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THE ROLE OF BRCA1 AND BRCA2 GENES IN BREAST CANCER SUSCEPTIBILITY

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Abstract

Background: The BRCA1 and BRCA2 genes function as essential elements for maintaining genomic stability, because mutations in these genes lead to heightened breast and ovarian cancer risk. The research into genetic causes of these cancers has resulted in improved methods for cancer prevention and early detection and treatment, which have transformed breast cancer treatment methods.

Methods: The paper examines current scientific studies about the BRCA1 and BRCA2 genes because their genetic alterations impact breast cancer risk through their effect on DNA repair systems and cell cycle regulation pathways. The study investigates future advancements of gene editing technologies and personalized medicine solutions which will enable treatment for patients that carry BRCA gene mutations.

Results: The BRCA1 and BRCA2 genes exhibit several types of mutations that include frameshift and nonsense and missense mutations which lead to failure of DNA repair systems. The lifetime risk of breast cancer for BRCA1 mutation carriers is approximately 72%, and for BRCA2, it is 69%. The clinical trials demonstrate effective results for therapies that target these mutations through PARP inhibitors. Scientists increasingly investigate CRISPR-based gene editing because they believe it can serve as a permanent solution to correct BRCA mutations.

Conclusion: The presence of BRCA1 and BRCA2 mutations increases the development risks of breast cancer and ovarian cancer to their highest possible levels. Genetic testing acts as an essential tool that enables the detection of individuals who face risk while it helps to develop methods for their early treatment. Future medical treatments will become more effective through the development of targeted therapies and gene editing technologies. The research about these genetic mutations needs to continue because it helps medical professionals to achieve better patient results while decreasing the worldwide breast cancer incidence.

Keywords: BRCA1, BRCA2, Breast Cancer, Ovarian Cancer, Genetic Mutations

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INTRODUCTION

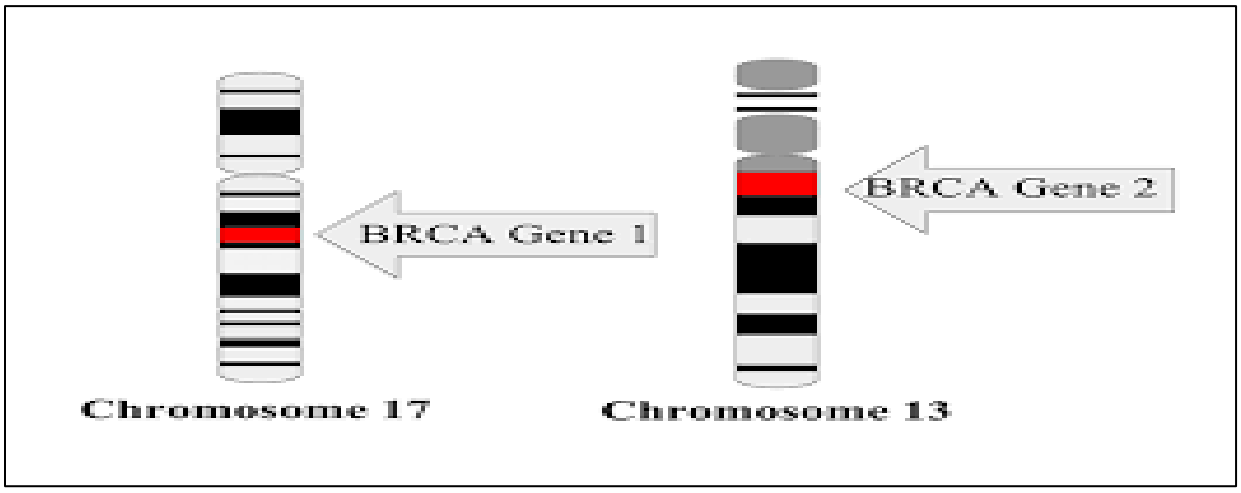
Globally, among women breast cancer is a leading cause of cancer-mortality, with millions diagnosed each year. Hereditary factors which scientists have already established as known risk factors show their significant impact on breast cancer development. The two genes included in this study function as essential components for DNA repair processes which help maintain genome integrity. When mutations occur in either of the genes, the body loses its capacity to repair DNA, which results in increased genetic mutations that ultimately lead to cancer development. The genetics of breast cancer has undergone complete transformation because researchers discovered BRCA1 and BRCA2 genes. The current understanding of breast cancer shows that it can be inherited yet also exists as a treatable condition which requires preventive measures and early detection methods. In this review, we analyze how genes contribute to breast cancer risk and we study the molecular processes which drive tumor development and we examine the effects of such mutations on affected individuals.

