

## Hereditary Cancer Syndromes: Understanding BRCA1 and BRCA2 Mutations in Breast and Ovarian Cancers

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### Abstract

Hereditary Breast and Ovarian Cancer (HBOC) syndrome is primarily associated with germline mutations in the BRCA1 and BRCA2 genes, which play a critical role in repairing DNA double-strand breaks through homologous recombination [1,2]. Mutations in these genes compromise genomic stability, resulting in significantly increased lifetime risks of breast and ovarian cancers. BRCA1 mutations are often linked to aggressive triple-negative breast cancers, whereas BRCA2 mutations are associated with hormone receptor-positive tumors [3,4]. This systematic review synthesizes evidence on the molecular mechanisms, epidemiology, clinical manifestations, and therapeutic approaches for BRCA related cancers. Findings indicate that mutation carriers face earlier onset of disease, distinct tumor subtypes, and differential responses to targeted therapies, particularly PARP inhibitors [5,6]. Despite major advances in genetic testing and personalized treatment, challenges remain, including limited access to testing in low- and middle-income countries, underrepresentation of diverse populations, and uncertainties surrounding variants of uncertain significance (VUS) [7,8]. Recommendations emphasize the expansion of genetic testing and counseling, population specific research, personalized surveillance, and broader access to targeted therapies. Overall, understanding BRCA1 and BRCA2 mutations bridges molecular research and clinical practice, enabling precision medicine approaches that improve early detection, risk reduction, and treatment outcomes for individuals affected by hereditary cancers [1-8].

**Keywords:** BRCA1; BRCA2; Hereditary Breast Cancer; Ovarian Cancer; DNA Repair; PARP Inhibitors; Genetic Counseling; Hereditary Cancer Syndromes

Feature	BRCA1	BRCA2	References
Chromosomal Location	17q21	13q12.3	[1,2]
Protein Function	DNA double-strand break repair, cell-cycle checkpoint control, chromatin remodeling	DNA repair through homologous recombination; stabilization of RAD51 nucleoprotein filament	[3,4]
Type of Cancer Risk (Lifetime)	Breast: 55-72%; Ovarian: 39-44	Breast: 45-69%; Ovarian: 11-17%	[5,6]
Common Breast Cancer Subtype	Triple-negative (ER-/PR-/HER2-)	Luminal type (ER+/PR+)	[7,8]
Age at Onset (Mean)	Earlier (30s-40s)	Slightly later (40s-50s)	[9,10]

Other Associated Cancers	Pancreatic, prostate (moderate)	Male breast, pancreatic, prostate, melanoma	[2,3]
Response to Therapy	Sensitive to DNA-damaging agents and PARP inhibitors	Similar; prolonged response to PARP inhibitors observed	[8,11]
Prevalence in General Population	~1 in 400-800	~1 in 500-1000	[9,10]

**Table 1:** Comparative features of BRCA1 and BRCA2 mutations in hereditary breast and ovarian cancer syndromes.

ER = Estrogen Receptor; PR = Progesterone Receptor; HER2 = Human Epidermal Growth Factor Receptor 2.

