HEREDITARY BREAST AND OVARIAN CANCER (HBOC) SYNDROME

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ABSTRACT

Genetic factors account for approximately 5-7% of breast cancer cases and 15-20% of epithelial ovarian cancer cases. Germline mutations in genes such as *BRCA1/2, PALB2, TP53, CHEK2, ATM,* and *RAD51C/D* have been identified as contributing to varying degrees of cancer risk. Current evidence indicates that carriers of *BRCA* mutations have a cumulative lifetime risk of up to 60-80% for breast cancer and 15-45% for ovarian cancer. The advent of next-generation sequencing (NGS) has significantly improved mutation detection rates, while also posing challenges in the interpretation of variants of uncertain significance (VUS). In terms of treatment, large clinical trials have demonstrated the superior efficacy of PARP inhibitors in patients harboring *BRCA* mutations, based on the mechanism of synthetic lethality, leading to improvements in progression-free survival and other survival outcomes. In addition, genetic counseling plays a central role in risk assessment, guiding genetic testing, and supporting clinical decision-making. Risk-reducing strategies, including enhanced surveillance and prophylactic surgery, have shown clear effectiveness. However, the implementation of these approaches in developing countries remains limited and requires further improvement.

Keywords: Breast cancer, HBOC, germline mutations, BRCA.

1. INTRODUCTION

Hereditary Breast and Ovarian Cancer (HBOC) syndrome is a clinically significant entity in oncology and medical genetics, characterized by an increased risk of breast cancer, ovarian cancer, and several other malignancies due to germline mutations in tumor suppressor genes. Among these, *BRCA1* and *BRCA2* are the most extensively studied genes. Individuals harboring pathogenic variants in these genes have a cumulative lifetime risk of up to 60-80% for breast cancer and approximately 15-45% for ovarian cancer, which is substantially higher than that of the general population [1].

HBOC is commonly associated with clinical features such as early-onset breast cancer, bilateral breast cancer, triple-negative breast cancer, epithelial ovarian cancer, and a strong family history of related malignancies. In addition, this syndrome has been linked to other cancers, including pancreatic cancer, prostate cancer, and melanoma. Early identification of HBOC is crucial for optimizing screening strategies, implementing preventive measures, and guiding personalized treatment approaches.

In recent years, advances in next-generation sequencing (NGS) technologies have expanded the spectrum of genes implicated in HBOC beyond *BRCA1/2* to include multiple DNA repair

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genes. Concurrently, clinical guidelines from international organizations such as the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) have emphasized the importance of genetic testing and genetic counseling in the management of high-risk individuals.

This is a narrative review aimed at updating recent understanding of HBOC syndrome and its management strategies. The article also addresses some challenges in implementing professional recommendations related to this syndrome in the Vietnamese context.

2. GENES IN HEREDITARY BREAST AND OVARIAN CANCER SYNDROME

2.1. BRCA1/2 Genes

BRCA1 and *BRCA2* are tumor suppressor genes that play essential roles in DNA repair through the homologous recombination (HR) pathway. The proteins encoded by these genes are involved in the recognition and repair of DNA double-strand breaks, thereby maintaining genomic stability.

Germline mutations in *BRCA1/2* result in loss of protein function, leading to impaired DNA repair capacity. Consequently, genetic damage accumulates, causing chromosomal instability and promoting carcinogenesis. This mechanism is particularly relevant in tissues with high proliferative activity, such as the breast and ovarian epithelium.

An important related concept is "synthetic lethality" [2]. In BRCA-deficient cells, inhibition of alternative DNA repair pathways such as poly (ADP-ribose) polymerase (PARP) leads to selective tumor cell death. This provides the biological rationale for the use of PARP inhibitors in the treatment of BRCA-associated cancers.

In addition, *BRCA1* is involved in transcriptional regulation and cell cycle control, whereas *BRCA2* plays a more direct role in facilitating RAD51 binding to DNA during homologous recombination. These functional differences partly explain the distinct disease spectrum and phenotypic variations observed between *BRCA1* and *BRCA2* mutations.