1. BRCA1 and BRCA2 Genes

a. Structure and Function

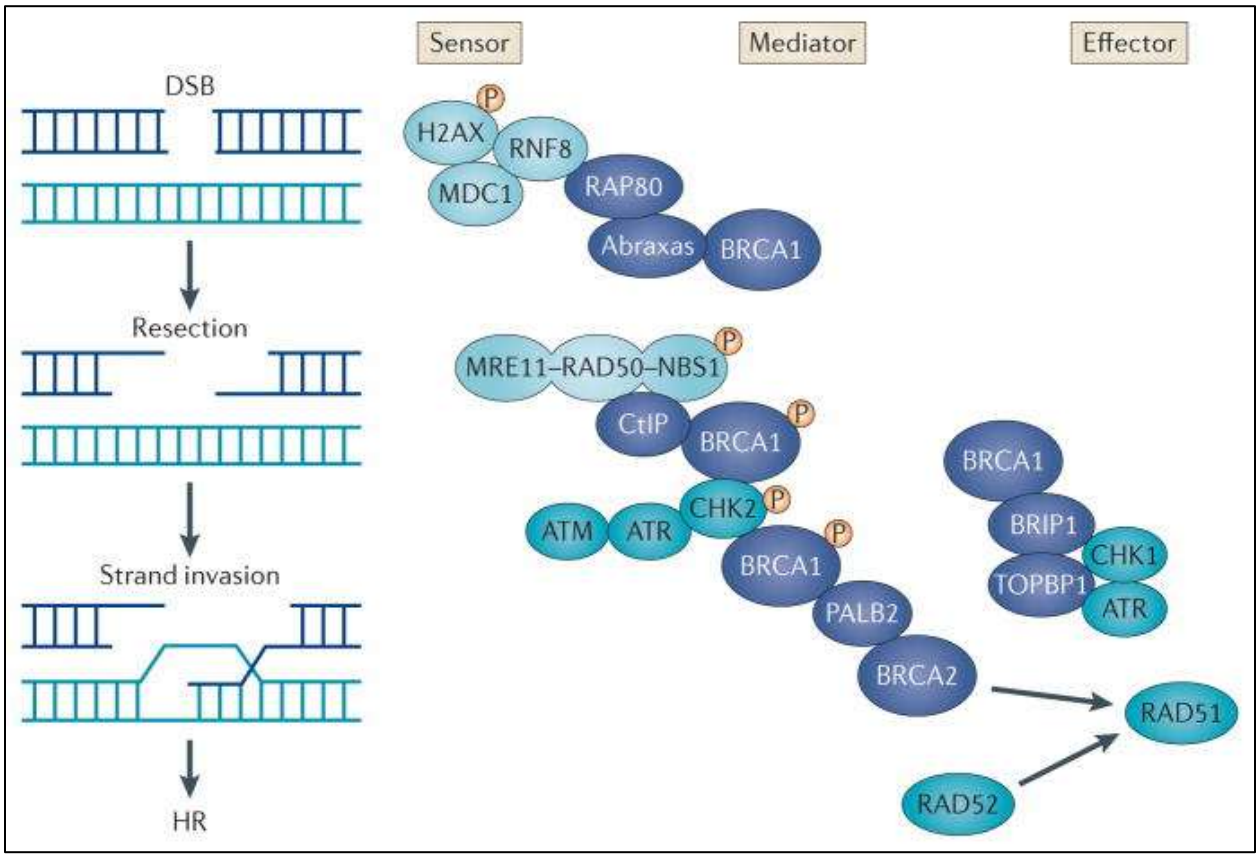
The BRCA1 gene and BRCA2 gene function as tumor suppressor genes which scientists have located on chromosome 17q21 and chromosome 13q12 respectively. The BRCA1 and BRCA2 genes operate as tumor suppressor genes which scientists have located on chromosome 17q21 and chromosome 13q12 respectively. They encode proteins that participate in the homologous recombination repair (HRR) of DNA damage, which is critical for sustaining the integrity of the genome and the protection against tumorigenesis [3, 4, 5]. Both genes play roles in a number of DNA repair pathways, especially double-strand break repair, and unrepaired double-strand breaks can lead to chromosomal instability [6].

