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Review Article

The BRCA1 and BRCA2 Mutation Spectrum in Women with Ovarian Cancer: Clinical, Pathogenetic, and Prognostic Features

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Abstract

This article comprehensively analyzes the clinical, pathogenetic, and prognostic features of the mutation spectrum observed in BRCA1 and BRCA2 genes in women diagnosed with ovarian cancer. The main aim of the study is to determine the role of BRCA1/2 gene mutations in the mechanisms of ovarian cancer, their impact on the clinical course of the disease, and their significance in predicting treatment outcomes. Studies show that pathogenic mutations in the BRCA1 and BRCA2 genes lead to disruption of DNA repair by homologous recombination, which results in loss of genome stability and an increased risk of malignant transformation. Clinically, ovarian cancer in BRCA-mutation carriers may be diagnosed at an earlier age, be associated with high-grade serous histological type, and be accompanied by familial cancer syndromes. From a prognostic perspective, patients with BRCA1/2 mutations are highly sensitive to platinum-based chemotherapy and PARP inhibitors, which allows for improved survival rates. In addition, the type and localization of the mutation may have different prognostic significance in terms of the risk of disease recurrence and long-term clinical outcomes. Consequently, molecular-genetic analysis of the BRCA1 and BRCA2 genes in ovarian cancer has important scientific and practical significance in terms of selecting personalized treatment strategies, early screening of individuals at risk, and optimizing the prognosis of the disease.

Keywords: ovarian cancer, BRCA1, BRCA2, gene mutations, pathogenesis, clinical features, prognosis, personalized treatment

1. Introduction

Ovarian cancer is considered one of the most aggressive and highly lethal malignant diseases of the female reproductive system. This disease ranks first in terms of mortality among gynecological oncological pathologies and is often characterized by being diagnosed at late stages. The non-specificity of clinical symptoms, the lack of clear clinical signs in the early stages, and the limitations of effective screening methods make the timely detection of ovarian cancer difficult. It is for this reason that studying the molecular-genetic basis of the disease has become one of the priority research directions in modern oncology [1].

Scientific research conducted in recent decades has shown that hereditary genetic factors play an important role in the pathogenesis of ovarian cancer. Pathogenic mutations, particularly in the BRCA1 and BRCA2 genes, are associated with a significantly increased risk of ovarian and breast cancer. These genes perform key functions in maintaining genome stability, repairing DNA damage, and regulating the cell cycle. As a result of the loss of functional activity of the BRCA1 and BRCA2 genes, DNA repair mechanisms are disrupted, genetic instability occurs, and the likelihood of malignant transformation of cells increases.

The occurrence and spectrum of BRCA1 and BRCA2 gene mutations in the case of women suffering from ovarian cancer differ according to various factors such as population, ethnicity, and hereditary cancers. Numerous investigations reveal the fact that a considerable number of cases of hereditary ovarian cancer are associated with mutations of these genes. Mutations in the BRCA1 gene are marked by early age of disease

manifestation, histological diagnosis of high-grade serous subtype, and aggressive character of the disease development. In contrast, BRCA2 mutations are revealed much later in life and may possess various distinctive features [2].

In connection with the emergence of molecular genetics, it has become possible to analyze mutation spectra in the BRCA1 and BRCA2 genes more accurately. The mutation spectra include base changes, small insertions/deletions, and major restructuring of the genome. The nature of the mutation and its localization play an important role in the pathogenesis and clinical aspects of the disease. In this regard, sequence analysis of the BRCA1 and BRCA2 genes is not only diagnostic, but also has prognostic and predictive significance.

The identification of BRCA mutations in clinical practice has led to the development of new approaches to the management of ovarian cancer. Thus, high sensitivity to platinum-based chemotherapy is observed in BRCA mutation carriers. In addition, the introduction of PARP inhibitors based on the principle of synthetic lethality has significantly increased the effectiveness of treatment in these patients. These drugs cause the accumulation of DNA damage in cells with impaired BRCA function, resulting in the selective destruction of tumor cells. Thus, the detection of BRCA1 and BRCA2 gene mutations has become one of the key indicators in the selection of personalized treatment strategies.

