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Genetic and Clinical Implications of BRCA Mutations in Hereditary Breast and Ovarian Cancer Syndrome (HBOC): A Review

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ABSTRACT

BRCA1 and BRCA2 mutations are critical in Hereditary Breast and Ovarian Cancer (HBOC) syndrome, influencing cancer risk and treatment strategies. This review synthesizes findings from recent studies on these mutations, noting that BRCA1 mutations are linked with a higher risk of breast and ovarian cancers than BRCA2. For instance, BRCA1 mutations show a lifetime breast cancer risk of 55-72% and ovarian cancer risk of 39-44%, while BRCA2 mutations show a 45-69% risk for breast cancer and 11-17% for ovarian cancer. Variability in risk estimates is attributed to differences in study design, sample size, and methodology. Large, long-term studies generally provide more stable estimates. Effective management strategies include regular screenings and preventive surgeries. Future research should focus on standardizing methodologies and considering diverse factors to enhance risk management for BRCA mutation carriers.

Introduction

Hereditary Breast and Ovarian Cancer syndrome (HBOC) is a genetic condition with a well-established association with mutations in the BRCA1 and BRCA2 genes which increase the probability of a person developing ovarian cancer, breast cancer, and other types, such as pancreatic and prostate cancer (American Cancer Society, 2024). This syndrome accounts for a significant portion of breast and ovarian cancer cases, with BRCA1 and BRCA2 mutations responsible for approximately 5-10% of breast cancer cases and 10-15% of ovarian cancer cases (Schwab et al., 2012). These mutations are inherited in an autosomal dominant manner, meaning that inheriting a single copy of the mutated gene from either parent increases the risk of developing cancer (Schwab et al., 2012).

The BRCA1 and BRCA2 genes are crucial for maintaining genomic stability through their roles in the homologous recombination repair (HRR) pathway. This pathway is essential for repairing double-strand breaks in DNA, which occur during cell division (Nunziato et al., 2023). In normal cells, BRCA1 and BRCA2 proteins work together to repair these breaks accurately, preventing the accumulation of mutations that can lead to cancer (Nunziato et al., 2023). However, when these genes are mutated, their ability to repair DNA is compromised, resulting in genomic instability—a hallmark of cancer development (Fanale et al., 2023). This dysfunction in DNA repair mechanisms is directly linked to an increased risk of carcinogenesis.

In-depth analysis of BRCA1 and BRCA2 mutations reveals specific patterns in cancer risk and characteristics. For BRCA1 mutations, the lifetime risk of developing breast cancer is estimated to be between 55-65%, and the risk of developing ovarian cancer is 39-44% by age 70 (Fanale et al., 2023). These mutations are particularly associated with early-onset breast cancer, often diagnosed in women under 30 years old. BRCA1-associated breast cancers are frequently triple-negative, lacking estrogen, progesterone, and HER2 receptors, which complicates treatment strategies and is linked to a more aggressive disease course (Fernandez Madrigal et al., 2023). This subtype of cancer is

less responsive to conventional hormonal therapies, necessitating alternative treatment approaches (Carnevali et al., 2019)

On the other hand, BRCA2 mutations are associated with a lifetime breast cancer risk of 45-69% and a somewhat lower ovarian cancer risk of 11-17% by age 70 (Castéra et al., 2018). BRCA2 mutations are more commonly linked to hormone receptor-positive breast cancers, which are generally more responsive to hormonal therapies than BRCA1-related cancers (Carnevali et al., 2019). This distinction is crucial for developing targeted treatment strategies and personalized care plans for patients with BRCA2 mutations (Nunziato et al., 2023).

The identification and management of BRCA mutations involve several strategies to mitigate cancer risk. Regular screening protocols for mutation carriers include earlier and more frequent mammograms and breast MRIs compared to the general population (Marmolejo et al., 2021). For high-risk individuals, preventive surgeries such as prophylactic mastectomy and salpingo-oophorectomy can significantly lower the risk of developing breast and ovarian cancers. Studies show that these interventions can reduce breast cancer risk by 90% and ovarian cancer risk by 80% (Powell et al., 2022). The effectiveness of these preventive measures shows the importance of early identification and proactive management of individuals with BRCA mutations.

Despite advances in genetic research, variability in cancer risk estimates among BRCA mutation carriers remains an ongoing challenge. This variability can be attributed to differences in study designs, population demographics, sample sizes, and methodologies (Alemar et al., 2016; Schwab et al., 2012). This paper aimed to review the current knowledge on BRCA mutations and their implications for HBOC.

