INNSPUB

International Journal of Biosciences | IJB |
ISSN: 2220-6655 (Print); 2222-5234 (Online)
Website: https://www.innspub.net
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Vol. 27, Issue: 1, p. 142-155, 2025

REVIEW PAPER OPEN ACCESS

Unraveling emerging genes and their functional pathways in breast cancer susceptibility and progression

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Key words: Breast cancer, BRCA genes, PALB, CHEK, ATM

DOI: https://dx.doi.org/10.12692/ijb/27.1.142-155 Published: July 07, 2025

ABSTRACT

Breast cancer remains one of the leading causes of cancer-related morbidity and mortality among women worldwide. While mutations in BRCA1 and BRCA2 have long been recognized as key drivers of hereditary breast cancer, recent advances in genomic research have uncovered a growing set of additional genes such as PALB2, CHEK2, ATM, FANCM, and RAD51C—that contribute to breast cancer susceptibility. These genes are involved in critical molecular pathways, including homologous recombination DNA repair, cell cycle checkpoint control, apoptosis, and tumor suppression. Dysfunction in these pathways, often triggered by germline mutations, can lead to genomic instability, uncontrolled proliferation, and tumorigenesis. This review provides a comprehensive analysis of these emerging genetic factors, detailing their mechanisms of action, pathway interactions (e.g., BRCA–PALB2–RAD51 axis, ATM–CHEK2–p53 checkpoint signaling), and their impact on both familial and sporadic forms of breast cancer. We also discuss the clinical relevance of integrating multi-gene panels and polygenic risk scores (PRS) into personalized risk assessment and prevention strategies. By highlighting the molecular pathways disrupted by these gene mutations, we emphasize the importance of expanding genetic testing beyond BRCA1/2. A deeper understanding of these pathways not only refines risk stratification but also opens new avenues for targeted therapy, early detection, and tailored clinical management of breast cancer.

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INTRODUCTION

Cancer comprises a group of diseases marked by uncontrolled cell growth, abnormal morphology, and disrupted cellular proliferation. One of the hallmarks of cancer is the loss of adhesion among cells, enabling malignant cells to invade surrounding tissues and metastasize to distant organs if not diagnosed and treated in time (Nenclares and Harrington, 2020; Kotamkar *et al.*, 2021). Breast cancer is the most common malignancy among women worldwide, accounting for approximately 2.3 million new cases and 685,000 deaths in 2020 alone (Glodzik *et al.*, 2020). By the end of that year, it had affected around 7.8 million individuals, becoming a major contributor to disability-adjusted life years (DALYs) lost among women globally. Although breast cancer can occur at any age following puberty, its incidence increases with advancing age (Luo *et al.*, 2022) (Fig. 1).

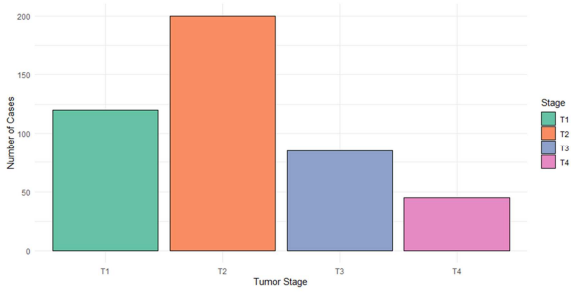

Fig. 1. Different stages of breast cancer (Tumor size).

Among the various subtypes, triple-negative breast cancer (TNBC) is particularly aggressive and difficult to treat due to the absence of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2). This phenotype renders conventional hormone therapies ineffective, necessitating the development of alternative treatment strategies (Swaminathan *et al.*, 2023; Nath *et al.*, 2024). Genetic mutations, especially in the BRCA1 gene, are associated with up to 70% of hereditary breast cancer cases, with a significant overlap seen in TNBC (Goldberg *et al.*, 2020). Current research indicates that the dysregulation of key signaling pathways that govern mammary gland development and stem cell maintenance may play a crucial role in the pathogenesis of TNBC. While chemotherapeutic agents and radiotherapy remain standard treatments, ongoing clinical trials are exploring targeted therapies that inhibit these aberrant pathways (Wang *et al.*, 2022). Despite these advancements, TNBC continues to exhibit poor prognosis and high recurrence rates, underscoring the urgent need for improved diagnostic and therapeutic approaches.

Multiple risk factors contribute to breast cancer, including genetic predisposition (e.g., family history and BRCA mutations), lifestyle factors (such as diet, obesity, smoking, and alcohol use), hormonal exposure (e.g., early menarche, late menopause, and hormone replacement therapy), and environmental influences like ionizing radiation (Liu *et al.*, 2021; Joshi *et al.*, 2022). However, there remains significant debate and inconsistency in the literature regarding the strength and interplay of these risk factors. Some women develop breast cancer despite lacking any known risk markers, further complicating prevention strategies (Zufiqar *et al.*, 2024; Pezzoli *et al.*, 2024). Therefore, a comprehensive approach is necessary to synthesize current evidence, clarify these associations, and guide clinical decision-making. The aim of this study is to review and analyze the known risk factors for breast cancer, with a particular focus on TNBC, in order to identify consistent patterns, highlight research gaps, and propose informed directions for future prevention and treatment strategies.