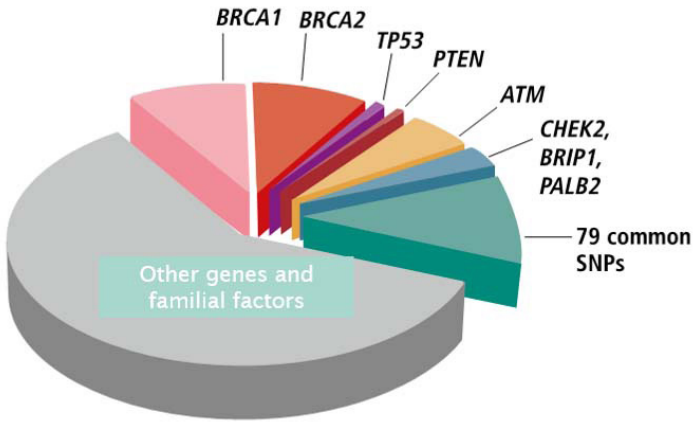

Fig.1. Breast and ovarian cancers - associated genes and familial factors

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2.2. Other Susceptibility Genes

Beyond *BRCA1* and *BRCA2*, multiple additional genes have been identified as contributing to an increased risk of breast and ovarian cancers. These genes are primarily involved in DNA repair pathways or cell cycle regulation.

Figure 1 illustrates the distribution of genes associated with hereditary breast and ovarian cancer (HBOC), with *BRCA* mutations accounting for approximately 50% of cases, and the remaining proportion attributable to other susceptibility genes [3]for an individual, may be more efficient and less expensive than sequential testing. The authors assessed the frequency of deleterious germline mutations among individuals with breast cancer who were referred for BRCA1 and BRCA2 (BRCA1/2.

It is noteworthy that more than 50% of familial breast and ovarian cancer cases lack an identifiable pathogenic mutation. Conversely, up to 50% of individuals with confirmed germline mutations may not have a clearly documented family history.

Several commonly implicated non-*BRCA* genes and their associated cancer risks are summarized below:

PALB2 (Partner and Localizer of BRCA2): *PALB2* encodes a protein that directly interacts with BRCA2 and facilitates homologous recombination-mediated DNA repair. Germline mutations in *PALB2* confer a lifetime breast cancer risk of approximately 35-60%, representing a moderate-to-high risk category.

TP53 encodes the p53 protein, often referred to as the "guardian of the genome." Germline mutations result in Li-Fraumeni syndrome, which is associated with a broad spectrum of malignancies, including early-onset breast cancer. Unlike *BRCA* genes, *TP53* affects multiple oncogenic pathways, including apoptosis and cell cycle control.

CHEK2 encodes a key kinase involved in the DNA damage response. Mutations in *CHEK2* are associated with a moderate increase in breast cancer risk and are more frequently observed in European populations.

ATM plays a central role in DNA damage signaling. Germline mutations in *ATM* are associated with an increased risk of breast cancer and may also be linked to pancreatic cancer.

RAD51C and RAD51D: These genes are integral components of the homologous recombination repair pathway. Mutations in *RAD51C/D* are particularly associated with an elevated risk of ovarian cancer.

In addition, other genes such as *BRIP1, BARD1,* and *NBN* also contribute to cancer susceptibility, although with varying degrees of risk. This heterogeneity has led to the classification of susceptibility genes into high-, moderate-, and low-penetrance groups, which is essential for guiding risk stratification, screening strategies, and preventive interventions.

The use of multigene panel testing in clinical practice enables simultaneous detection of multiple pathogenic variants, thereby improving the diagnostic yield for HBOC. However, it also introduces challenges in interpreting variants of uncertain significance (VUS), which remain a critical issue in clinical genetics.

3. ROLE OF BRCA MUTATIONS IN THE TREATMENT OF BREAST AND OVARIAN CANCER

Germline *BRCA* mutations have been established as key therapeutic targets in the personalized management of breast and ovarian cancers. Evidence from phase III trials such as OLYMPIA, OLYMPIAD, SOLO-1, and SOLO-2 has defined the central role of poly (ADP-ribose) polymerase (PARP) inhibitors, particularly Olaparib in patients harboring *BRCA* mutations.

The biological rationale for this approach is based on the concept of "synthetic lethality," whereby tumor cells with *BRCA1/2* mutations, already deficient in homologous recombination–mediated DNA repair, become highly susceptible to PARP inhibition.

In breast cancer, the OLYMPIAD trial demonstrated the efficacy of olaparib in patients with metastatic HER2-negative breast cancer carrying germline *BRCA* mutations. The study reported a median progression-free survival (PFS) of 8.0 months compared with 3.8 months in the standard chemotherapy group (HR ≈ 0.51), along with improved response rates and quality of life. However, the overall survival (OS) benefit in the final analysis did not reach clear statistical significance (19.3 vs. 17.1 months). In contrast, the OLYMPIA trial, conducted in the adjuvant setting for high-risk early-stage breast cancer, demonstrated that olaparib significantly improved invasive disease-free survival (iDFS) and distant disease-free survival (dDFS), with a trend toward improved OS, thereby reinforcing the role of PARP inhibitors in early-stage disease [4].