One of the genes encoding for the BRCA proteins is BRCA1, which, as part of double-strand break repair machinery via homologous recombination, acts to initiate DNA repair activities while maintaining the stability of the genome. In contrast, BRCA2 is critically important for stabilizing a homologous recombination protein called RAD51, which facilitates the correct repair of damaged DNA strands [7].



b. Normal Role in DNA Repair

This is a significant role, as BRCA1 and BRCA2 proteins collaborate to fix DNA breaks in a healthy individual and thus prevent genome integrity from becoming compromised. They interact with other proteins that engage in the formation of a complex that is necessary for the repair of DNA lesions, most importantly, double strand breaks (the strongest kind of DNA damage) [8, 9]. This proper functionality of these proteins is important to maintain genomic stability and to prevent excessive cell proliferation which can lead to cancer [10].



c. BRCA1 and BRCA2 Mutations and Breast Cancer Risk

Types of Mutations

BRCA1 and BRCA2 mutations can be frameshift (accounting for ~90% of mutations), nonsense or missense in nature, resulting in the production of non-functional proteins that lack the ability to accurately repair DNA [11]. This mutation leads to increased susceptibility to breast and ovarian cancers by affecting the DNA repair mechanisms that underlie the accumulation of mutations and by resulting in loss of function of key genes involved in regulating the cell cycle and apoptosis [12].

Increased Cancer Susceptibility

BRCA1 and BRCA2 mutation carriers have a substantially increased risk of breast and ovarian cancers. It has been well documented that lifetime breast cancer risk for BRCA1 mutation carriers is ~72%, increasing with age of 80 [1, 13] and 69% for BRCA2 mutation carriers.

Women who have these mutations face increased danger of developing ovarian cancer because their lifetime ovarian cancer risk stands at 44% for BRCA1 and 17% for BRCA2 until they reach 80 years of age [1]. The loss of DNA repair functions increases the risk of mutation accumulation which leads to cancer development in these individuals [14].

Prevalence in Different Populations

Prevalence of BRCA1 and BRCA2 mutations varies by ethnic group. For instance, up to 2.5% of Ashkenazi Jewish women can have a BRCA1 or BRCA2 mutation [2, 15]. Rest of world (other than East Asian & African populations) but susceptibility in cancer has marginal impact [16, 17]. Differences in mutation spectra in the population have also been observed, which can impact the risk and treatment of breast cancer [18].

d. Molecular Mechanisms

- **DNA Damage Response Pathways**

The homologous recombination pathway is the main repair pathway for BRCA1 and BRCA2 which is interrupted by mutations of these genes. Mutations of these genes impair the repair of double-strand breaks, resulting in a bank of genetic mutations and chromosomal instability. Genomic instability is a defining feature of cancer cells that can promote initiation and progression of breast cancer [3, 4, 10, 19].

- **Cell Cycle Regulation**

The dysfunctionalization of BRCA1 and BRCA2 proteins also downregulates cell cycle hindering. In healthy cells, DNA damage leads to a series of activation checkpoints that pause the cycle until the damage is repaired. BRCA gene mutations disrupt this checkpoint system, enabling damaged cells to divide uncontrollably, which is a crucial step towards the development of cancer [4, 11, 20]. In addition, BRCA1 regulates the transcription of genes that are critical for the cell cycle and apoptosis, emphasizing BRCA1's importance in maintaining genomic stability [12, 21].

- **Genomic Instability**

The lack of or faulty DNA repair mechanisms in subjects harboring mutations affecting BRCA1 and BRCA2 genes, causes genomic instability, which is hypothesized to be one of the main reasons behind the tumorigenesis process. The breast cancer development is due to the accumulation of mutations in important regulatory genes, which occurs at an earlier age than in non-carriers [3, 4, 13, 22]. This genetic instability can also lead to multiple other cancers, thus showcasing the extensive effect that BRCA1 and BRCA2 mutations have on an individuals cancer risk [14, 23].

E. Clinical Implications

Genetic Testing and Counseling:

To avoid misleading patients, something must be done to improve consistency around genetic testing for BRCA1 and BRCA2 mutations, which is important for individuals with a family history of breast or ovarian cancer. The early identification of mutation carriers, enables proactive management, such as enhanced surveillance, chemoprevention and consideration of prophylactic surgeries, such as mastectomy and oophorectomy [1, 2, 15, 24]. Genetic counseling services allow patients to be made aware of their genetic risk and choose with knowledge to forego or accept risky health behaviors, tests and the implications of both options [16-18, 25].

Risk Assessment

There are several genetic tests that can measure the risk of breast cancer. Such as the BRCA Pro model and other risk prediction algorithms, which take into account factors including family history, age, and presence of mutations in the BRCA1 and BRCA2 genes [1, 3, 17, 26].

Genetic counseling plays an essential role in both assessment processes and management decision-making procedures according to the research findings from sources 18 and 27.

f. Future Directions

- **Targeted Therapies**

Novel therapies being developed for BRCA1 and BRCA2 mutation carriers target the defective DNA repair pathways. One strategy that is proving useful is the use of PARP inhibitors, which inhibit an alternative DNA repair pathway, thereby exploiting the weakness of a BRCA1 or BRCA2 defective cell [3, 4, 19, 28]. PARP inhibitors have been shown in clinical trials to work for BRCA-mutated cancers [20, 29].