The role of BRCA mutations in prognostic terms is also being extensively studied. Several scientific studies. It suggests that overall and disease-free survival rates may be higher in BRCA-mutation-positive ovarian cancer patients. However, this advantage may vary depending on the type of mutation, treatment strategy, and clinical stage. At the same time, detailed analysis of the mutation spectrum is of particular importance in terms of relapse risk and long-term clinical outcomes [3].

All these points illustrate that studying the clinical, pathogenetic, and prognostic features of the mutation spectrum in the BRCA1 and BRCA2 genes in women diagnosed with ovarian cancer is one of the current and strategically important directions of modern oncology. This topic is of great importance both in terms of deepening fundamental scientific knowledge and in terms of early diagnosis, risk assessment, and the application of effective treatment models in clinical practice. As a result, the molecular genetic study of the BRCA1 and BRCA2 genes serves as one of the most important pillars of personalized medicine in relation to ovarian cancer treatment and presents wide perspectives for future research.

2. Prevalence and Structure of BRCA1/2 Mutations in Ovarian Cancer

Analysis of the mutation spectrum in BRCA1 and BRCA2 genes in patients with ovarian cancer reveals that not only does it increase the likelihood of developing this disease, but it also affects its course, biology, and therapy. As shown in modern oncogenetics, ovarian cancer caused by BRCA mutations differs considerably from sporadic forms in terms of its molecular and clinical characteristics [4].

An analysis of the frequency of mutations in BRCA1 and BRCA2 genes proves that these abnormalities predominantly occur in high-grade serous ovarian carcinomas. Based on various international research, mutations in one of the genes, BRCA1 or BRCA2, can be found in 10–20% of cases among patients with ovarian cancer. It is worth mentioning that mutations in the BRCA1 gene happen more often and correlate with the early age at the moment of disease onset. The reasons for such high frequency are connected with the broad range of functions fulfilled by BRCA1 in cells – regulation of cell division and response to damage to the DNA [5].

Special attention should also be paid to the structure of the mutation spectrum. Alongside point mutations, small deletions, insertions, and genome rearrangements are quite common. In particular, frameshift and nonsense mutations cause the synthesis of functional protein to stop, completely losing the tumor-suppressor function of the gene. These types of mutations play a significant role in shaping the more aggressive molecular phenotype of ovarian cancer [6].

