Journal of Cancer Research and Cellular Interventions (JCCRCI)

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Short Review

Beyond BRCA: The Expanding Landscape of Hereditary Breast Cancer

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Citation: Gronwald J (2025). Beyond BRCA: The Expanding Landscape of Hereditary Breast Cancer. V1(2)

Abstract

Hereditary breast cancer (HBC) accounts for approximately 5-10% of all breast cancer cases and results from germline pathogenic variants in cancer predisposition genes. While BRCA1 and BRCA2 remain the most well-known susceptibility genes, advances in next-generation sequencing have revealed a growing network of associated genes, including PALB2, CHEK2, ATM, and TP53. Thesemutations not only increase lifetime cancer risks but also influence tumor biology and therapeutic response. This review summarizes the current understanding of the genetic architecture of HBC, discusses risk stratification and clinical management strategies, and highlights emerging evidence regarding expanded cancer spectra associated with hereditary syndromes

Introduction

Breast cancer is the most commonly diagnosed malignancy worldwide, with a significant subset attributable to inherited genetic factors. Hereditary breast cancer (HBC) is characterized by germline pathogenic or likely pathogenic variants (PVs/LPVs) in genes involved in essential cellular processes, most notably the DNA damage response pathway. Although HBC constitutes a minority of overall cases, its identification carries profound implications not only for the affected individual but also for at-risk family members. The landscape of HBC has evolved dramatically with the advent of multigene panel testing, moving beyond the traditional BRCA-centric

Genetic Architecture of Hereditary Breast Cancer

The genes associated with HBC are typically classified by the level of breast cancer risk they confer. High-penetrance genes, which increase lifetime risk by more than fourfold, include *BRCA1*, *BRCA2*, *PALB2*, *TP53* (associated with Li-Fraumeni syndrome), and *PTEN* (associated with Cowden syndrome) . Moderate-penetrance genes, such as *CHEK2* and *ATM*, confer a two- to fourfold increased risk, while a growing list of genes, including *RAD51C* and *RAD51D*, are associated with lower risk levels.

The BRCA1 and BRCA2 genes are the most frequently implicated in HBC, accounting for approximately 30-40% of hereditary cases . These tumor suppressor genes are critical for homologous recombination repair of double-strand DNA breaks. Carriers of BRCA1 mutations face a lifetime breast cancer risk of 60-85%, while BRCA2 carriers face a risk of approximately 45-60% . In recent years, *PALB2* (Partner and Localizer of BRCA2) has emerged as a key high-risk gene, functioning as a bridge between BRCA1 and BRCA2 in the DNA repair complex. Pathogenic variants in *PALB2* confer a breast cancer risk comparable to that of *BRCA2*, with estimates reaching up to 50%.

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Clinical Implications and Management

Identifying a hereditary predisposition fundamentally alters clinical management. Genetic testing is recommended for individuals with early-onset breast cancer (≤50 years), triple-negative breast cancer, male breast cancer, a significant family history, or ancestry associated with foundermutations . The National Comprehensive Cancer Network (NCCN) and other international bodies provide guidelines for risk assessment, which often incorporate models like Tyrer-Cuzick or BRCAPro to quantify pre-test probabilities

For confirmed carriers, management is tailored to the specific gene and risk level. High-risk carriers (e.g., *BRCA1/2*, *PALB2*, *TP53*) are typically advised to initiate intensified surveillance at a young age, including annual breast MRI with contrast starting at age 25-30, often alternating with mammography . Risk-reducing mastectomy (RRM) is an effective preventive strategy, reducing breast cancer risk by approximately 90-95%

Expanding the Spectrum of Associated Cancers

While HBC has traditionally focused on breast and ovarian cancer risk, large-scale population studies are broadening our understanding of associated malignancies. A recent comprehensive review analyzing data from over 60,000 patients in a Japanese biobank revealed significant associations between *BRCA* mutations and cancers beyond the traditional spectrum . *BRCA1* mutations were linked to an increased risk of gastric (OR 5.2), biliary tract(OR 17.4), uterine, and cervical cancers. *BRCA2* mutations showed significant associations with esophageal (OR 15.89 in a Chinese cohort), gastric, and gallbladder cancers . These findings, while requiring further validation in diverse populations, suggest that surveillance protocols may eventually need to expand to include these organ sites.

The Role of Moderate-Penetrance Genes and ture Directions

The widespread use of panel testing has led to the increased detection of variants in moderate-penetrance genes like CHEK2 and ATM. The clinical management of these variants is nuanced, as risks can be influenced by family history and specific variant type. For example, the CHEK2 c.470T>C (p.Ile157Thr) variant has a more modest effect compared to truncating variants, making counseling complex . Additionally, the frequent identification of Variants of Unknown Significance (VUS) presents a challenge, requiring careful communication to avoid unwarranted anxiety or intervention.

Conclusion

Hereditary breast cancer is a complex and rapidly evolving field. The genetic landscape has expanded well beyond *BRCA1/2* to include a diverse array of genes with varying penetrance. Identifying these mutations is critical for guiding personalized surveillance, prevention, and treatment strategies, including the use of targeted therapies like PARP inhibitors. As evidence emerges regarding broader cancer risks, genetic counseling and management protocols must adapt to ensure comprehensive care for mutation carriers and their families

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Journal of Cancer Research and Cellular Interventions (JCCRCI)

 DOI:10/JCCRCI/2025/010