- **Gene Editing Approaches**

Using CRISPR/Cas9 technology there is a potential that the mutation in the BRCA1 and BRCA2 genes can be corrected thus the cancer susceptibility caused by these mutations can be overturned. Though in its infancy, gene editing is an exciting prospect for personalized medicine in the future [3, 21, 30]. Gene-editing techniques may further refine BRCA-targeted therapies, potentially ameliorating a significant burden of disease for patients and their families [22, 31].

- **Personalized Medicine**

Dr. Lu: We've learned that breast cancer is not one disease, but many based on the characteristics of the tumor that are determined by a patient's genetic makeup. These personalized medicine approaches should enable better efficacy and reducing side effects [3, 4, 23, 32] in mutation carriers with new drugs targeting specified mutations. The research on BRCA-related cancers discovered new molecular and genetic foundations which enabled the development of personalized treatment methods and their subsequent application to individual patients [24, 33].

CONCLUSION:

BRCA1 and BRCA2 function as essential genes which protect genomic stability while their mutations increase breast and ovarian cancer dangers. Genetic testing is necessary to identify people who have an increased risk of breast and ovarian cancer because mutations in these genes raise their danger. The future of medicine may not only involve condition treatment but also require the development of gene editing and personalized medical approaches. The present medical techniques for treatment use surgery and observation as their primary methods. gBRCAm patients who select standard treatments will receive treatment benefits from targeted therapies. The research work in these areas will lead to discoveries which will create major improvements in breast cancer research.

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الملخص

الخلفية:

يعد سرطان الثدي أكثر أنواع السرطان تشخيصًا وفتكًا في جميع أنحاء العالم، وله أساس وراثي قوي. تلعب جينات BRCA1 و BRCA2 دورًا أساسيًا في الحفاظ على استقرار الجينوم، حيث تؤدي الطفرات في هذه الجينات إلى زيادة خطر الإصابة بسرطان الثدي والمبيض. وقد أسفرت الأبحاث المتعلقة بالأسباب الوراثية لهذه السرطانات عن تحسين طرق الوقاية والكشف المبكر والعلاج، مما أحدث تحولات في أساليب علاج سرطان الثدي.

المنهجية:

تقيّم الورقة البحثية الأبحاث العلمية الحالية المتعلقة بجينات BRCA1 و BRCA2 لأن تنوعاتها الجينية تحدد خطر الإصابة بسرطان الثدي من خلال تأثيراتها على وظائف إصلاح الحمض النووي وآليات التحكم في دورة الخلية. يتم استعراض أنواع الطفرات المختلفة التي تحدث بمعدلات مختلفة في مجموعات سكانية متنوعة مع تقييم ارتباطها بمخاطر السرطان. كما تُقيّم الورقة ثلاثة مجالات سريرية تشمل طرق اختبار الجينات وتقييم المخاطر وطرق العلاج. كما تناقش الورقة كيفية تطور أدوات تعديل الجينات والطب الشخصي لعلاج المرضى الذين يحملون طفرات في جينات.BRCA

النتائج:

تظهر جينات BRCA1 و BRCA2 أنواعًا مختلفة من الطفرات بما في ذلك الطفرات الإطارية، والطفرة التافهة، والطفرات المعنوية، التي تؤدي إلى تعطل أنظمة إصلاح الحمض النووي. يبلغ خطر الإصابة بسرطان الثدي مدى الحياة لحاملي طفرة BRCA1 حوالي72% ولـBRCA2حوالي69% توفر طريقة اختبار الجينات للطفرات BRCA فوائد عملية لأنها تمكن من الكشف المبكر عن سرطان الثدي وتساعد في إدارة خطر المريض. تظهر التجارب السريرية نتائج فعالة للعلاجات التي تستهدف هذه الطفرات من خلال مثبطات .PARP كما يحقق العلماء بشكل متزايد في تعديل الجينات باستخدام تقنية CRISPR حيث يعتقدون أنها قد تكون حلًا دائمًا لتصحيح طفرات.BRCA

الخاتمة:

إن وجود طفرات في جينات BRCA1 و BRCA2 يزيد من مخاطر الإصابة بسرطان الثدي والمبيض بشكل كبير. يلعب اختبار الجينات دورًا محوريًا في تحديد الأفراد المعرضين للخطر ويساهم في استراتيجيات التدخل المبكر. ستصبح العلاجات الطبية المستقبلية أكثر فعالية من خلال تطوير العلاجات المستهدفة وتقنيات تعديل الجينات. يجب أن تستمر الأبحاث حول هذه الطفرات الجينية لأنها تساعد المتخصصين الطبيين على تحقيق نتائج أفضل للمرضى وتقليل معدل الإصابة بسرطان الثدي عالميًا.