Genes associated with breast cancer

The genetic architecture of breast cancer (BC) susceptibility shares similarities between women and men, featuring high-, moderate-, and low-penetrance risk variants (Valentini *et al.*, 2024). However, some sex-specific differences have been identified. Inherited high-penetrance pathogenic variants (PVs) in the BRCA1 and BRCA2 genes represent the most significant genetic risk factors for BC (Fanale *et al.*, 2024).

BRCA1 PVs are more commonly linked to an increased risk of female BC, while BRCA2 PVs are more strongly associated with male BC (Fanale *et al.*, 2024). Importantly, BRCA-related breast cancers exhibit sex-specific pathological features (Neagu *et al.*, 2024).

Advancements in next-generation sequencing technologies have provided deeper insights into the role of moderate-penetrance BC risk variants, particularly in genes such as PALB2, CHEK2, and ATM (Rocca *et al.*, 2024). Additionally, international collaborative genome-wide association studies have identified common low-penetrance BC risk variants, shedding light on their combined effects in polygenic models and their role as risk modulators in BRCA1/2 PV carriers (Di Micco *et al.*, 2023). These studies suggest that while the genetic basis of male BC is similar to that of female BC, there may be important differences between the two (Chatterji *et al.*, 2023). Recognizing male BC as a distinct entity from female BC is a crucial step toward improving personalized risk assessment and treatment options for both sexes, aiming for gender equality in BC care (Mendes *et al.*, 2022).

Additionally, recent work by Liu *et al.* (Liu *et al.*, 2024) identified biomarker gene sets for CD8+ tissue-resident memory T cells (CD8Tex) in breast cancer. Subtyping systems and prognostic models based on CD8Tex performed well in differentiating patients with varying immune relevance and survival outcomes. CRTAM, CLEC2D, and KLRB1 were identified as hub genes for CD8Tex, demonstrating their potential clinical relevance and impact on immune therapy (Ge *et al.*, 2024).

Hereditary breast cancer syndromes

Hereditary breast cancer syndromes account for approximately 10–15% of all breast cancer (BC) cases, though they represent a significant group due to their high penetrance and implications for early diagnosis, treatment, and risk management (Garutti *et al.*, 2023). The well-studied genes associated with hereditary breast cancer include BRCA1 and BRCA2, but mutations in other high-penetrance genes such as TP53, PTEN, CDH1, and STK11, as well as moderate-penetrance genes like CHEK2, ATM, and BRIP1, have also been implicated in increasing lifetime BC risk (Peleg Hasson *et al.*, 2020; Huber-Keener, 2022).

Advances in genetic research have led to improved diagnostic and screening strategies, and there is growing interest in these genetic pathways as therapeutic targets (Fig. 2).

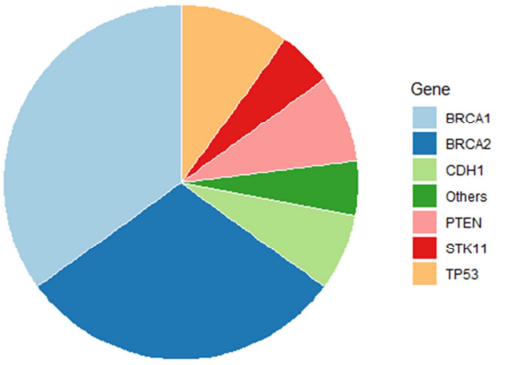

Fig. 2. Breast cancer patients with genetic mutations. Approximately 10–15% of breast cancer cases are associated with hereditary syndromes, and the majority of them will carry a deleterious mutation in BRCA1 and BRCA2. Other rare highly penetrant syndromes are Cowden (PTEN) and Li-Fraumeni (p53). After excluding BRCA-positive and syndromic genes, there are pathogenic mutation in other genes.

BRCA1 and BRCA2

The BRCA1 gene, located on chromosome 17, was identified in 1994 as the first major gene associated with hereditary breast and ovarian cancer (HBOC) syndrome (Pourmasoumi *et al.*, 2024). BRCA1 encodes a protein critical for DNA repair, cell cycle regulation, and transcriptional control. Mutations in BRCA1 increase the risk of BC, with studies estimating a cumulative BC risk of 72% by age 80 for women carrying germline mutations, compared to 13% in the general population. Male BRCA1 mutation carriers have a much lower risk (0.4%), though the incidence is notably higher in specific populations

with a founder effect (10–16%). BRCA1-related BCs are typically triple-negative (ER-negative, PR-negative, HER2-negative) and of higher grade (Calabrese *et al.*, 2026).

BRCA2, identified in 1995, is located on chromosome 13 and encodes a protein involved in homologous recombination DNA repair (Lim *et al.*, 2024). BRCA2 mutations confer a lifetime BC risk of approximately 69% by age 80, with male carriers at an elevated risk of BC (around 4%) compared to the general male population (Fanale *et al.*, 2024). BRCA2-related BCs tend to exhibit a luminal phenotype, with higher rates of estrogen receptor (ER) and progesterone receptor (PR) positivity, as opposed to the triple-negative phenotype often seen in BRCA1 mutations. Both BRCA1 and BRCA2 mutations also increase the risk of ovarian, pancreatic, and stomach cancers (Bono *et al.*, 2024).