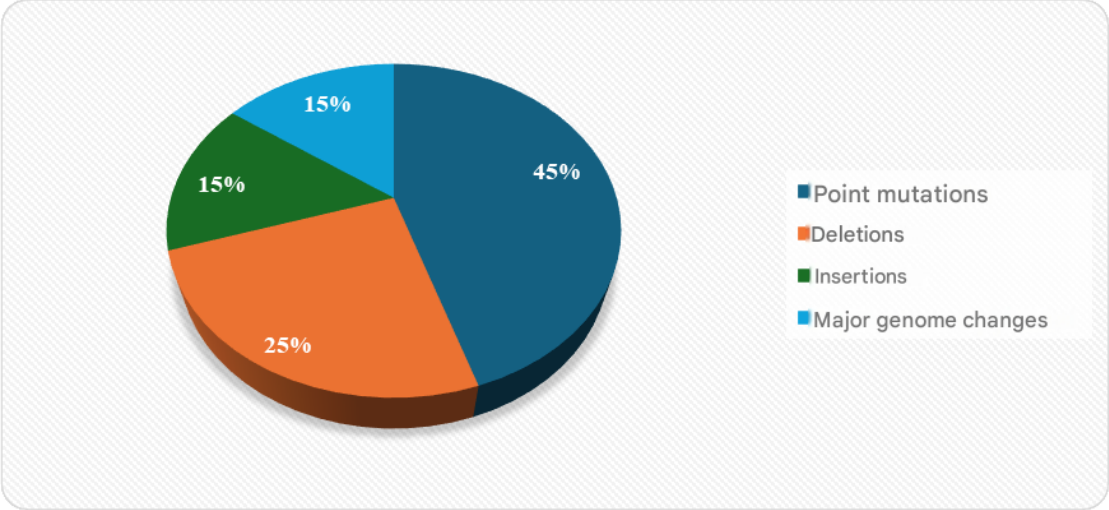

Figure 1. Distribution of mutation types in the BRCA1 and BRCA2 genes.
Source: *Author's own elaboration based on [7].*

Figure 1 illustrates the relative distribution of the main types of mutations found in the BRCA1 and BRCA2 genes in women diagnosed with ovarian cancer. As can be seen from the diagram, point mutations account for the largest share of the mutation spectrum. Deletions, insertions, and large genomic alterations are observed less frequently but play an important role in disrupting the functional activity of genes [5]. This diversity reflects the molecular heterogeneity of BRCA-mutation-associated ovarian cancer and has a significant impact on the pathogenesis of the disease, as well as on the characteristics of response to treatment [8].

3. Pathogenesis of BRCA-Mutation-Positive Ovarian Cancer

From a pathogenetic perspective, the main mechanism of action of BRCA1 and BRCA2 mutations is related to the disruption of DNA repair through homologous recombination. Under normal conditions, these genes maintain genome stability by ensuring the accurate repair of double-strand breaks. However, the failure of this mechanism as a result of mutation leads to the activation of alternative, error-prone DNA repair pathways. As a result, the mutation load in cells increases, chromosomal aberrations accumulate, and a favorable molecular environment for malignant transformation is formed [9].

This is one of the most important mechanisms determining the characteristics of these tumors. Despite their high growth rate, these tumors are also characterized by a high sensitivity to those drugs that induce damage to DNA. The peculiarity of these tumors is their aggressive nature, as well as sensitivity to treatment. These features are characteristic of BRCA-positive ovarian tumors [10].

4. Clinical Features and Histological Classification

As a result of the clinical analysis, it was concluded that, among the BRCA1 mutation carriers, there is a prevalence of diagnosis before menopause and a frequent presence of a positive family history for breast or ovarian cancer. Among patients carrying the BRCA2 mutation, the disease develops somewhat later and may follow other clinical courses. The above findings were determined due to the functional specificity of genes and their impact on intracellular signaling pathways [11].

Ovarian cancer associated with the presence of BRCA mutations mostly presents as a high-grade serous tumor. The probability of the occurrence of BRCA mutations among other histological subtypes of cancer (e.g., endometrioid or mucinous) is much lower. This fact indicates that BRCA mutations are closely associated with specific tumor biological phenotypes and increases the importance of molecular classification in clinical practice.

Table 1. Distribution of histological types of ovarian cancer according to BRCA-mutation status.

Histological type	BRCA-mutations positive (%)	BRCA-mutations negative (%)
High-grade serous carcinoma	70–80	40–50
Endometrioid carcinoma	8–12	15–20
Clear cell carcinoma	3–6	10–15
Mucinous carcinoma	1–3	10–12
Other rare histological types	2–5	5–8

Source: *Compiled by the author based on data from [12].*

5. Treatment Responses and Future Research Directions

Prognostic analyses suggest that patients with BRCA1 and BRCA2 mutations may have a more favorable response to treatment than BRCA-negative patients. Particularly high sensitivity to platinum-based chemotherapy regimens allows for longer disease-free survival in this group of patients. This condition is explained by the inability of BRCA-mutation-positive tumor cells to effectively repair DNA damage.

