Limitations of the Study

This study was conducted as a narrative literature review, which is associated with certain methodological limitations. The analysis was based primarily on English-language publications and studies originating from highly developed clinical centers.

Some data regarding prognosis and treatment efficacy were derived from retrospective studies and meta-analyses, which may be affected by heterogeneity among the analyzed patient populations [11–14]. Moreover, the rapid development of targeted therapies has resulted in frequent changes in treatment standards, which may influence the long-term relevance of some findings.

It should also be emphasized that most clinical trials investigating PARP inhibitors included selected patient populations meeting specific eligibility criteria; therefore, direct extrapolation of the results to the general patient population may be limited.

Despite these limitations, the analysis of the available literature enables a comprehensive assessment of the clinical significance of BRCA1 and BRCA2 mutations in breast cancer.

12. Summary

1. BRCA1 and BRCA2 mutations represent some of the most important risk factors for hereditary breast cancer.

2. The presence of these mutations influences the biological characteristics of the tumor, the clinical course of the disease, and patient prognosis.

3. BRCA1-associated breast cancer more frequently exhibits a triple-negative phenotype and an aggressive clinical course.

4. Genetic diagnostics play a crucial role in identifying high-risk patients and enabling personalized treatment strategies.

5. PARP inhibitors have significantly improved treatment outcomes in patients with BRCA mutations.

6. Platinum-based chemotherapy demonstrates high efficacy in patients with homologous recombination defects.

7. Prophylactic surgery and intensive oncological surveillance may reduce cancer risk and improve survival outcomes.

8. Further research should focus on mechanisms of treatment resistance and the identification of novel predictive biomarkers.

9. The continued development of personalized medicine may contribute to further improvements in the prognosis of patients with hereditary breast cancer.

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