BRCA1 and BRCA2 pathways in DNA repair and tumor suppression

The BRCA1 and BRCA2 genes play critical roles in maintaining genomic stability through their involvement in the homologous recombination (HR) DNA repair pathway. BRCA1 is primarily involved in sensing DNA double-strand breaks and recruiting other repair proteins to the damage site. It forms complexes with other tumor suppressors, such as BARD1 and is essential in regulating cell cycle checkpoints, particularly at the G2/M transition. By facilitating DNA end resection and promoting RAD51 loading onto single-stranded DNA, BRCA1 ensures high-fidelity repair of double-strand breaks. Mutations in BRCA1 impair these processes, leading to error-prone repair mechanisms, chromosomal instability, and increased susceptibility to tumorigenesis. Notably, BRCA1-associated tumors often exhibit triple-negative phenotypes (ER-, PR-, HER2-) and high-grade features (Xu *et al.*, 2025; Calheiros *et al.*, 2025; Pasaol *et al.*, 2025).

BRCA2, on the other hand, directly mediates the recruitment and stabilization of RAD51 onto resected DNA during homologous recombination. While BRCA1 initiates early repair signaling, BRCA2 acts at the core of the HR mechanism by facilitating RAD51 nucleoprotein filament formation, which is essential for the strand invasion step of DNA repair (Pasaol *et al.*, 2025). Loss-of-function mutations in BRCA2 compromise homologous recombination, making cells more reliant on alternative, error-prone pathways such as non-homologous end joining (NHEJ). This results in genomic instability, a hallmark of cancer development (Khalizieva *et al.*, 2025). BRCA2-associated breast cancers tend to be estrogen receptor-positive and exhibit luminal features. Both genes are also involved in protecting stalled replication forks and maintaining telomere integrity, further emphasizing their central role in genomic maintenance and cancer prevention (Fig. 3).

Fig. 3. Illustrate BRCA1 and BRCA2 Pathways (Homologous Recombination Repair). BRCA2: Facilitates RAD51 filament formation and strand invasion

PALB2

The PALB2 gene, which interacts with BRCA1 and BRCA2 in DNA repair, is another key contributor to hereditary BC susceptibility (Peleg *et al.*, 2020). PALB2 mutations are associated with a 50% lifetime risk of BC, with male carriers exhibiting a significantly increased risk (Pal *et al.*, 2025). In addition to BC, PALB2 mutations are linked to increased risks of ovarian and pancreatic cancers. Recent studies have found a higher frequency of PALB2 mutations in high-risk male BC cases compared to general populations, with its mutations resembling those observed in BRCA2 families, especially in cases with other cancers such as melanoma and prostate cancer (Shumilova *et al.*, 2024).

PALB2 pathway in DNA repair

PALB2 (Partner and Localizer of BRCA2) acts as a crucial mediator in the homologous recombination (HR) DNA repair pathway. It functions as a molecular bridge between BRCA1 and BRCA2, enabling efficient

recruitment of BRCA2 to DNA damage sites (Graham *et al.*, 2025). Upon a DNA double-strand break, BRCA1 initially detects the damage and promotes end resection. PALB2 is recruited to the damage site through its interaction with BRCA1's coiled-coil domain (Giordano *et al.*, 2025). Once localized, PALB2 binds to BRCA2 via its WD40 domain and ensures BRCA2 is correctly positioned to load RAD51 onto single-stranded DNA. This BRCA1–PALB2–BRCA2 axis is central to orchestrating high-fidelity HR repair, a key mechanism to maintain genomic stability.

When PALB2 is mutated, the interaction between BRCA1 and BRCA2 is disrupted, leading to inefficient RAD51 loading and defective homologous recombination (Pappas *et al.*, 2025). This causes cells to resort to error-prone repair pathways like non-homologous end joining (NHEJ), thereby increasing the likelihood of chromosomal aberrations and tumor development (Billing and Sfeir, 2025). PALB2 mutations confer a significantly elevated risk for breast cancer (up to 50–58% lifetime risk), and are also implicated in pancreatic and ovarian cancers (Wong *et al.*, 2025). Due to its role in BRCA2 localization and RAD51 function, PALB2 is now recognized not only as a BRCA2 partner but also as a standalone tumor suppressor and emerging target for PARP inhibitor therapy in homologous recombination-deficient cancers (Fig. 4).

Fig. 4. Illustrate the PALB2-mediated homologous recombination pathway. PALB2 acting as the molecular bridge linking BRCA1 to BRCA2, facilitating RAD51-mediated DNA repair.

CHEK2

The CHEK2 gene, located on chromosome 22, encodes a protein kinase involved in the DNA damage response (Hanker *et al.*, 2022). A specific truncating mutation, c.1100delC, confers a 2.5-fold increased risk of BC in the general population, and up to a 4.8-fold risk in familial BC cases. In males, this mutation is associated with a significant risk of BC, accounting for about 9% of familial male breast cancer (MBC) cases. Other CHEK2 mutations, particularly missense variants, have been identified but confer a lower risk. CHEK2 mutations are primarily linked to ER-positive BC and are not commonly associated with triple-negative breast cancer (TNBC) (Valentini *et al.*, 2024).