Methodology

The ScienceDirect online database was used to find the relevant research papers for the review. The search employed the keywords "BRCA gene" and "HBOC" (“BRCA gene” “HBOC”, to be exact). The inclusion criteria were peer-reviewed research articles, in English, published between 2014 and 2024. This approach aimed to capture studies directly discussing the BRCA gene and its association with HBOC. Articles published within the last decade were included to ensure the review encompasses the most current research findings.

The selection process involved an initial broad search. The results were filtered based on the above-mentioned inclusion criteria. After the review of papers, the lack of specific data on BRCA or HBOC was established as an exclusion criterion. The remaining papers were categorized based on their focus, such as genetic mechanisms, clinical implications, and therapeutic strategies related to BRCA mutations and HBOC.

Results

According to the review’s objective, sixty-three papers were reviewed with eighteen that met the purpose of the study remaining (Table 1).

Table 1. Authors, dates, and subject areas of the papers included in this review. The papers are organized in alphabetical order by author’s last name.

Authors	Date	Subject area
Alemar et al.	2016	BRCA Mutations and Prevalence
Anne-Marie et al.	2024	Clinical Implications of BRCA-Mutated Cancers
Calabrese et al.	2024	Clinical Implications of BRCA-Mutated Cancers
Carnevali et al.	2019	BRCA Testing and Screening Strategies
Castera et al.	2018	Risk Assessment and Management of BRCA Mutations
Castillo-Guardiola et al.	2022	BRCA Testing and Screening Strategies

Dawoud et al.	2023	BRCA Mutations and Prevalence
Fanale et al.	2023	Risk Assessment and Management of BRCA Mutations
Fanale et al.	2022	Risk Assessment and Management of BRCA Mutations
Fernandez Madrigal et al.	2023	BRCA Mutations and Prevalence
Gomez Garcia et al.	2022	BRCA Mutations and Prevalence
Jackson et al.	2023	BRCA Mutations and Prevalence
Marmolejo et al.	2021	BRCA Mutations and Prevalence
Morrow, M.	2021	BRCA Mutations and Prevalence
Nunziato et al.	2023	Risk Assessment and Management of BRCA Mutations
Powell et al.	2022	Risk Assessment and Management of BRCA Mutations
Robinson et al.	2015	BRCA Testing and Screening Strategies

BRCA Mutations and Prevalence

Alemar et al. (2016) conducted a study focusing on the prevalence of BRCA mutations among Hispanic populations, emphasizing the genetic differences observed among various Latin American groups. Their research identified that BRCA1 and BRCA2 mutations are prevalent within this demographic, with a higher occurrence of BRCA2 mutations. This finding highlights the necessity of considering ethnic variations when conducting genetic testing and assessing cancer risk, as these variations can significantly influence the accuracy and efficacy of genetic screening and counseling.

Dawoud et al.(2023) examined the prevalence of BRCA mutations within a diverse cohort, focusing on the impact of demographic factors such as age, ethnicity, and family history. Their findings revealed significant variation in mutation rates across different ethnic groups, with higher mutation prevalence observed in populations of Ashkenazi Jewish descent, because of their predisposition to BRCA 1 mutations. This study highlights the necessity for targeted genetic counseling and testing strategies tailored to specific demographic groups to improve the detection and management of hereditary cancer risk.

Marmolejo et al. (2021) explored the impact of BRCA mutations on survival rates among breast cancer patients. The study found that patients with BRCA1 mutations had poorer survival outcomes compared to those with BRCA2 mutations or non-mutated cases (the study reported that the 5-year overall survival rate for BRCA1 mutation carriers was approximately 70%, whereas, for BRCA2 mutation carriers, it was closer to 80%). This suggests that the type of BRCA mutation not only influences the likelihood of developing cancer but also affects prognosis and survival, which has significant implications for personalized treatment strategies. The poorer prognosis observed in BRCA1 mutation carriers is likely due to the biological characteristics of BRCA1-associated tumors. These tumors are more often triple-negative, meaning they lack estrogen, progesterone, and HER2 receptors. Triple-negative breast cancers are generally more aggressive and have fewer treatment options because they do not respond to hormone therapies that target these receptors. This aggressive nature leads to faster progression and higher recurrence rates, contributing to poorer survival outcomes in BRCA1 mutation carriers. On the other hand, BRCA2-associated breast cancers are more likely to express hormone receptors, making them more amenable to treatments that target these pathways, such as tamoxifen or aromatase inhibitors.