The introduction of PARP inhibitors into clinical practice in recent years has marked the beginning of a new phase in the treatment of BRCA-mutation-associated ovarian cancer. Based on the principle of synthetic lethality, these drugs cause the selective destruction of tumor cells by blocking the additional DNA repair pathway in cells with impaired BRCA function. As shown by the data of clinical trials, PARP inhibitors increase the probability of disease-free survival and lower the chances of recurrence.

Nevertheless, there are exceptions to a favorable treatment response even among patients with BRCA mutations. These include the nature of the mutation itself, its location in the gene structure, and the existence of other molecular alterations. Thus, the presence of secondary "reversing" mutations may lead to the functional recovery of BRCA and the acquisition of resistance to the applied medications.

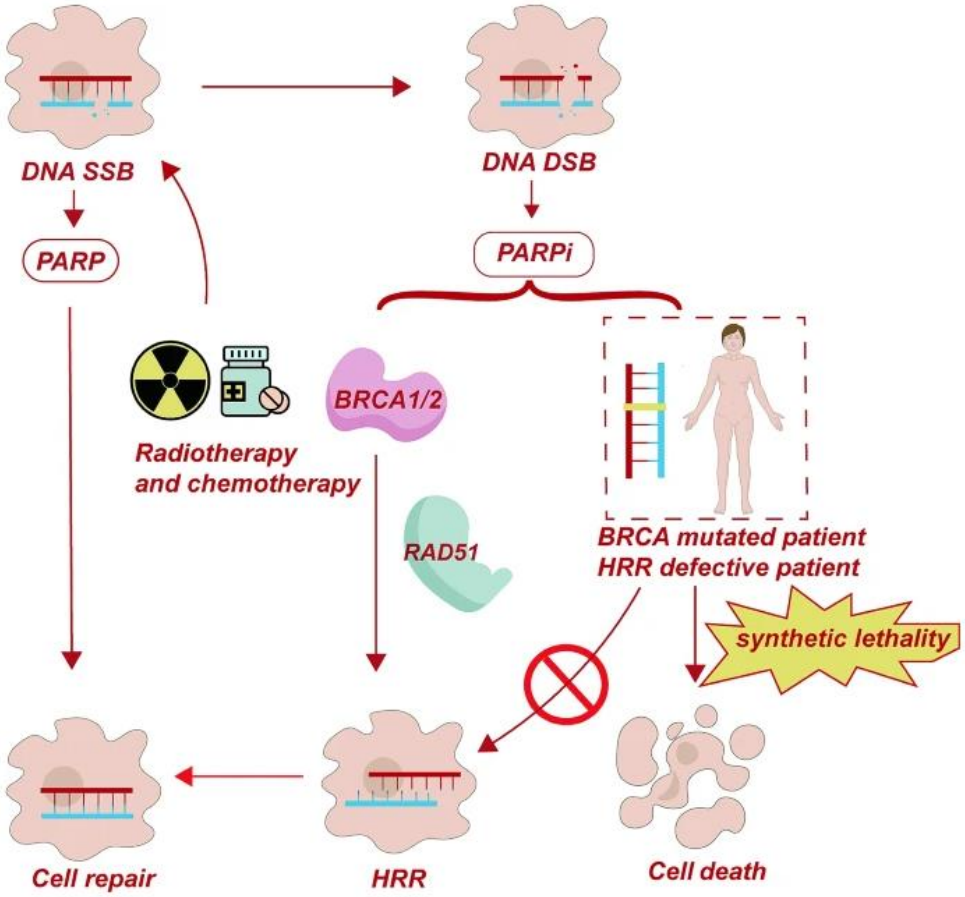

Figure 2. Mechanism of synthetic lethality of PARP inhibitors in the setting of BRCA1/2 mutation [13].