CHEK2 pathway in DNA damage response

CHEK2 (Checkpoint Kinase 2) is a critical regulator of the DNA damage response, particularly in response to double-strand breaks (DSBs). Upon DNA damage, the upstream kinase ATM (Ataxia-Telangiectasia Mutated) becomes activated through autophosphorylation and recruits CHEK2 (Qian *et al.*, 2025). ATM phosphorylates CHEK2 at threonine 68, triggering CHEK2 dimerization, autophosphorylation, and full activation. Once activated, CHEK2 phosphorylates several downstream substrates including p53, CDC25A, and BRCA1, thereby initiating a cascade of cellular responses such as cell cycle arrest (particularly at the G1/S and G2/M checkpoints), DNA repair, and apoptosis (Nabi *et al.*, 2025). Through these mechanisms, CHEK2 maintains genomic integrity and prevents the propagation of damaged DNA.

CHEK2 mutations, especially the c.1100delC truncating variant, impair its kinase activity, thereby weakening the cell's response to DNA damage. This leads to failure in halting the cell cycle and improper DNA repair, increasing the likelihood of genomic instability and carcinogenesis (An *et al.*, 2025). CHEK2 mutations are associated with a moderately increased risk of breast cancer, especially estrogen receptor-positive subtypes, and also contribute to familial male breast cancer. CHEK2 functions in both BRCA1-dependent and independent repair pathways, making it a vital node in DNA surveillance (Chen *et al.*, 2024). Given its role in cell cycle regulation and interaction with other tumor suppressors, CHEK2 is an important biomarker for hereditary cancer syndromes and a potential therapeutic target in DNA damage response-deficient tumors (Fig. 5).

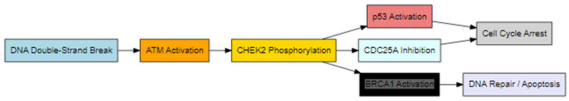

Fig. 5. Illustrate CHEK2-Mediated DNA damage response pathway. ATM → CHEK2 → downstream effectors (p53, CDC25A, BRCA1)

ATM

The ATM gene, located on chromosome 11, is involved in DNA damage repair and cell cycle regulation (Varadhan *et al.*, 2024). Mutations in ATM are rare but have been found to increase the risk of BC, especially in women. Germline ATM mutations are present in 0.6%–2.7% of familial BC cases and may confer a 2- to 5-fold increased risk. For male carriers, ATM mutations appear to increase MBC risk by up to 4 times. ATM mutations are also linked to an elevated risk of other cancers, including pancreatic, prostate, and gastric cancers (Podralska *et al.*, 2024).

ATM pathway in DNA damage response

ATM (Ataxia-Telangiectasia Mutated) is a master regulator of the cellular response to DNA double-strand breaks (DSBs), one of the most lethal types of DNA damage. In its inactive state, ATM exists as a homodimer in the nucleus (Varadhan *et al.*, 2025). Upon DSB detection often mediated by the MRN complex (MRE11, RAD50, NBS1) ATM undergoes rapid autophosphorylation at serine 1981, leading to monomerization and activation. Once activated (Lee, 2024), ATM phosphorylates a wide range of substrates including CHEK2, p53, H2AX, NBS1, and BRCA1. These phosphorylation events initiate pathways responsible for cell cycle arrest (via p53 and CHEK2), DNA repair (via BRCA1 and RAD51 recruitment), and apoptosis if the damage is irreparable. ATM also activates γ-H2AX, which marks the damage site and recruits repair proteins.

Mutations in ATM impair this response, resulting in defective DNA repair, unchecked cell cycle progression, and increased genomic instability a hallmark of cancer. Germline ATM mutations are associated with ataxia-telangiectasia, a rare neurodegenerative disorder, and are linked to increased risks of breast, pancreatic, prostate, and gastric cancers (Rameshkumar *et al.*, 2024). In heterozygous carriers, the cancer risk is elevated due to partial loss of ATM function. ATM is also crucial for maintaining replication fork stability and telomere length. The ATM pathway's central role in genome surveillance makes it a key therapeutic target, particularly in tumors with homologous recombination deficiencies, where ATM inhibitors may act synergistically with PARP inhibitors or radiotherapy (Fig. 6).

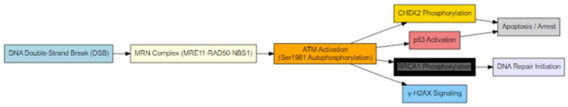

Fig. 6. Illustrate ATM-mediated DNA damage response pathway. ATM lies at the top of the DSB response hierarchy. It triggers both repair (via BRCA1, γ-H2AX) and cell fate decisions (via p53, CHEK2).

Other genes

In addition to the high-penetrance genes discussed, several moderate-penetrance genes are also associated with BC risk. These include BRIP1, FANCM, and RAD51C, among others. BRIP1 mutations, while primarily associated with ovarian cancer, have also been linked to a modest increase in BC risk (Rodrigues *et al.*, 2024). FANCM mutations are associated with both BC and ovarian cancer, with an increased risk for ER-negative and TNBC subtypes. Genes such as CDH1, TP53, PTEN, and STK11, which are involved in other hereditary cancer syndromes, can also contribute to increased BC risk, though these mutations are less common (Pal *et al.*, 2024). CDH1 mutations, for example, are linked to hereditary diffuse gastric cancer and increased BC risk, particularly for lobular breast cancer (Rahmati *et al.*, 2023).