Fernandez Madrigal et al. (2023) focused on the incidence of BRCA mutations in triple-negative breast cancer (TNBC) patients. Their research demonstrated a higher frequency of BRCA1 mutations in TNBC cases compared to other breast cancer subtypes. This association suggests that BRCA1 mutations are particularly relevant in aggressive and difficult-to-treat breast cancer types, thereby emphasizing the need for BRCA testing in TNBC patients to guide therapeutic decisions.

Jackson et al. (2023) analyzed the prevalence and distribution of BRCA mutations in a large cohort of breast and ovarian cancer patients. The study reported that BRCA1 mutations were more common in younger breast cancer

patients, while BRCA2 mutations were more frequently observed in ovarian cancer patients. The research provides valuable insights into the age and cancer-type-specific patterns of BRCA mutations, supporting the need for age-targeted genetic testing and preventive strategies.

Morrow's (2021) work centered on the clinical implications of BRCA mutations in breast cancer patients. The study emphasized that BRCA1 and BRCA2 mutations not only increase cancer risk but also influence the disease's course and treatment outcomes. Morrow argued for the integration of genetic testing into routine clinical practice to improve personalized treatment plans for affected individuals.

Gomez Garcia et al. (2022) provided an extensive overview of BRCA mutation prevalence across different geographic regions, with a focus on the disparities in mutation detection rates. The study highlighted the importance of increasing accessibility to genetic testing in low-resource settings to ensure that all at-risk individuals may benefit from early detection and prevention measures.

Risk Assessment and Management of BRCA Mutations

Powell et al. (2022) expanded the scope of HBOC research by addressing the challenges in managing cancer risk for patients with non-BRCA pathogenic variants associated with HBOC. Their study highlighted that, although BRCA1 and BRCA2 are the most well-known genes linked to HBOC, other genetic variants also contribute significantly to cancer risk. Effective management of these risks requires a comprehensive approach that includes the consideration of these non-BRCA genetic factors.

Fanale et al. (2022) investigated the role of BRCA1 and BRCA2 variants of uncertain significance (VUS) in HBOC syndrome. The study highlighted the ongoing challenge of interpreting these variants and understanding their potential impact on cancer risk. While some VUS may be associated with an increased risk of breast and ovarian cancer, the clinical relevance of these variants often remains ambiguous. This uncertainty points to the need for further research to clarify the implications of VUS in the context of HBOC, as accurately classifying these variants is critical for guiding clinical decision-making.

The later study of Fanale et al. (2023) delved into lifetime cancer risk assessment for BRCA1 and BRCA2 mutation carriers, providing detailed risk estimates based on comprehensive data analysis. The study highlighted the variability in risk depending on factors such as age, family history, and the presence of other genetic mutations, reinforcing the need for personalized risk assessment in clinical practice.

The utility of multigene panels for identifying predisposition to breast and ovarian cancer was further validated by Nunziato et al. (2023). Their study demonstrated that these panels offer valuable insights into a patient's genetic risk profile, extending beyond BRCA1 and BRCA2 mutations. The results indicated that multigene panels can enhance the precision of risk assessment and facilitate more personalized management strategies for individuals at risk of developing breast or ovarian cancer.

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BRCA Testing and Screening Strategies

Carnevali et al. (2019) focused on the strategies for BRCA testing, particularly the role of next-generation sequencing (NGS) in identifying BRCA mutations. Their study highlighted the advantages of NGS, including its high sensitivity and ability to detect a wide range of mutations, including rare variants that traditional testing methods may miss. The researchers also discussed the challenges of NGS, such as the interpretation of variants of uncertain significance and

the need for appropriate genetic counseling to ensure that patients understand their test results and the implications for their health.

Castillo-Guardiola et al. (2022) examined the effectiveness of various screening strategies for detecting BRCA mutations, comparing traditional methods such as single-gene testing with more comprehensive approaches like multigene panels and whole-exome sequencing. Their findings indicated that while traditional methods are useful for identifying well-known BRCA mutations, multigene panels, and whole-exome sequencing offer broader insights into an individual's genetic risk. The study advocated for these more comprehensive screening strategies in clinical practice to improve the detection of BRCA mutations and the management of hereditary cancer risk.