In ovarian cancer, the SOLO-1 and SOLO-2 trials provide even more compelling evidence [5]niraparib, and rucaparib in patients with OC and discusses their role in disease management, with a focus on the use of PARPis as maintenance therapy in the United States (US. The SOLO-1 trial, involving newly diagnosed advanced-stage patients with *BRCA* mutations who responded to platinum-based chemotherapy, demonstrated an approximately 70% reduction in the risk of disease progression or death (HR ~0.30), with median PFS not reached compared to 13.8 months in the placebo group. Notably, after 6 years, approximately 48% of patients receiving olaparib remained progression-free compared to 21% in the control group, with sustained long-term benefits in extended follow-up analyses. Meanwhile, the SOLO-2 trial, conducted in patients with platinum-sensitive relapsed disease, showed that olaparib prolonged median PFS to 19.1 months compared with 5.5 months (HR ~0.30), while also improving quality-of-life measures and delaying time to subsequent therapy.

Overall, evidence from these four trials demonstrates that *BRCA*-targeted therapy with olaparib provides consistent survival benefits in both breast and ovarian cancers, with particularly pronounced efficacy in the maintenance setting of ovarian cancer. These findings have transformed clinical practice, establishing *BRCA* testing as an essential component of personalized cancer therapy. Other PARP inhibitors, such as niraparib and veliparib also demonstrated survival benefits in selected groups of ovarian cancer patients. However, these medication are currently not available in Vietnam.

4. DIAGNOSTIC TESTING FOR HEREDITARY BREAST AND OVARIAN CANCER (HBOC)

The diagnosis of HBOC is primarily based on genetic testing aimed at identifying germline mutations in susceptibility genes.

Currently, next-generation sequencing (NGS) is the most widely used method. NGS plays a pivotal role in detecting germline mutations in the *BRCA1* and *BRCA2* genes due to its ability to perform massively parallel sequencing with high coverage. This technology enables the simultaneous detection of multiple types of variants, including single-nucleotide variants, small insertions/deletions, and when combined with appropriate analytical approaches copy number variations (CNVs). Compared with conventional techniques, NGS offers advantages in terms of time and cost efficiency, as it allows the analysis of multiple cancer-associated genes in a single run, thereby improving diagnostic yield. However, NGS has certain limitations,

including the potential to miss large structural variants without complementary techniques, the identification of variants of uncertain significance (VUS), and the requirement for advanced bioinformatics infrastructure [6].

Genetic testing strategies may include single-gene analysis of *BRCA1/2* or the use of multigene panels. In addition, Multiplex Ligation-dependent Probe Amplification (MLPA) is employed to detect copy number variations.

Sanger sequencing, developed by Frederick Sanger and considered a first-generation sequencing method, is typically used when a specific mutation site is already known. This technique was instrumental in the Human Genome Project, completed in 2001 after more than a decade of global collaboration. Although it has lower sensitivity compared to modern sequencing technologies, Sanger sequencing remains useful for confirming NGS results when variant allele frequency is sufficiently high (approximately ≥25%), or when targeted sequencing of a specific gene or DNA fragment is required [7].

Genetic testing is commonly performed using peripheral blood or saliva samples. Results are interpreted according to the American College of Medical Genetics and Genomics (ACMG) classification system, which categorizes variants into five groups: pathogenic, likely pathogenic, variant of uncertain significance, likely benign, and benign.

5. INDICATIONS FOR GERMLINE BRCA TESTING

Germline *BRCA* mutation testing is recommended for individuals identified as being at high risk for hereditary breast and ovarian cancer. These criteria are adapted from the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Cancer, with modifications to suit the Vietnamese population [8]. Individuals meeting any of the following criteria should be referred for pre-test genetic counseling:

1. Diagnosis of breast cancer before the age of 50.

2. Bilateral breast cancer (synchronous or metachronous).

3. Male breast cancer.

4. Triple-negative breast cancer.

5. Invasive lobular breast cancer with a personal or family history of diffuse gastric cancer.

6. Epithelial ovarian cancer.

7. Having at least one first-degree relative meeting any of the criteria listed in items 1 to 6.

8. Indication for germline *BRCA* testing to guide treatment decisions.

9. Having ≥3 relatives on the same side of the family with breast cancer and/or prostate cancer (at any age).

10. Having a first-degree relative with a known germline *BRCA* mutation or other high-risk breast cancer susceptibility gene mutation.