Pathways of other moderate penetrance genes in breast cancer

Several moderate-penetrance genes such as BRIP1, FANCM, and RAD51C function primarily in DNA

repair pathways, especially homologous recombination (HR), and contribute to genomic stability. BRIP1 (BRCA1-interacting protein 1) encodes a DNA helicase that partners with BRCA1 to resolve stalled replication forks and maintain replication fork stability (Kaur and Singh, 2024). Mutations in BRIP1 can disrupt BRCA1 interaction and impair DNA repair, predisposing cells to accumulation of genetic errors. FANCM is part of the Fanconi Anemia (FA) DNA repair complex, which responds to interstrand crosslinks by coordinating HR-mediated repair. Loss-of-function mutations in FANCM are associated with increased risk of estrogen receptor-negative (ER-) and triple-negative breast cancer (TNBC), likely due to impaired resolution of replication stress and chromosomal breaks (Ganatra *et al.*, 2024).

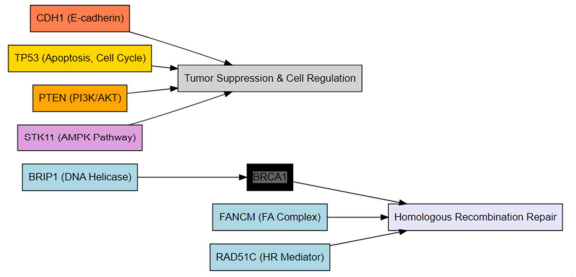

Fig. 7. Illustrate the pathways of moderate-risk genes in breast cancer. Left group: Moderate-risk genes involved in DNA repair via homologous recombination. Right group: Genes involved in tumor suppression, adhesion, and signaling.

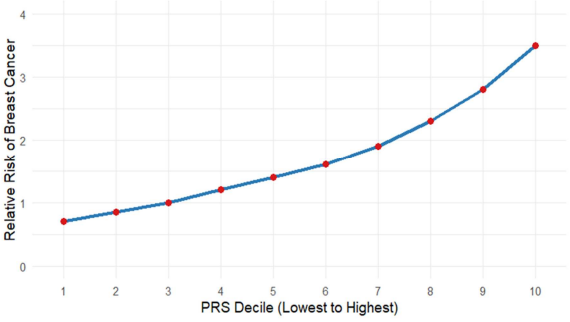

Fig. 8. This figure illustrates the relationship between polygenic risk score (PRS) deciles and relative breast cancer risk. Individuals in higher PRS deciles exhibit a markedly increased risk, with the top 10% showing over 3-fold greater risk compared to the average. The plot emphasizes the value of PRS in stratifying population-level risk and guiding personalized screening strategies.

Other genes like CDH1, TP53, PTEN, and STK11 contribute to breast cancer susceptibility through pathways beyond HR repair. CDH1, which encodes E-cadherin, is crucial for cell-cell adhesion and epithelial integrity (Razack and Prabhuswamimath, 2024). Its loss results in enhanced invasion and metastasis, particularly in lobular breast cancer. TP53, the "guardian of the genome," coordinates cellular responses to stress by inducing apoptosis, senescence, or cell cycle arrest. Mutations in TP53 remove this control, allowing proliferation despite DNA damage. PTEN acts as a tumor suppressor by antagonizing the PI3K/Akt signaling pathway, thus regulating cell survival and proliferation (Saundarya *et al.*, 2024). Similarly, STK11, implicated in Peutz-Jeghers syndrome, controls cell metabolism and polarity through the AMPK pathway. Disruptions in any of these genes compromise cellular checkpoints and tissue homeostasis, thereby increasing breast cancer risk (Fig. 7).

Polygenic risk scores (PRS)

In addition to high- and moderate-penetrance genes, genome-wide association studies (GWAS) have identified over 300 common genetic variants associated with BC (McClellan *et al.*, 2024). These single nucleotide polymorphisms (SNPs) each confer a small individual risk but can collectively contribute to a significant overall genetic predisposition (Liao *et al.*, 2024). Polygenic risk scores (PRS) that aggregate the effects of multiple SNPs have been developed to predict an individual's overall BC risk, helping to stratify individuals for targeted screening and prevention strategies (Ayoub *et al.*, 2024). These PRS models have shown utility not only in women but also in male carriers of high-risk mutations, offering a personalized approach to BC risk management (Mbuya-Bienge *et al.*, 2023). The growing body of evidence linking genetic mutations to breast cancer susceptibility has dramatically improved our

understanding of hereditary cancer risks (Neiger *et al.*, 2021). While BRCA1 and BRCA2 mutations remain the most prominent, other genes such as PALB2, CHEK2, ATM, and others are now recognized as contributing factors (Graffeo *et al.*, 2022) (Table 1). Genetic testing, including multigene panels, has become crucial in identifying high-risk individuals, enabling more effective surveillance and personalized treatment options (Reid and Pal, 2022). Further research into the role of common genetic variants and the development of refined polygenic risk scores will likely enhance risk prediction and prevention strategies in both female and male breast cancer patients (Fig. 8).

