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BRCA Gene Mutation Testing in Ovarian Cancer Patients and Its Impact on Targeted Therapy

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Abstract. Ovarian cancer is a highly fatal gynecological malignancy, with its early symptoms being subtle, resulting in most patients being diagnosed at an advanced stage. Studies have shown that BRCA gene mutations hold significant clinical importance in ovarian cancer patients. Mutations in the BRCA1 and BRCA2 genes are not only closely linked to the onset of ovarian cancer but also play a crucial role in its progression and treatment. The advancement of gene sequencing technology has provided more efficient and accurate methods for detecting BRCA mutations, particularly with the application of next-generation sequencing (NGS), which has greatly improved both detection rates and accuracy. In the field of targeted therapy, PARP inhibitors, as a novel treatment strategy, have been widely applied to ovarian cancer patients with BRCA mutations. These inhibitors work by suppressing the DNA repair pathway, inducing apoptosis in cancer cells, thereby significantly extending patient survival. However, resistance to PARP inhibitors in some patients remains a key challenge in current research. With the deepening of individualized treatment concepts, BRCA mutation testing not only assists doctors in assessing patient sensitivity to PARP inhibitors but also provides critical insights for developing personalized treatment plans. This paper reviews the clinical applications of BRCA gene mutations in ovarian cancer, explores gene testing technologies and their impact on targeted therapy, and emphasizes the analysis of the mechanisms and resistance issues associated with PARP inhibitors, aiming to provide theoretical support for precision medicine in ovarian cancer patients.

Keywords: ovarian cancer, genetic testing, targeted therapy.

1. Etiology and Pathogenesis of Ovarian Cancer

1.1. Epidemiological Characteristics of Ovarian Cancer

Ovarian cancer is the seventh most common cancer among women globally and is one of the leading causes of death from gynecological cancers. Its incidence and mortality rates vary significantly across different regions and populations. According to global cancer statistics, the incidence of ovarian cancer is relatively higher in developed countries, while it is lower in developing countries. However, despite the differences in incidence, the mortality rate of ovarian cancer remains consistently high worldwide, mainly due to its insidious clinical manifestations and the lack of effective early screening methods. The average age of onset for ovarian cancer is over 50 years, with the vast majority of patients being postmenopausal women. The occurrence of this disease is associated with multiple risk factors, including family history, genetic background (such as BRCA gene mutations), reproductive history,

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hormone exposure, and environmental factors. Notably, individuals carrying BRCA1 and BRCA2 gene mutations have a significantly increased lifetime risk of developing ovarian cancer, with BRCA1 mutation carriers having a risk as high as 40-60%, and BRCA2 mutation carriers having a risk of 20-30%. Additionally, women who have never given birth or who gave birth at a later age are at an increased risk of ovarian cancer due to prolonged exposure of the ovaries to the rupture-repair cycle during ovulation. It is important to note that the early symptoms of ovarian cancer are not obvious, often manifesting as mild bloating, pelvic discomfort, and other non-specific symptoms, resulting in most patients being diagnosed at an advanced stage, with a five-year survival rate of only 30-40% [1]. Therefore, epidemiological studies play a crucial role in identifying high-risk populations and developing effective screening strategies. With the development of molecular biology techniques, identifying high-risk groups through genetic testing, early prevention, and personalized treatment strategies have gradually become important directions in epidemiological research. Through these studies, we can better understand the pathogenesis of ovarian cancer and provide more precise medical solutions to reduce its incidence and improve patient survival rates.

1.2. Molecular Biological Mechanisms of Ovarian Cancer

The molecular biological mechanisms of ovarian cancer are highly complex, involving abnormalities in multiple genes, signaling pathways, and cellular processes. Its occurrence and progression are closely related to various molecular mechanisms, such as gene mutations, chromosomal aberrations, and epigenetic regulation. Among these, mutations in the BRCA1 and BRCA2 genes are important genetic factors contributing to the development of ovarian cancer. These two genes are primarily responsible for DNA damage repair, particularly regulating the homologous recombination repair (HRR) pathway. When BRCA gene mutations occur, this repair pathway is impaired, leading to the accumulation of DNA damage, which in turn causes genomic instability and promotes cancer development. Moreover, BRCA mutations also affect the regulation of the cell cycle, further accelerating the proliferation of cancer cells. In addition to BRCA gene mutations, ovarian cancer is often accompanied by mutations or abnormal expression of other key genes, such as TP53, PIK3CA, and PTEN. TP53 gene mutations are highly prevalent in ovarian cancer patients and often enable cancer cells to evade immune surveillance and acquire resistance to apoptosis. Furthermore, abnormal activation of the PI3K/AKT/mTOR signaling pathway is closely related to the invasiveness and drug resistance of ovarian cancer, with PIK3CA gene mutations directly causing sustained activation of this pathway, thereby promoting cancer cell growth and metastasis. Epigenetic regulation also plays an important role in the development and progression of ovarian cancer. Abnormal DNA methylation, histone modification, and non-coding RNA (such as miRNA) expression can lead to the silencing of tumor suppressor genes or the activation of oncogenes, further facilitating the carcinogenic process. Research has also shown that microenvironmental factors, such as immune cells and stromal cells within the tumor microenvironment, interact with each other to influence the progression of ovarian cancer and its response to treatment.