Robinson et al. provided a historical overview of the discovery of BRCA mutations and the evolution of genetic testing strategies. The paper traced the development of BRCA testing from its inception to the present day, highlighting milestones and technological advancements that have improved the accuracy and accessibility of genetic testing. The authors also discussed the ethical and social implications of BRCA testing, including issues related to genetic privacy, discrimination, and the psychological impact of learning one's genetic risk for cancer. The study emphasized the importance of ongoing research and dialogue to address these challenges and ensure that BRCA testing continues to benefit patients and their families.

Clinical Implications of BRCA-Mutated Cancers

Calabrese et al. investigated the role of BRCA mutations in the development and progression of ovarian cancer. Their study revealed that BRCA mutations are not only associated with an increased risk of developing ovarian cancer but also influence the disease's response to treatment. Patients with BRCA-mutated ovarian cancer were found to be more responsive to platinum-based chemotherapy and PARP inhibitors, leading to improved survival outcomes. The research shows the importance of BRCA testing in guiding treatment decisions for ovarian cancer patients and the potential for targeted therapies to improve patient outcomes.

Anne-Marie et al. explored the clinical implications of BRCA-mutated cancers, focusing on the impact of these mutations on treatment outcomes and survival rates. Their research found that BRCA-mutated cancers, particularly those associated with BRCA1 mutations, tend to be more aggressive and have poorer prognoses compared to non-BRCA-mutated cancers. However, the study also highlighted the potential benefits of targeted therapies, such as PARP inhibitors, which have shown promise in improving outcomes for patients with BRCA-mutated cancers. The authors emphasized the need for personalized treatment approaches that account for the specific genetic and clinical characteristics of each patient's cancer.

Discussion

The prevalence and impact of BRCA mutations may vary across different ethnic groups, as highlighted by Schwab et al. (2012) and Alemar et al. (2016), who found that BRCA2 mutations are more common in Hispanic populations than in other ethnic groups. Other genetic variants and factors such as family history can influence individual risk profiles, suggesting the need for comprehensive and personalized risk assessments (Nunziato et al., 2023).

Future research should focus on standardizing methodologies and incorporating diverse populations to refine risk estimates and enhance preventive strategies. Multi-gene panel testing, which evaluates multiple genes associated with breast and ovarian cancer susceptibility, offers a more comprehensive approach to genetic risk assessment. Castéra et al. (2018) and Nunziato et al. (2023) demonstrate that these panels can improve risk assessment accuracy by identifying additional pathogenic variants beyond BRCA1 and BRCA2. This approach facilitates more tailored and effective management strategies for individuals with hereditary cancer risks.

While BRCA1 mutations are generally linked to higher cancer risks than BRCA2 mutations, the specific risk levels reported in various studies can vary due to study design and methodology. Future research efforts must aim to

standardize methods and include more diverse populations to enhance the accuracy of risk estimates and improve preventive strategies for individuals carrying BRCA mutations or other HBOC-related genetic variants.

The results of this study show the pivotal role of BRCA1 and BRCA2 mutations in hereditary breast and ovarian cancer (HBOC) syndrome, while also highlighting the increasing significance of additional genetic factors and the complexity of genetic risk assessment.

Research shows that BRCA1 and BRCA2 mutations contribute to approximately 5-10% of breast cancer cases and 10-15% of ovarian cancer cases (Alemar et al., 2016). Studies such as Schwab et al. (2012) and Alemar et al. (2016) highlight ethnic variations in mutation prevalence. For instance, Alemar et al. (2016) reported a higher prevalence of BRCA2 mutations among Hispanic populations than other ethnic groups. This finding emphasizes the need for ethnic-specific considerations in genetic testing and cancer risk assessments, as the prevalence of these mutations can vary significantly across different populations.

BRCA1 and BRCA2 mutations impair the HRR pathway, which is crucial for repairing DNA double-strand breaks. In BRCA1-mutated cells, this impairment is particularly pronounced, leading to genomic instability that manifests as an increased risk for aggressive cancers. BRCA1 mutations are associated with a 55-65% lifetime risk of breast cancer and a 39-44% risk of ovarian cancer by age 70 (Fanale et al., 2023). Notably, BRCA1-related breast cancers are often triple-negative, lacking estrogen, progesterone, and HER2 receptors, which complicates treatment due to the lack of targeted hormonal therapies (Fernandez Madrigal et al., 2023).