Table 1. Details of genes associated with breast cancer

Gene Name	Location	Function	Classification	Abnormality after mutation
BRCA1	17q21	DNA repair and genomic stability	Tumor suppressor gene	Impairs the DNA repair function.
BRCA2	13q12	DNA repair of double stand break	Tumor suppressor gene	Impairs the DNA repair function.
HER2	17q12	Cell division and growth	Oncogene	Leads to uncontrolled cell growth and division.
EGFR	7p12	Cell division and growth	Oncogene	Mutations cause constitutive activation of the EGFR receptor, leading to uncontrolled cell growth, division and progression of BC.
c-Myc	8q24	Regulation of cell growth differentiation and apoptosis.	Oncogene	Leads to dysregulated cell growth, impaired differentiation and decreased apoptosis, contributing to the development and progression of BC.
Ras	(Harvey) H-Ras - 11p15 (Kristen) K-Ras - 12p12 (Neuroblastoma) N-Ras - 1p22	Cell division and growth espically normal cell growth, differentiation and survival.	Oncogene	Leads to constitutive activation of the Ras protein, resulting in uncontrolled cell growth, impaired differentiation and resistance to apoptosis.
TP53	17p13.1	Plays a critical role in maintaining genomic stability and preventing the development of cancer by promoting cell cycle arrest, DNA repair and apoptosis.	Tumor suppressor gene	Leads to the accumulation of genetic damage and promoting the development and progression of BC.
NME1	10q23	Plays a critical role in inhibiting tumor invasion and metastasis through its involvement in nucleotide metabolism, cell migration and signaling pathways.	Tumor suppressor gene	Leads to the development and progression of BC by promoting tumor invasion and metastasis and is associated with a poorer prognosis.
RB1	13.2	Regulates cell cycle progression, differentiation and apoptosis by controlling the activity of E2F transcription factors and other downstream targets.	Tumor suppressor gene	Leads to uncontrolled cell proliferation, impaired differentiation and resistance to apoptosis.
PTEN	3p14.2	Regulates cell growth, proliferation and survival by negatively regulating the PI3K/Akt signaling pathway and promoting apoptosis and cell cycle arrest.	Tumor suppressor gene	Leads to constitutive activation of the PI3K/Akt pathway, promoting uncontrolled cell growth, proliferation and survival.
ATM	11q22-q23	Plays a critical role in detecting and repairing DNA damage, promoting cell cycle arrest and inducing apoptosis in response to	Tumor suppressor gene	Impair the ability of cells to respond to DNA damage, leading to

		genotoxic stress.		genomic instability and an increased risk of developing BC.
CDH1	16q22.1	Encodes the E-cadherin protein, which plays a critical role in maintaining cell–cell adhesion, polarity and tissue architecture and regulating cell proliferation and differentiation.	Tumor suppressor gene	Leads to reduced cell adhesion, impaired tissue integrity and enhanced cell motility and invasion.
FHIT	3p14.2	Plays a critical role in regulating cell proliferation, DNA damage response and apoptosis, by promoting the cleavage of diadenosine triphosphate (Ap3A) and inhibiting signaling through the Wnt/β-catenin pathway.	Tumor suppressor gene	Impair the ability of cells to respond to DNA damage and undergo apoptosis, promoting uncontrolled cell growth.
Maspin	18q21.33	Promote tumor growth, invasion and metastasis and is associated with a poorer prognosis in BC.	Tumor suppressor gene	Promote tumor growth, invasion and metastasis and is associated with a poorer prognosis in BC.
CCND1	11q13	Encodes cyclin D1, a protein that promotes cell cycle progression by activating cyclin-dependent kinases and facilitating the transition from G1 to S phase and also has non-cycling functions in transcriptional regulation, cell migration and apoptosis.	Oncogene	Activate the PI3K pathway, leading to uncontrolled cell proliferation, survival and invasion.
PIK3CA	3q26.3	Encodes the p110α subunit of phosphatidylinositol 3-kinase (PI3K), a critical signaling molecule that regulates cell growth, survival and metabolism, by activating the AKT/mTOR pathway and other downstream effectors.	Oncogene	Overexpression or amplification of CCND1 can drive excessive cell proliferation, survival and invasion.

SUMMARY AND FUTURE PERSPECTIVE

The exploration of emerging genes associated with breast cancer has significantly advanced our understanding of its genetic landscape. While BRCA1 and BRCA2 remain pivotal in hereditary breast cancer risk, the identification of additional genes, such as PALB2, CHEK2, and ATM, has enriched the field. These genes contribute to various cellular mechanisms, including DNA repair and cell cycle regulation, highlighting the complexity of breast cancer etiology. As genomic technologies continue to evolve, the integration of multi-gene panels and whole-genome sequencing into clinical practice is becoming increasingly feasible. This shift will enable more comprehensive risk assessments, allowing healthcare providers to tailor surveillance and preventive strategies to individual patients. Furthermore, the development of polygenic risk scores promises to enhance risk stratification by considering multiple genetic variants simultaneously.

Looking ahead, the focus should not only be on identifying new genetic factors but also on understanding their interactions with environmental and lifestyle factors. Collaborative research efforts across diverse populations are essential to ensure that findings are broadly applicable and to address health disparities in breast cancer care. In conclusion, as our knowledge of the genetic underpinnings of breast cancer expands, so too does the potential for personalized medicine. Continued investment in research, education, and clinical implementation will be vital in translating these discoveries into meaningful advancements in prevention, diagnosis, and treatment of breast cancer.