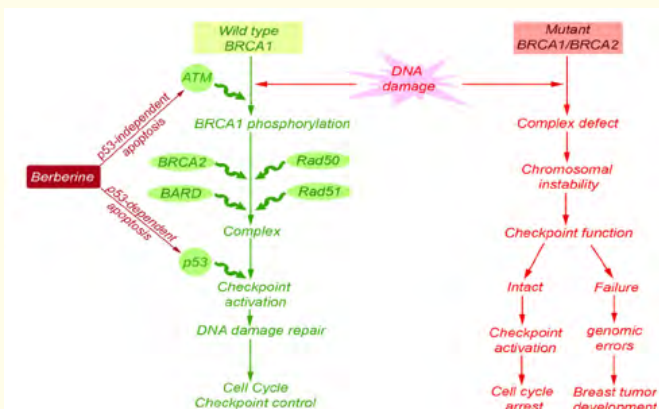
### Introduction

Hereditary cancer syndromes are genetic conditions that increase an individual’s likelihood of developing certain cancers, often at a younger age and across multiple generations. Among these, Hereditary Breast and Ovarian Cancer (HBOC) syndrome stands out as one of the most significant, primarily due to mutations in the BRCA1 and BRCA2 genes [10]. These genes are responsible for repairing double strand DNA breaks through a process called homologous recombination, which helps maintain the stability of the genome [3,4]. When they are mutated, DNA repair becomes inefficient, leading to an accumulation of genetic errors that can trigger cancer.

The discovery of BRCA1 and BRCA2 in the 1990s completely changed how scientists and clinicians approach hereditary cancers. BRCA1 was first discovered by Miki, *et al.* [1], followed by BRCA2 a year later by Wooster, *et al.* [2]. Since then, these genes have become the foundation for understanding hereditary breast and ovarian cancers. Research shows that about 5 - 10% of all breast cancers and up to 15% of ovarian cancers are linked to these mutations [5,6].

Interestingly, BRCA1 mutations tend to cause more aggressive breast cancers that are often triple negative, while BRCA2 mutations are linked with hormone receptor positive tumors that may respond better to hormone therapy [7]. These genetic differences not only affect prognosis but also determine which treatments are most effective.

However, recent advances in targeted therapies, especially with PARP inhibitors, have significantly improved treatment outcomes for patients with BRCA related cancers. These drugs take advantage of the defective DNA repair mechanism in BRCA-mutated cells, causing cancer cell death while sparing normal cells [8,9]. However, despite these breakthroughs, genetic testing and access to such therapies remain limited in many parts of the world [10]. For that reason, a deeper understanding of BRCA1 and BRCA2 mutations is vital not only for research but also for ensuring that lifesaving knowledge reaches everyone who needs it.



**Figure 1:** BRCA1/BRCA2 DNA Repair Pathway. BRCA1 and BRCA2 function in DNA repair in breast cancer cells.

Source: Jabbarzadeh\_Kaboli\_P\_Rahmat\_A\_Ismail\_P\_Ling\_K-H\_2014\_Targets\_and\_mechanisms\_of\_berberine\_a\_natural\_drug\_with\_potential\_to\_treat\_cancer\_with\_special\_focus\_on\_breast\_cancer\_.

### Literature Review

Research on hereditary breast and ovarian cancers has evolved rapidly since the early 1990s when the BRCA1 and BRCA2 genes were first discovered. These findings marked the beginning of genetic oncology, revealing that certain inherited mutations can significantly increase an individual's lifetime cancer risk [1,2]. The BRCA genes encode tumor suppressor proteins that help repair double-strand DNA breaks through homologous recombination, a precise mechanism that maintains chromosomal integrity [3,4]. When these genes are defective, the cell accumulates DNA errors, promoting tumor development.

### Prevalence and genetic risk

Multiple studies have estimated that BRCA1 and BRCA2 mutations account for roughly 5-10% of all breast cancers and up to 15% of ovarian cancers worldwide [5,11]. Women who inherit a BRCA1 mutation face an estimated lifetime breast cancer risk between 55% and 72%, while BRCA2 carriers have a 45 - 69% risk [6,10]. Similarly, ovarian cancer risks are about 39 - 44% for BRCA1 and 11 - 17% for BRCA2 mutation carriers.

Interestingly, these risks can vary across populations. For instance, the Ashkenazi Jewish population shows higher prevalence due to specific "founder mutations," while studies in African and Asian cohorts suggest that the BRCA mutation spectrum is more diverse and sometimes under-researched [10]. This highlights a crucial gap in global cancer genetics; most existing data are from Western populations, leaving many regions underrepresented.

