Journal ofCancer Research and Cellular Interventions (JCCRCI)

OLITES PUBLISHERS
A Global Approach For Research

Open Access

Review Article

Hereditary Ovarian Cancer Syndromes: Genetic Basis, Clinical Manifestations, and Management Strategies

Bellcross C, Wangensteen T, Chan G, Cybulski C
1Department of Genetics and Pathology, Szczecin, Poland.
***Corresponding Author:** Bellcross C, Department of Genetics and Pathology, Szczecin, Poland
Citation: Bellcross C (2021). Hereditary Ovarian Cancer Syndromes: Genetic Basis, Clinical Manifestations, and ManagementStrategies.V1(1)

Received date: May 17, 2025: **Accepted date**: May 24, 2025: **Published date**: May 31, 2025
Keywords: hereditary ovarian cancer, BRCA1, BRCA2, Lynch syndrome, risk-reducing surgery, PARP inhibitors

Abstract

Ovarian cancer remains the most lethal gynaecologic malignancy worldwide, with hereditary syndromes accounting for approximately 10-25% of all cases. This review examines the three principal hereditary ovarian cancer syndromes—hereditary breast and ovarian cancer syndrome (HBOC), Lynch syndrome, and site-specific ovarian cancer syndrome with particular emphasis on their genetic underpinnings, clinical presentation, and management implications. The predominance of BRCA1 and BRCA2 mutations in hereditary ovarian cancer is discussed alongside emerging evidence regarding moderate-penetrance genes including PALB2, RAD51C, RAD51D, and BRIP1. Recent insights into ovarian cancer pathogenesis, particularly the role of fallopian tube epithelial precursors in high-grade serous carcinoma development, have transformed understanding of disease initiation and prevention. Risk-reducing strategies, including salpingo-oophorectomy and emerging surveillance protocols, are evaluated in the context of specific genetic mutations. The expanding role of poly ADP-ribose polymerase inhibitors in treating hereditary ovarian cancers highlights the critical importance of genetic testing for all ovarian cancer patients and their at-risk relatives.

Introduction

Ovarian cancer ranks as the sixth most common cancer and the fifth most deadly malignancy among women worldwide, representing a significant medical problem across all populations . While most ovarian cancers (75-90%) arise sporadically through accumulation of somatic mutations confined to tumor tissue, approximately10-25% of cases have an inherited basis . The recognition of hereditary ovarian cancer syndromes has profound implications not only for affected individuals but also for their family members, who may carry the same genetic predisposition and require targeted preventive strategies.

The past decade has witnessed remarkable advances in understanding the genetic architecture of hereditary ovarian cancer. Beyond the well-characterized BRCA1 and BRCA2 genes, next-generation sequencing technologies have identified numerous additional genes that confer increased ovarian cancer risk, many of which participate in DNA repair pathways . Concurrently,

insights into disease pathogenesis have shifted the paradigm of high-grade serous ovarian cancer origin from the ovarian surface epithelium to the fallopian tube epithelium, fundamentally altering approaches to risk reduction and early detection.

Major Hereditary Ovarian Cancer Syndromes

Hereditary ovarian cancer syndromes encompass several distinct clinical entities characterized by specific genetic alterations and associated cancer risks. The three principal

The prevalence of BRCA1/2 mutations in the general population is approximately 1:400, though specific founder mutations occur at higher frequencies in certain ethnic groups, particularly individuals of Ashkenazi Jewish descent. Among ovarian cancer patients, germline BRCA mutations are identified in 14-18% of cases, with somatic mutations accounting for an additional 7-8%. High-grade serous ovarian carcinoma demonstrates the highest frequency of BRCA mutations, though genetic testing should not be limited

to this histologic subtype, as other subtypes show comparable mutation rates.

Lynch Syndrome

Lynch syndrome, also known as hereditary non-polyposis colorectal cancer syndrome, results from germline mutations in DNA mismatch repair genes including MLH1, MSH2, MSH6, PMS2, and EPCAM . While best known for colorectal cancer predisposition, Lynch syndrome confers substantially elevated ovarian cancer risk, with lifetime estimates of 11% for MLH1, 17.4% for MSH2, and 10.8% for MSH6 mutation carriers by age 75 . Ovarian cancers arising in Lynch syndrome patients often demonstrate non-serous histologies, including endometrioid and clear cell subtypes, and may present at earlier ages than sporadic cases

Non-BRCA Hereditary Ovarian Cancer Genes

Comprehensive genetic testing has identified numerous additional genes associated with moderate penetrance for ovarian cancer. These include PALB2, ATM, BRIP1, RAD51C, and RAD51D, all of which participate in the Fanconi anemia/BRCA pathway of DNA repair . Walsh and colleagues identified pathogenic variants in these genes among 6.1% of ovarian cancer patients studied, emphasizing the clinical utility of broad genetic panels beyond BRCA1/2 analysis . The lifetime risks associated with these genes vary, and current evidence regarding optimal management strategies continues to evolve.

Therapeutic Implications

The identification of hereditary ovarian cancer has direct therapeutic consequences. Poly ADP-ribose polymerase (PARP) inhibitors exploit the homologous recombination deficiency characteristic of BRCA-mutated cancers through synthetic lethality, demonstrating significant efficacy in both initial treatment and recurrence settings. The presence of a germline BRCA mutation predicts response to PARP inhibitor therapy, and testing results guide treatment selection.

Platinum-based chemotherapy also shows enhanced efficacy in BRCA-mutated ovarian cancers, reflecting the sensitivity of homologous recombination-deficient tumors to DNA-damaging agents. This therapeutic vulnerability extends totumors with mutations in other homologous recombination pathway genes, supporting the use of broader genetic panels to identify additional patients who may benefit from targeted therapies

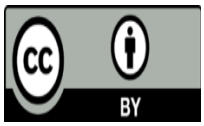
Conclusion

Hereditary ovarian cancer syndromes represent a significant proportion of ovarian cancer cases and provide critical opportunities for prevention, early detection, and targeted therapy. The expanding understanding of genetic predisposition beyond BRCA1 and BRCA2, combined with insights into fallopian tube pathogenesis, has transformed clinical approaches to at-risk women. Multidisciplinary

References

1. Tandon D, Munne K, Pande SS. Hereditary breast and ovarian cancers: A comprehensive overview of genetic testing, counseling, and treatment. Wadia Journal of Women and Child Health. 2024;3:74-8
2. Targeting Ovarian Neoplasms: Subtypes and Therapeutic Options. Medicina. 2025;61(12):2246
3. Systematic review of the molecular basis of hereditary breast and ovarian cancer syndrome in Brazil: the current scenario. European Journal of Medical Research. 2024;29:187
4. Horackova K, Janatova M, Kleiblova P, et al. Genetic predisposition to early-onset ovarian cancer. International Journal of Molecular Sciences. 2023;24(23):17020
5. The Keio HBOC Center: A Model of Hereditary Breast and Ovarian Cancer Management. Keio Journal of Medicine. 2025;74(3):124-129
6. Hereditary Ovarian Carcinoma: Cancer Pathogenesis Looking beyond BRCA1 and BRCA2. Cells. 2022;11(3):539
7. Genetic Basis of Breast and Ovarian Cancer: Approaches and Lessons Learnt from Three Decades of Inherited Predisposition Testing. Genes. 2024;15(2)

Journal of Cancer Research and Cellular Interventions (JCCRCI)



 DOI:10/JCCRCI/2025/002