2. The Relationship Between BRCA Gene Mutations and Ovarian Cancer

2.1. Structure and Function of the BRCA Genes

The BRCA genes, including BRCA1 and BRCA2, are key tumor suppressor genes responsible for regulating DNA damage repair. Their primary function is to maintain genomic stability and prevent malignant cellular transformation. BRCA1 is located on the long arm of human chromosome 17 (17q21), and the protein it encodes is involved in several DNA repair pathways, such as homologous recombination repair (HRR) and non-homologous end joining (NHEJ). The BRCA1 protein forms complexes with various repair factors, such as RAD51, BARD1, and CtIP, to accurately locate sites of DNA double-strand breaks and facilitate high-fidelity repair of damaged DNA. If BRCA1 is mutated, the DNA repair capacity is compromised, leading to genomic instability and an increased accumulation of oncogenic mutations, thus raising the risk of cancer. BRCA2, located on the long arm of chromosome 13 (13q12.3), functions similarly to BRCA1 and plays a crucial role in homologous recombination repair.

The BRCA2 protein primarily regulates the accurate pairing and recombination of broken DNA strands with homologous sequences by interacting with RAD51. Mutations in BRCA2 also weaken the DNA repair capacity, leading to uncontrolled cell proliferation and genomic instability. Besides their roles in DNA repair, the BRCA genes are involved in regulating the cell cycle and maintaining the balance of cell proliferation. With the assistance of BRCA1, cells can halt at the G2/M phase to repair damaged DNA. When BRCA1 or BRCA2 is mutated, this regulatory function is lost, allowing cells with unrepaired DNA damage to progress into the next cell cycle, further promoting tumor formation.

2.2. Detection Rate and Mutation Types of BRCA Gene Mutations in Ovarian Cancer

The detection rate of BRCA gene mutations in ovarian cancer varies based on factors such as ethnicity, region, and family history. According to current epidemiological studies, about 15-25% of ovarian cancer patients carry germline mutations in the BRCA1 or BRCA2 genes, with most of these mutations being hereditary. Additionally, approximately 5-10% of ovarian cancer patients exhibit somatic mutations, which are non-hereditary BRCA gene mutations. The detection rate of BRCA1 mutations in ovarian cancer patients is higher than that of BRCA2, particularly among patients with a family history of breast or ovarian cancer, where the risk of BRCA1 mutations is further increased. BRCA2 mutation carriers generally display a milder clinical course and have a relatively longer survival period. Regarding the types of BRCA mutations, the most common ones are missense mutations, nonsense mutations, frameshift mutations, and splice site mutations. These mutations typically result in the loss of BRCA protein function, impairing DNA damage repair and increasing genomic instability, which promotes cancer development and progression. Missense mutations involve single base changes that cause amino acid substitutions, affecting protein function, while nonsense mutations lead to the premature termination of protein synthesis. Frameshift mutations result from insertions or deletions that significantly alter the encoded protein sequence, ultimately causing the loss of protein function [2]. Advanced techniques such as next-generation sequencing (NGS) have significantly improved the detection rate of BRCA gene mutations, particularly in identifying both germline and somatic mutations with high sensitivity and accuracy. This provides a critical basis for the individualized treatment of ovarian cancer patients.

3. Detection Methods for BRCA Gene Mutations

3.1. Gene Sequencing Technology

Gene sequencing technology is increasingly being applied in medical research and clinical diagnosis, particularly in genetic studies of cancer, where it has become an essential tool for exploring pathogenic gene mutations. Traditional gene sequencing methods, such as Sanger sequencing, though highly accurate, are inefficient for handling large-scale genomic data and cannot quickly or comprehensively detect multi-gene mutations. As a result, with the development of next-generation sequencing (NGS) technology, the clinical application of gene sequencing has been significantly advanced. NGS can perform parallel sequencing of millions of DNA fragments simultaneously, offering high throughput, high precision, and lower costs. NGS technology can detect a wide range of BRCA1 and BRCA2 gene mutations, including point mutations, insertions/deletions, and copy number variations, while also analyzing multiple genes in a single test. This improves the efficiency and sensitivity of detecting gene mutations. Compared to traditional Sanger sequencing, NGS provides more information in a shorter time, especially in identifying somatic and germline mutations. Furthermore, gene sequencing technology has facilitated the development of non-invasive detection methods, such as liquid biopsy. Liquid biopsy analyzes circulating tumor DNA (ctDNA) in the blood to detect BRCA gene mutations, providing new avenues for early tumor diagnosis, therapeutic monitoring, and resistance evaluation. This non-invasive method offers the advantage of dynamic monitoring, allowing real-time reflection of changes in the tumor's molecular characteristics.