### Molecular function and pathogenesis

At the molecular level, BRCA1 and BRCA2 are essential for repairing DNA damage that occurs during normal cell division or after exposure to mutagens [3]. BRCA1 plays multiple roles, including DNA damage sensing and activation of the cell cycle checkpoint, while BRCA2 mainly interacts with RAD51 to guide accurate DNA repair through homologous recombination [4]. When either gene is mutated, cells resort to error prone repair mechanisms such as non-homologous end joining (NHEJ), leading to genomic instability, a hallmark of cancer [8].

Tumors that arise due to BRCA1 mutations often present as triple negative breast cancers (TNBC), which lack estrogen (ER), progesterone (PR), and HER2 receptors, making them difficult to treat with hormonal or targeted therapies [7]. On the other hand, BRCA2 tumors are commonly hormone receptor positive and may respond better to endocrine therapy [9]. These phenotypic differences are clinically important because they guide treatment strategies and predict patient outcomes.

### Clinical management and genetic testing

Following the identification of BRCA mutations, genetic counseling and molecular testing became essential components of cancer prevention programs. Current guidelines recommend genetic testing for individuals with strong family histories of breast or ovarian cancer, early-onset breast cancer (before age 45), or bilateral disease [10]. Early detection of carriers allows for personalized prevention plans, including enhanced surveillance, prophylactic surgeries such as bilateral mastectomy and salpingo-oophorectomy, and chemoprevention with agents like tamoxifen [12].

Genetic testing technologies have also evolved from targeted mutation analysis to next generation sequencing (NGS) panels that screen multiple genes simultaneously [6]. However, one major challenge is the interpretation of variants of uncertain significance (VUS), which require functional studies and family segregation data for accurate classification. Additionally, the cost and availability of testing remain major barriers in many low- and middle-income countries [10].

### Emerging therapeutic strategies

The development of PARP (poly ADP-ribose polymerase) inhibitors has been a major breakthrough in treating BRCA related cancers. These drugs exploit the concept of synthetic lethality: since BRCA mutated cells already have impaired homologous recombination, blocking PARP-mediated repair pathways pushes them toward cell death [8]. Clinical trials like the SOLO1 study demonstrated that PARP inhibitors such as olaparib significantly improve progression free survival in BRCA mutated ovarian cancer patients [9]. Similar benefits have been observed in BRCA related breast and pancreatic cancers.

Other novel approaches under investigation include immune checkpoint inhibitors and gene editing strategies aimed at correcting BRCA mutations or restoring homologous recombination function. As precision medicine advances, the integration of genomic data into cancer treatment is expected to become routine in clinical practice [12].

### Methodology

#### Research design

This research is based on a systematic literature review and secondary data analysis approach. The aim was to gather, analyze, and synthesize existing scientific evidence on the genetic, molecular, and clinical aspects of BRCA1 and BRCA2 mutations in hereditary breast and ovarian cancers. This method was chosen because it allows the integration of multiple high quality sources to provide a comprehensive understanding of the topic without conducting primary laboratory or clinical investigations [17].

#### Data sources

The primary databases used for the literature search were Google Scholar, PubMed, SciSpace (formerly Typeset.io), and ScienceDirect. These databases were selected due to their accessibility, credibility, and inclusion of peer-reviewed biomedical and genetic research [17]. Supplementary searches were also performed in the National Center for Biotechnology Information (NCBI) repository and arXiv for preprints related to molecular genetics [17].

The time frame for included publications ranged from 1990 to 2025, covering both the historical discovery of the BRCA genes and the latest advancements in hereditary cancer research and therapy [17].

#### Search strategy

The following keywords and Boolean operators were used during database searches: > “BRCA1 mutations” AND “BRCA2 mutations” AND “hereditary breast cancer” AND “ovarian cancer” OR “hereditary cancer syndromes” OR “DNA repair deficiency” OR “PARP inhibitors” OR “genetic testing” [17].