REFERENCES

An Y, Gao D, He Y, Ge N, Guo J, Sun S, Wang C, Yang F. 2025. Guarding against digestive-system cancers: Unveiling the role of Chk2 as a potential therapeutic target. Genes & Diseases **12**(1), 101191.

Ayoub A, Lapointe J, Nabi H, Pashayan N. 2023. Risk-stratified breast cancer screening incorporating a polygenic risk score: A survey of UK general practitioners' knowledge and attitudes. Genes **14**(3), 732.

Billing D, Sfeir A. 2025. The role of microhomology-mediated end joining (MMEJ) at dysfunctional telomeres. Cold Spring Harbor Perspectives in Biology **17**(2), a041687.

Bono M, Guadagni F, Vincenzi B, Russo A. 2024. Multigene panel testing in hereditary breast and ovarian cancer: An effective liquid biopsy approach to identify mutations in genes involved in the homologous recombination pathway.

Calabrese A, von Arx C, Tafuti AA, Pensabene M, De Laurentiis M. 2024. Prevention, diagnosis and clinical management of hereditary breast cancer beyond BRCA1/2 genes. Cancer Treatment Reviews **113**, 102785.

Calheiros J, Silva R, Barbosa F, Morais J, Moura SR, Almeida S, Fiorini E, Mulhovo S, Aguiar TQ, Wang T, Ricardo S. 2025. A first-in-class inhibitor of homologous recombination DNA repair counteracts tumour growth, metastasis and therapeutic resistance in pancreatic cancer. Journal of Experimental & Clinical Cancer Research **44**(1), 129.

Chatterji S, Niehues JM, van Treeck M, Loeffler CM, Saldanha OL, Veldhuizen GP, Cifci D, Carrero ZI, Abu-Eid R, Speirs V, Kather JN. 2023. Prediction models for hormone receptor status in female breast cancer do not extend to males: Further evidence of sex-based disparity in breast cancer. NPJ Breast Cancer **9**(1), 91.

Chen Y, Zhu Z, Wu X, Li H, Guan W, Ren H. 2024. CHEK2 knockout is a therapeutic target for TP53-mutated hepatocellular carcinoma. Cell Death Discovery **10**(1), 37.

Di Micco R, Esposito E, Accardo G, Sibilio A, Kouloura A, Costa M, Gentilini OD. 2023. Hereditary breast cancer non-CDH1 associated. In Hereditary Gastric and Breast Cancer Syndrome*: CDH1:* One Genotype with Multiple Phenotypes. Cham: Springer International Publishing, 361–386.

Fanale D, Corsini LR, Brando C, Randazzo U, Bono M, Pedone E, Perez A, Sciacchitano R, Cancelliere D, Piraino P, Giurintano A. 2024. BRCA-associated hereditary male cancers: Can gender affect the prevalence and spectrum of germline pathogenic variants? Frontiers in Oncology **14**, 1414343.

Fanale D, Corsini LR, Brando C, Randazzo U, Bono M, Pedone E, Perez A, Sciacchitano R, Cancelliere D, Piraino P, Giurintano A. 2024. BRCA-associated hereditary male cancers: Can gender affect the prevalence and spectrum of germline pathogenic variants? Frontiers in Oncology **14**, 1414343.

Ganatra H, Tan JK, Simmons A, Bigogno CM, Khurana V, Ghose A, Ghosh A, Mahajan I, Boussios S, Maniam A, Ayodele O. 2024. Applying whole-genome and whole-exome sequencing in breast cancer: A review of the landscape. Breast Cancer **31**(6), 999–1009.

Garutti M, Foffano L, Mazzeo R, Michelotti A, Da Ros L, Viel A, Miolo G, Zambelli A, Puglisi F. 2023. Hereditary cancer syndromes: A comprehensive review with a visual tool. Genes **14**(5), 1025.

Ge J, Tao M, Zhang G, Cai J, Li D, Tao L. 2024. New HCC subtypes based on CD8 Tex-related lncRNA signature could predict prognosis, immunological and drug sensitivity characteristics of hepatocellular carcinoma. Journal of Hepatocellular Carcinoma **13**, 31–55.

Giordano C, Puzzo M, Malivindi R, Cristofaro D, Gelsomino L, Bonofiglio D, Capalbo C, Andò S, Barone I, Catalano S. 2025. Complex interplay between obesity and BRCA1/2-associated breast cancer: An overview. Obesity Reviews **e13969**.

Glodzik D, Bosch A, Hartman J, Aine M, Vallon-Christersson J, Reuterswärd C, Karlsson A, Mitra S, Niméus E, Holm K, Häkkinen J. 2020. Comprehensive molecular comparison of BRCA1 hypermethylated and BRCA1 mutated triple negative breast cancers. Nature Communications **11**(1), 3747.

Goldberg M, D'Aloisio AA, O'Brien KM, Zhao S, Sandler DP. 2020. Pubertal timing and breast cancer risk in the Sister Study cohort. Breast Cancer Research **22**, 1.

Graffeo R, Rana HQ, Conforti F, Bonanni B, Cardoso MJ, Paluch-Shimon S, Pagani O, Goldhirsch A, Partridge AH, Lambertini M, Garber JE. 2022. Moderate penetrance genes complicate genetic testing for breast cancer diagnosis: ATM, CHEK2, BARD1 and RAD51D. The Breast **65**, 32–40.