Figure 2 illustrates the repair of DNA single-strand breaks (SSB) under normal conditions by the PARP enzyme and the repair of double-strand breaks (DSB) by homologous recombination (HR) involving the BRCA1/2 and RAD51 proteins. When mutations exist in the BRCA1 and BRCA2 genes, the homologous recombination mechanism is disrupted, and the cell is unable to effectively repair DNA damage. The administration of PARP inhibitors (PARPi) also blocks the alternative DNA repair pathway, which leads to the accumulation of DNA damage and ultimately selective cell death, synthetic lethality in tumor cells carrying the BRCA mutation. Radiotherapy and chemotherapy enhance the effectiveness of this mechanism by further contributing to increased DNA damage.

Analysis of the available scientific literature exhibits that although the role of BRCA1 and BRCA2 gene mutations in ovarian cancer has been extensively studied, there are still open questions. The majority of studies were done retrospectively, while there is a lack of information about certain groups of patients. Nevertheless, the results concerning the influence of other homologous recombination-related genes other than BRCA genes on the progression of the disease have not been finalized yet.

Among the priorities for future research, the comparative analysis of the mutation pattern within diverse ethnicities, an understanding of the interaction of mutations within BRCA genes with other molecular alterations, and a better prediction of the prognosis of the disease based on the molecular markers are worth mentioning.

6. Role of BRCA1 and BRCA2 Mutations in the Molecular Genetic Mechanisms of Ovarian Cancer

The BRCA1 gene and BRCA2 gene mutations are associated with the progression of ovarian cancer. The two genes have significant roles, particularly in the maintenance of genomic stability and the repair of DNA damage. The two mutations cause instability of the genomes, making them more susceptible to cancer formation. In addition, these gene mutations are important in choosing suitable treatment options that are highly sensitive to such drugs as PARP inhibitors [14].

7. Conclusion

The obtained data demonstrate that the spectrum of mutations of the BRCA1 and BRCA2 genes in patients with ovarian cancer is an important factor for understanding the processes of formation of the disease, its progression, and further therapy. The important contribution of the mentioned genes in DNA repair by homologous recombination suggests their mutations to be one of the important molecular markers of ovarian cancer.

It follows from the total results of the research that BRCA1 mutations tend to be found in early years, be of high-grade serous histological type, and possess the aggressive nature of the clinical picture. As for BRCA2 mutations, they have somewhat different clinical manifestations and tend to predict better treatment results and prognosis in some cases. The character of mutations and the sites of their localization have a great influence on pathogenetic properties of ovarian cancer and the tendency to relapses.

From the clinical point of view, patients with BRCA mutations have a higher sensitivity to the platinum and PARP inhibitors. This is justified by the synthetic lethality concept and proves that the BRCA mutations represent a key factor in predicting the efficacy of such types of therapy. Therefore, the introduction of molecular-genetic tests into medical practice leads to a significant increase in the efficiency of the personalized approach in the treatment of this pathology.

At the same time, numerous sources indicate that not all patients with mutations in their BRCA genes are characterized by identical therapeutic effects. Other genetic changes, reversion mutations, and heterogeneous molecular characteristics of the tumors could be among the mechanisms underlying the formation of therapy resistance in such patients. Hence, there should be not only the consideration of BRCA status but also the HRD problem from a broader point of view in treating ovarian cancer.

Accordingly, a detailed examination of the spectrum of mutations within the BRCA1 and BRCA2 genes in women suffering from ovarian cancer represents a significant problem for further research in terms of prevention and therapy improvement. Further research needs to be done on a comparative study of mutations in various population groups, the role of genes that are involved in the HR pathway apart from BRCA, and

additional prognostic factors. Such a strategy would help enhance the molecular-based treatment model of ovarian cancer.

Author Contributions

The author confirms responsibility for the conception and final approval of the manuscript.

Conflict of Interest

The author declares no competing interests.

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Abbreviations

Breast Cancer 1 Gene (BRCA1), Breast Cancer 2 Gene (BRCA2), Deoxyribonucleic Acid (DNA), Double-Strand Break (DSB), Single-Strand Break (SSB), Homologous Recombination (HR), Homologous Recombination Deficiency (HRD), Poly (ADP-ribose) Polymerase (PARP).

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