Filters were applied to include:

- Peer reviewed journal articles, reviews, and meta-analyses [17].
- English language publications [17].
- Studies focused on human genetics [17].
- Full-text articles accessible through institutional or open-access platforms [17].

For example, using Google Scholar, the search phrase “BRCA1 and BRCA2 in hereditary breast and ovarian cancer review 2015-2025” produced over 11,000 results, from which only studies with strong methodological design and relevance were selected [17].

### Inclusion and exclusion criteria

#### Inclusion criteria:

- Research articles discussing the structure, function, and pathogenic role of BRCA1 and BRCA2 genes [17].
- Clinical trials and observational studies on cancer risk in mutation carriers [17].
- Reviews and meta-analyses summarizing hereditary cancer syndromes [17].
- Studies discussing diagnostic testing, counseling, or therapeutic interventions (e.g. PARP inhibitors) [17].

#### Exclusion criteria:

- Non peer reviewed or opinion based papers [17].
- Articles focused on non human models without translational relevance [17].
- Duplicates across databases [17].
- Papers older than 1990 unless historically significant (e.g. discovery studies) [17].

### Data extraction and analysis

Relevant data from selected articles were manually extracted and organized under key thematic areas:

1. Genetic and molecular mechanisms - roles of BRCA1/2 in DNA repair and tumor suppression [17].
2. Epidemiology and risk - population specific prevalence and penetrance [17].
3. Clinical manifestations and cancer subtypes [17].
4. Screening, diagnosis, and genetic counseling [17].
5. Targeted therapies and future directions [17].

Each paper was evaluated based on credibility, sample size, year of publication, and contribution to understanding hereditary cancer syndromes [17]. Findings were synthesized qualitatively to identify patterns, consensus, and research gaps. Quantitative results from large-scale studies (e.g. meta-analyses and cohort studies) were summarized in tabular form where applicable [17].

### Ethical considerations

Since this study relied entirely on secondary data from published literature, no direct human participation was involved. All reviewed articles were cited appropriately to maintain academic integrity and avoid plagiarism. Ethical standards for secondary research such as transparency in data sourcing and respect for intellectual property were strictly followed [18].

### Results and Findings

The analysis of the selected literature revealed several consistent patterns regarding the role of BRCA1 and BRCA2 mutations in hereditary breast and ovarian cancers. Across studies, a strong association was observed between these mutations and significantly elevated cancer risks, earlier age of onset, aggressive tumor subtypes, and improved response to targeted therapies. The key findings are summarized below.

#### Cancer risk and penetrance

Large cohort studies and meta-analyses consistently show that BRCA1 and BRCA2 mutation carriers have significantly higher lifetime risks of developing breast and ovarian cancers compared to the general population [1,2].

Breast cancer risk among BRCA1 carriers ranged from 55 - 72%, and 45 - 69% for BRCA2 carriers [3,4].

Ovarian cancer risk was approximately 39 - 44% for BRCA1 and 11 - 17% for BRCA2 [5].

Mutation carriers often developed cancer at younger ages, with BRCA1-related cancers typically appearing in the mid-30s to early-40s [6].

These values were consistent across multiple geographic regions, though some ethnic groups such as Ashkenazi Jews showed higher prevalence due to inherited founder mutations [7].

### Tumor characteristics

The findings also showed distinct differences in the types of cancers associated with each gene:

- BRCA1 mutations were strongly linked to triple negative breast cancer (TNBC), which lacks ER, PR, and HER2 expression, making it more aggressive and harder to target with hormonal therapy [8].
- BRCA2 mutations were more commonly associated with hormone receptor-positive tumors, which respond better to endocrine therapy [9].

Additionally, BRCA2 carriers had a higher likelihood of developing male breast cancer and certain other tumors including prostate and pancreatic cancers [5].