3.2. Other Detection Techniques (e.g., Multiplex PCR, NGS, etc.)

In addition to gene sequencing, several other detection techniques play critical roles in detecting BRCA gene mutations. Among them, multiplex PCR (Polymerase Chain Reaction) is a classic molecular biology technique that can amplify multiple target gene fragments simultaneously, greatly enhancing detection efficiency. Multiplex PCR can effectively detect common BRCA gene mutation sites and identify rare mutation types through the design of specific primers. This technology is cost-effective, simple to operate, and quick, making it suitable for large-scale screening projects. However, its sensitivity and resolution are relatively low, and it cannot comprehensively cover all BRCA gene mutations. Next-generation sequencing (NGS) offers higher throughput and precision than multiplex PCR. NGS can deeply sequence the entire coding sequence of the BRCA genes, detecting not only point mutations but also complex mutations like insertions and deletions. Additionally, NGS can simultaneously analyze multiple cancer-related genes, providing ovarian cancer patients with a comprehensive mutation profile. This technology is particularly suited for in-depth analysis of complex mutations and cases with high genetic heterogeneity, especially when patients have a family history or exhibit multi-gene mutations. Moreover, digital PCR (dPCR), an emerging precise quantification technology, is gradually being used in detecting BRCA mutations [3]. dPCR partitions PCR reactions into numerous micro-reactions, allowing for the precise detection of low-frequency mutations, especially in ctDNA detection during liquid biopsies.

4. The Impact of BRCA Gene Mutations on Targeted Therapy

4.1. Mechanism of Action and Efficacy of PARP Inhibitors

PARP (Poly ADP-ribose polymerase) inhibitors are a class of targeted drugs used to treat cancers associated with BRCA gene mutations. Their primary mechanism of action is based on the vulnerability of cancer cells' DNA repair systems. Mutations in BRCA1 and BRCA2 genes impair the cells' ability to repair DNA double-strand breaks through homologous recombination repair (HRR), forcing the cells to rely on alternative repair pathways, such as PARP-mediated single-strand break repair. PARP inhibitors block the activity of PARP proteins, preventing the repair of single-strand breaks, leading to the accumulation of DNA damage. When cancer cells are unable to repair these damages, they undergo cell cycle arrest and eventually apoptosis. Therefore, PARP inhibitors can selectively kill BRCA-mutant tumor cells with minimal impact on normal cells. In the treatment of ovarian cancer, PARP inhibitors such as Olaparib, Niraparib, and Rucaparib have been widely used in patients with BRCA gene mutations, significantly prolonging progression-free survival (PFS). Studies have shown that PARP inhibitors are most effective in patients with germline or somatic BRCA mutations, with therapeutic effects lasting several months or even years. Additionally, research has found that even in the absence of BRCA mutations, tumors with other homologous recombination defects (HRD) may also be sensitive to PARP inhibitors. Despite the significant efficacy of PARP inhibitors in treating BRCA-mutant ovarian cancer patients, resistance remains a major challenge in clinical practice. Mechanisms of resistance include secondary BRCA mutations restoring function, compensation for DNA repair defects through alternative repair pathways, and structural changes in PARP proteins that prevent drug binding. Future research will aim to overcome resistance and further optimize treatment strategies, potentially by combining therapies or developing new targeted drugs to enhance therapeutic outcomes.

4.2. Mechanisms of Resistance to PARP Inhibitors in BRCA Gene Mutations

Although patients with BRCA gene mutations initially respond well to PARP inhibitor treatment, some develop resistance over time, limiting the long-term efficacy of the therapy. The mechanisms of resistance are complex and varied, with one primary mechanism being secondary mutations in the BRCA genes. Secondary mutations can partially or fully restore the function of BRCA1 or BRCA2 proteins, reactivating the homologous recombination repair (HRR) pathway and enabling cancer cells to repair the DNA damage caused by PARP inhibitors, thus evading apoptosis. Additionally, cancer cells may activate alternative DNA repair pathways to compensate for HRR deficiency. For example, the loss of 53BP1 and the Shieldin complex can activate the non-homologous end joining (NHEJ) repair pathway, compensating for the repair defects caused by BRCA mutations and reducing sensitivity to PARP inhibitors. Structural alterations in the PARP protein itself also contribute to resistance. Studies have found that some cancer cells produce mutated variants of the PARP protein, making it difficult for PARP inhibitors to bind effectively, thus weakening the drug's inhibitory effect. Furthermore, changes in the tumor microenvironment, such as increased angiogenesis or the formation of an immunosuppressive microenvironment, may negatively affect the efficacy of PARP inhibitors.