In contrast, BRCA2 mutations are linked to a slightly lower breast cancer risk of 45-69% and an 11-17% risk of ovarian cancer by age 70 (Castéra et al., 2018). BRCA2-associated cancers are more frequently hormone receptor-positive, which often makes them more responsive to hormonal therapies. This distinction is crucial for developing tailored treatment strategies. For example, while BRCA1-related cancers might necessitate alternative treatment approaches due to their triple-negative status, BRCA2-associated cancers may benefit from existing hormonal therapies (Nunziato et al., 2023).

Our review confirms the findings of Alemar et al. (2016), who reported that BRCA1 and BRCA2 mutations are present in approximately 17% of Hispanic women with hereditary breast and ovarian cancer, with notable differences across Latin American populations. This regional variation necessitates localized approaches in genetic screening and counseling. For instance, while BRCA1 mutations are prevalent in about 60% of the cases, BRCA2 mutations account for approximately 40% of cases in the studied population, suggesting a need for tailored genetic testing strategies in different regions (Marmolejo et al., 2021).

The data from Castéra et al. (2018) demonstrate that pathogenic variants in a broader range of genes are relevant to HBOC risk, with 34% of HBOC families harboring mutations in genes beyond BRCA1 and BRCA2. Similarly, Castillo-Guardiola et al. (2022) reported that multigene panel testing, which includes genes like PALB2, CHEK2, and ATM, is essential for identifying additional genetic risks. Their study highlights that 25% of patients with negative BRCA1/BRCA2 tests may still have pathogenic variants in other actionable genes, showing the importance of comprehensive genetic panels.

The clinical impact of these findings is supported by Fernández Madrigal et al. (2023), who documented that non-BRCA genes influence risk-reducing surgery decisions. Their study shows that 20% of patients with non-BRCA pathogenic variants were recommended for prophylactic mastectomy or oophorectomy, reflecting the complexity of HBOC syndrome and the need for individualized management strategies. Powell et al. (2022) further emphasized that non-BRCA pathogenic variants, such as those in the RAD51C and RAD51D genes, account for 10% of the HBOC syndrome cases in their large Californian healthcare system, reinforcing the need for personalized risk management.

The variability in the clinical significance of BRCA variants, as discussed by Fanale et al. (2022) and Gomez Garcia et al. (2022), highlights the importance of accurate interpretation. Fanale et al. (2022) found that among BRCA1/2 variants of unknown significance, about 15% could be reclassified as pathogenic with further research, impacting risk prediction models. Gomez Garcia et al. (2022) reported that specific BRCA1 variants are associated with different prognoses, with some linked to higher risks of ovarian cancer (up to 60% lifetime risk) compared to others (around 30%).

In summary, while BRCA1 and BRCA2 mutations remain central to understanding HBOC syndrome, this study highlights the growing importance of a comprehensive genetic approach. Incorporating multigene panel testing and considering a broader range of genetic factors are essential for enhancing diagnostic accuracy and optimizing patient management strategies. Future research should focus on refining genetic testing methods and elucidating the clinical implications of various genetic variants to advance personalized care for HBOC syndrome patients.

While BRCA1 and BRCA2 mutations significantly contribute to hereditary breast and ovarian cancer, understanding their implications requires a detailed analysis of genetic, clinical, and therapeutic aspects. Continued research and advancements in genetic testing will enhance risk assessment and management strategies, ultimately improving outcomes for individuals affected by HBOC syndrome.

Conclusion

This review concludes that BRCA1 and BRCA2 mutations significantly increase the risk of breast and ovarian cancer, with BRCA1 mutations presenting a higher risk compared to BRCA2. The lifetime risk for breast cancer is approximately 72% for BRCA1 and 65% for BRCA2, while the risk for ovarian cancer is 44% for BRCA1 and 14% for BRCA2. The variability in risk estimates across studies highlights the influence of study design, sample size, and methodology on the results. Despite these differences, individuals with BRCA mutations, who are at high risk for hereditary breast and ovarian cancer (HBOC), require targeted screening and preventive measures to mitigate cancer risk. Future research should standardize methodologies and incorporate genetic, environmental, and lifestyle factors to refine risk estimates and enhance preventive strategies. Implementing regular screenings and preventive surgeries has been shown to improve early detection and survival rates, which highlights the importance of personalized cancer risk management for BRCA mutation carriers and those at risk for HBOC.

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