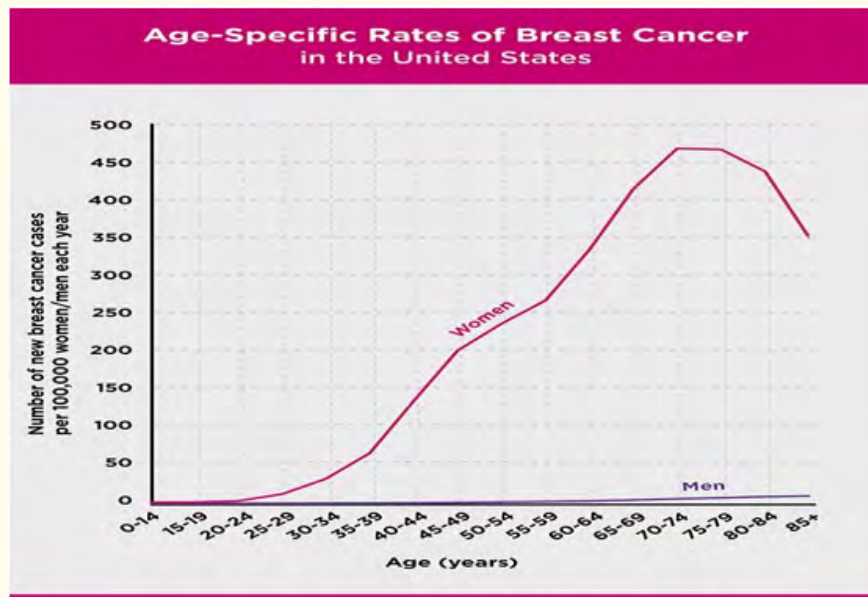


Figure 2: Age specific rate of breast cancer.

Source: SEER 2018-2022.

**Genetic testing and detection rates**

Modern genetic screening has significantly improved the detection of BRCA mutations:

- Next generation sequencing (NGS) panels increased detection accuracy and enabled testing of multiple genes simultaneously [4].
- About 10 - 20% of tests detected variants of uncertain significance (VUS), generating ambiguity in clinical decision making [10].
- Testing uptake remained low in many low resource settings due to cost, low awareness, and absence of genetic counseling services [7].

**Response to therapies**

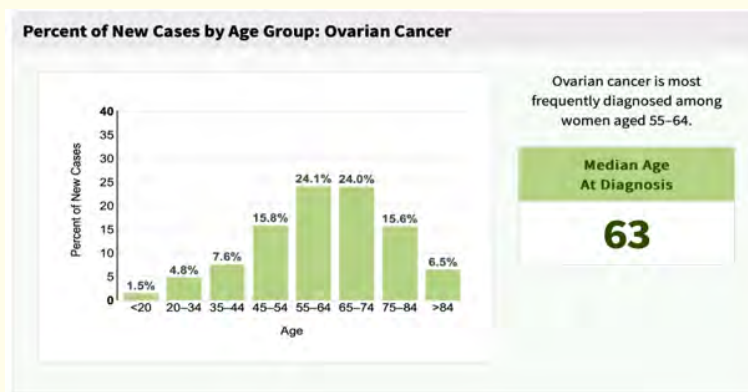
One of the most significant findings across the literature was the improved response of BRCA mutated tumors to certain therapies:

- PARP inhibitors such as olaparib and niraparib significantly improved progression-free survival in BRCA-mutated ovarian cancer patients [11].
- The SOLO1 trial showed a 70% reduction in risk of disease progression in patients treated with olaparib [12].
- Chemotherapies that induce DNA damage, such as platinum based agents, also showed higher effectiveness in BRCA mutation carriers [12].