5. The Clinical Application and Prospects of BRCA Gene Testing

5.1. Personalized Treatment Strategies

With an increasing understanding of the molecular mechanisms of ovarian cancer, personalized treatment strategies have garnered growing attention in clinical settings. Personalized treatment for ovarian cancer patients is primarily based on factors such as their genetic mutations, tumor molecular markers, and clinical manifestations, aiming to formulate the most effective treatment plan for each individual. BRCA gene mutation testing is a key aspect of personalized treatment. For patients carrying BRCA mutations, PARP inhibitors have been proven to be highly effective, and as a result, these patients are often prioritized for this targeted therapy. However, personalized treatment is not limited to BRCA mutation patients. Patients with homologous recombination repair defects (HRD) or other gene mutations may also benefit from drugs targeting specific molecular pathways to enhance therapeutic efficacy. For example, patients with abnormal activation of the PI3K/AKT/mTOR signaling pathway may consider treatment with drugs that inhibit this pathway. Moreover, dynamic monitoring methods such as liquid biopsies provide new tools for personalized treatment, enabling real-time tracking of changes in tumor molecular characteristics, allowing doctors to adjust treatment plans based on the patient's response to therapy for optimal results [4]. With the rapid development of genomics technologies and biomarker research, future personalized treatment plans will become more precise, better suited to the specific molecular characteristics of patients' tumors, maximizing efficacy while minimizing side effects. The continuous refinement of this strategy not only extends patient survival but also improves quality of life, achieving the goal of precision medicine.

5.2. Clinical Prospects and Challenges of BRCA Gene Testing

BRCA gene testing has broad clinical prospects, particularly in the early diagnosis, prognosis assessment, and personalized treatment of ovarian cancer. By testing for BRCA1 and BRCA2 gene mutations, high-risk individuals can be identified, allowing for more targeted prevention strategies such as regular monitoring and prophylactic surgery. Additionally, for patients already diagnosed with ovarian cancer, BRCA gene testing results can help doctors select appropriate targeted therapies, such as PARP inhibitors, to improve treatment outcomes and extend progression-free survival (PFS). With advancements in genetic testing technologies, such as next-generation sequencing (NGS) and non-invasive methods like liquid biopsies, the detection rate and accuracy of BRCA gene mutations have significantly improved, providing a solid foundation for clinical application [5]. However, BRCA gene testing in clinical practice still faces many challenges. First, interpreting the test results can be complex, especially for variants of uncertain significance (VUS), where a lack of standardized interpretation guidelines may complicate clinical decision-making. Second, since the frequency and types of BRCA mutations vary across different regions and populations, establishing local BRCA mutation databases and interpretation systems is particularly important. Furthermore, genetic testing may raise ethical and psychological concerns, such as the psychological impact on patients and their families, privacy protection, and the potential for genetic discrimination. These issues necessitate thorough informed consent and psychological counseling before testing. In summary, while BRCA gene testing holds great potential for personalized treatment in ovarian cancer, its clinical application requires further optimization of strategies, refinement of technical standards, and strengthened ethical regulations to ensure safe and effective patient care.

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6. Conclusion

In summary, BRCA gene mutations play a crucial role in the onset, progression, and treatment of ovarian cancer. Through testing for BRCA1 and BRCA2 genes, clinicians can better identify high-risk individuals, implement early interventions, and develop more precise treatment strategies for diagnosed patients. The advancement of gene sequencing technologies, particularly the application of next-generation sequencing (NGS) and liquid biopsy techniques, has not only improved the detection rate and accuracy of BRCA gene mutations but also provided a solid technical foundation for the implementation of personalized treatment. In terms of targeted therapy, PARP inhibitors have brought significant survival benefits to ovarian cancer patients carrying BRCA gene mutations. However, resistance to treatment remains one of the current challenges in research, making it crucial to further investigate its mechanisms and develop new combination therapy strategies. Despite the promising clinical prospects of BRCA gene testing, it also faces challenges related to ethics, psychology, and technical standards. Future research should continue to focus on how to better interpret complex genetic testing results and enhance the widespread applicability of testing, especially for different populations. By optimizing testing and treatment strategies, BRCA gene testing and its targeted therapies will open up broader prospects for precision medicine in ovarian cancer, ultimately achieving the goal of improving patient survival rates and quality of life.

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