6. ROLE OF GENETIC COUNSELING

Genetic counseling is an essential component in the management of Hereditary Breast and Ovarian Cancer (HBOC) syndrome. This process includes risk assessment, interpretation of genetic testing, decision-making support, and provision of psychosocial care. All individuals indicated for germline *BRCA* or other HBOC-related genetic testing-whether for diagnostic or therapeutic purposes—should receive comprehensive pre-test and post-test genetic counseling [9].

Prior to testing, genetic counseling helps assess the likelihood of carrying a pathogenic variant and ensures that patients understand the benefits, limitations, and possible outcomes of testing. Post-test counseling focuses on interpreting the

results and developing appropriate surveillance or risk-reduction strategies.

In addition, genetic counseling plays a key role in identifying at-risk family members and facilitating cascade testing. This approach contributes to early detection and cancer prevention at the population level.

In Vietnam, the implementation of genetic counseling and testing services faces several challenges, including high costs, limited availability of trained specialists, and low public awareness. Furthermore, legal frameworks and health insurance systems have yet to provide comprehensive support for these services.

7. RISK-REDUCING STRATEGIES FOR BRCA MUTATION CARRIERS

7.1. Cancer screening and early detection

Individuals carrying, or related to carriers of, germline mutations associated with HBOC are recommended to undergo intensified screening programs for early detection of associated malignancies. Intensified screening refers to the use of more sensitive modalities, earlier initiation, and increased screening frequency. The following recommendations are adapted from ESMO guidelines for the management of HBOC [1].

Breast Cancer Screening:

- For individuals with *BRCA1/2* mutations, ESMO recommends initiating breast cancer screening either 5 years prior to the earliest age of diagnosis in the family or starting at age 30.

- The standard screening modality is breast magnetic resonance imaging (MRI) performed every 6 months.

- In settings where MRI is unavailable: For women aged 30–39 years: breast ultrasound combined with mammography may be considered. For women aged ≥40 years: mammography is recommended, with adjunctive ultrasound when indicated, particularly as breast density decreases with age.

Ovarian cancer screening for germline BRCA mutation (gBRCAm) carriers: according to ESMO's guidelines, screening for ovarian cancer in gBRCAm carriers may include transvaginal ultrasound combined with serum CA-125 measurement every 6 months, starting at the age when risk-reducing salpingo-oophorectomy is typically recommended.

7.2. Risk-Reducing Interventions

Risk-reducing interventions involve prophylactic surgical removal of organs at high risk of malignancy due to germline mutations associated with HBOC. These strategies are typically recommended for individuals confirmed to carry high-risk pathogenic variants. The most targeted organs for prophylactic surgery are breasts and ovaries.

Risk-Reducing Salpingo-Oophorectomy (RRSO): Prophylactic bilateral salpingo-oophorectomy has been shown to reduce overall mortality by up to 77%. Its effect on reducing breast cancer risk remains less clearly defined. RRSO is generally recommended after completion of childbearing, starting at age 35-40 years for *BRCA1* mutation carriers and 40-45 years for *BRCA2* mutation carriers.

Risk-Reducing Mastectomy: Prophylactic bilateral mastectomy can reduce the risk of breast cancer by up to 90%, not only in carriers of pathogenic *BRCA* variants but also in individuals with high-risk mutations in other genes such as *TP53, PTEN,* and *PALB2* [1,10].

For individuals who do not undergo prophylactic mastectomy, endocrine chemoprevention may reduce breast cancer risk by approximately 30-60%. Tamoxifen is commonly prescribed at a dose of 20

mg daily, or alternatively, aromatase inhibitors (AIs) may be used for a duration of 5 years.

8. CONCLUSIONS

Hereditary Breast and Ovarian Cancer (HBOC) syndrome represents a prototypical model of hereditary cancer, with a biological basis rooted in mutations of DNA repair genes, particularly *BRCA1/2*. Advances in genetic testing technologies have significantly expanded the capacity to identify and manage high-risk individuals. Genetic counseling plays a central role in optimizing the benefits of testing and supporting informed clinical decision making. At the same time, targeted therapies such as PARP inhibitors have substantially improved outcomes for patients harboring *BRCA* mutations. However, the widespread implementation of these services remains challenging, particularly in developing countries such as Vietnam. Therefore, comprehensive strategies are needed to enhance awareness, strengthen workforce training, and improve access to genetic services.

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