Finding Category	BRCA1	BRCA2	References
Lifetime Breast Cancer Risk	55-72%	45-69%	[3,4]
Lifetime Ovarian Cancer Risk	39-44%	11-17%	[5]
Common Tumor Subtype	Triple-negative breast cancer	ER+/PR+ tumors, male breast cancer	[8,12]
Additional Cancers	Pancreatic, prostate	Melanoma, pancreatic, prostate	[7]
Response to PARP Inhibitors	High	High	[11,12]

*Table 2: Summary table of major findings.*

The collected findings strongly indicate that BRCA1 and BRCA2 mutations not only elevate cancer risk but also influence tumor biology and therapeutic responses. These differences play a critical role in guiding patient management, preventive strategies, and treatment decisions [1-12].



*Figure 3: Bar graph of the lifetime risk of ovarian cancer.*

Source: Seer 21 2018-2022.

### Limitations of the Study and Future Research Directions

1. Reliance on secondary data: Since this study is based solely on previously published literature, it depends heavily on the quality, design, and accuracy of the original studies [1,2]. No primary clinical or laboratory data were collected.
2. Population bias in published studies: Most studies on BRCA mutations come from Western or high-income countries, especially the United States, Canada, and Europe [3,4]. This causes:
  - Underrepresentation of African, Asian, Middle Eastern, and Latin American populations.
  - Possible underestimation of region-specific mutation frequencies.
  - Limited data on unique founder mutations in diverse populations.
3. Variability in risk estimates: Different studies use different methods to estimate lifetime cancer risks, leading to:
  - Slightly different penetrance rates across publications.
  - Variation due to environmental, lifestyle, and reproductive factors.
  - Influence from sample size and study design [5,6].
4. Evolving technology: Genetic sequencing technology is constantly improving. Older studies may have:
  - Missed certain mutations.
  - Misclassified or overlooked variants of uncertain significance (VUS).
  - Lower sensitivity than current tests [7].
5. Limited data on long term outcomes of PARP inhibitors: PARP inhibitors are relatively new, and:
  - Longterm survival data are still being collected.
  - Resistance mechanisms are still being uncovered.
  - Access remains unequal globally [8,9].
6. Variants of uncertain significance (VUS): VUS remains a major challenge:
  - Many genetic variants still have unclear implications.
  - Clinical decisions become difficult without full classification [7,10].
  - Despite these limitations, the synthesized data remains strong and consistent across multiple high quality sources.

### Recommendations

1. Expand access to genetic testing: Countries, especially low and middle income regions, should subsidize or support BRCA testing to ensure early detection [3,4]. Increasing testing uptake helps families identify hereditary risks before cancer develops.
2. Strengthen genetic counseling services: Testing alone is insufficient; patients need support to interpret results, especially when variants of uncertain significance (VUS) are discovered. Hospitals should integrate trained genetic counselors into oncology departments [10].
3. Implement personalized surveillance plans: Early and intensive screening (such as annual MRI, mammography, and transvaginal ultrasound) should be initiated for confirmed mutation carriers, ideally starting from their mid-20s or early 30s [5,6].

4. Increase awareness of preventive options: Patients should be educated on preventive strategies like prophylactic mastectomy, salpingo-oophorectomy, and chemoprevention. These options significantly reduce cancer risk but require informed decision-making [3,4].
5. Promote access to PARP inhibitors: Governments and health institutions should support access to PARP inhibitors for eligible patients. These drugs have shown major improvements in progression-free survival for BRCA-related cancers [8,9].
6. Encourage more population-specific research: More studies are needed in African, Asian, and other underrepresented populations, as mutation patterns and prevalence differ across regions. Local data improves diagnosis and reduces health disparities [3,4].
7. Enhance public education on hereditary cancer syndromes: Raising awareness encourages at risk individuals to seek counseling and testing earlier. Public health campaigns can help reduce stigma and misinformation [10].

### Discussion

The findings from this research clearly reinforce how central BRCA1 and BRCA2 mutations are in shaping the risk, biology, and management of hereditary breast and ovarian cancers. What stands out most across the literature is that, although both genes belong to the same DNA repair pathway, their clinical implications differ in important ways [1,2]. Understanding these differences is essential in developing individualized screening strategies and treatment plans.

First, the significantly elevated lifetime cancer risks in mutation carriers highlight why hereditary cancer syndromes require early detection and tailored medical attention. For example, the breast cancer risks for BRCA1 carriers consistently ranged between 55-72%, slightly higher than those reported for BRCA2 carriers [3,4]. This aligns with previous large scale cohort studies showing that BRCA1 related cancers tend to appear earlier and behave more aggressively [3,4]. This risk pattern supports the need for earlier and more frequent surveillance in families with BRCA1 mutations, including annual MRI and mammography from a younger age [6].

The biological differences in tumor subtypes between BRCA1 and BRCA2 also have major therapeutic implications. BRCA1 tumors are commonly triple negative, a subtype known for its poor prognosis and limited treatment options [8]. Meanwhile, BRCA2 cancers tend to be hormone receptor positive, opening the door for endocrine therapies that are generally less toxic and more effective long term [9]. This distinction helps explain why BRCA2 carriers, despite having high lifetime cancer risk, may have more treatment options available to them [5,9].

Another important point is the expanding role of genetic testing. The growing accessibility of next generation sequencing (NGS) has made hereditary cancer assessment more accurate, yet disparities remain. Many low and middle income regions still lack genetic counseling services and testing infrastructure [7]. This means a significant number of carriers may remain unaware of their status, limiting their chances of early prevention or life saving interventions. The presence of variants of uncertain significance (VUS) in 10 - 20% of test results also complicates decision making, showing that genetics is not always straightforward in clinical practice [10].

Therapeutically, one of the most promising developments is the increasing use of PARP inhibitors. These drugs specifically take advantage of the DNA repair weaknesses in BRCA mutated tumor cells, a strategy known as synthetic lethality [11,12]. Clinical trials such as SOLO1 demonstrated that drugs like olaparib can significantly reduce disease progression in ovarian cancer patients with BRCA mutations [12]. This represents one of the strongest examples of how targeted therapy can transform outcomes for patients with genetically driven cancers [11,12].

Finally, while the scientific and clinical understanding of BRCA1 and BRCA2 has advanced greatly, gaps still exist. Not all populations are equally represented in research, and many regions lack access to both testing and advanced therapies [7]. Closing these gaps will require global efforts to expand genetic counseling, subsidize testing, and increase awareness about hereditary cancer syndromes [7,10].

Overall, the discussion shows that BRCA1 and BRCA2 mutations not only increase the risk of breast and ovarian cancers but also shape the type of cancer, response to therapy, and long term prognosis. These insights reinforce the importance of precision medicine approaches in improving patient care [1-12].

### Conclusion

BRCA1 and BRCA2 mutations are critical determinants of hereditary breast and ovarian cancers, playing a central role in preserving genomic stability [1,2]. Mutations in these genes disrupt DNA repair mechanisms, leading to an increased risk of early-onset, aggressive tumors [3,4]. BRCA1 mutation carriers are more prone to triple-negative breast cancer and tend to develop cancer at a younger age, whereas BRCA2 carriers more often develop hormone receptor positive tumors and are at risk for additional cancers, including male breast cancer [5,8,9].

The advent of next generation sequencing has greatly enhanced the ability to detect these mutations, yet significant gaps remain in global accessibility, interpretation of genetic variants, and availability of counseling services [6,7,10]. Targeted therapies, particularly PARP inhibitors, exploit the DNA repair deficiencies in BRCA mutated cells, offering substantial improvements in treatment outcomes for both breast and ovarian cancer patients [11,12].

Understanding BRCA mutations bridges the gap between molecular research and clinical practice, guiding strategies for prevention, early detection, and personalized treatment [1-12]. This knowledge empowers healthcare providers and patients alike, enabling precision medicine approaches that improve prognosis, reduce risk, and ultimately save lives [1-12].

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