Graham E, Rampazzo L, Leung CW, Wall J, Gerőcz EZ, Liskovykh M, Goncharov N, Saayman X, Gundogdu R, Kanemaki MT, Masumoto H. 2025. The homologous recombination factors BRCA2 and PALB2 interplay with mismatch repair pathways to maintain centromere stability and cell viability. Cell Reports **44**(2).

Hanker A, Rajkumar KS, He Z, Ohneda O, Nguyen HN, Kawahara M, Vuong CK, Fukushige M, Yamashita T. 2023. Women in breast cancer: 2022, volume II. **6**.

Huber-Keener KJ. 2022. Cancer genetics and breast cancer. Best Practice & Research Clinical Obstetrics & Gynaecology **82**, 3–11.

Joshi DC, Sharma A, Prasad S, Singh K, Kumar M, Sherawat K, Tuli HS, Gupta M. 2024. Novel therapeutic agents in clinical trials: Emerging approaches in cancer therapy. Discover Oncology **15**(1), 342.

Kaur S, Singh D. 2024. Genetic contribution to breast cancer: A critical analysis of penetrance alleles as susceptible genes. Journal of Exploratory Research in Pharmacology **9**(1), 60–64.

Khalizieva A, Moser SC, Bouwman P, Jonkers J. 2025. BRCA1 and BRCA2: From cancer susceptibility to synthetic lethality. Genes & Development **39**(1–2), 86–108.

Kotamkar S, Jha RK, Bankar N. 2021. A brief research on cancer. Journal of Pharmaceutical Research International **33**(38B), 323–329.

Lee JH. 2024. Targeting the ATM pathway in cancer: Opportunities, challenges and personalized therapeutic strategies. Cancer Treatment Reviews **129**, 102808.

Liao YC, Wang LH, Hung MC, Cheng TC, Lin YC, Chang J, Tu SH, Wu CH, Yen Y, Hsieh YC, Chen LC. 2024. Investigation of the α9-nicotinic receptor single nucleotide polymorphisms induced oncogenic properties and molecular mechanisms in breast cancer. Human Molecular Genetics **33**(22), 1948–1965.

Lim PX, Zaman M, Feng W, Jasin M. 2024. BRCA2 promotes genomic integrity and therapy resistance primarily through its role in homology-directed repair. Molecular Cell **84**(3), 447–462.

Liu H, Dong A, Rasteh AM, Wang P, Weng J. 2024. Identification of the novel exhausted T cell CD8+ markers in breast cancer. Scientific Reports **14**(1), 19142.

Liu YP, Zheng CC, Huang YN, He ML, Xu WW, Li B. 2021. Molecular mechanisms of chemo- and radiotherapy resistance and the potential implications for cancer treatment. MedComm **2**(3), 315–340.

Luo C, Wang P, He S, Zhu J, Shi Y, Wang J. 2022. Progress and prospect of immunotherapy for triple-negative breast cancer. Frontiers in Oncology **12**, 919072.

Mbuya-Bienge C, Pashayan N, Kazemali CD, Lapointe J, Simard J, Nabi H. 2023. A systematic review and critical assessment of breast cancer risk prediction tools incorporating a polygenic risk score for the general population. Cancers **15**(22), 5380.

McClellan JC, Li JL, Gao G, Huo D. 2024. Expression- and splicing-based multi-tissue transcriptome-wide association studies identified multiple genes for breast cancer by estrogen-receptor status. Breast Cancer Research **26**(1), 51.

Mendes J, Domingues J, Aidos H, Garcia N, Matela N. 2022. AI in breast cancer imaging: A survey of different applications. Journal of Imaging **8**(9), 228.

Nabi N, Nisa MU, Khan MS, Gillani SQ. 2025. Role of signaling pathways regulating cell cycle progression in cancer. In Cell Signaling Pathways and Their Therapeutic Implication in Cancers. Singapore: Springer Nature Singapore, 357–393.

Nath A, Taneja R, Thadi YS, Sarveswaran G, Mathur P. 2024. A comparative study of incidence, mortality and disability adjusted life years (DALYs) for leading cancers in BRICS countries. ecancermedicalscience **18**, 1773.

Neagu AN, Bruno P, Johnson KR, Ballestas G, Darie CC. 2024. Biological basis of breast cancer-related disparities in precision oncology era. International Journal of Molecular Sciences **25**(7), 4113.

Neiger HE, Siegler EL, Shi Y. 2021. Breast cancer predisposition genes and synthetic lethality. International Journal of Molecular Sciences **22**(11), 5614.

Nenclares P, Harrington KJ. 2020. The biology of cancer. Medicine **48**(2), 67–72.

Pal M, Das D, Pandey M. 2024. Understanding genetic variations associated with familial breast cancer. World Journal of Surgical Oncology **22**(1), 271.

Pappas K, Ferrari M, Smith P, Nandakumar S, Khan Z, Young SB, LaClair J, Russo MV, Huang-Hobbs E, Schultz N, Abida W. 2025. BRCA2 reversion mutation–independent resistance to PARP inhibition through impaired DNA prereplication complex function. Proceedings of the National Academy of Sciences **122**(23), e2426743122.

Pasaol JC, Śmieszek A, Pawlak A. 2025. Exploring the therapeutic potential of BRCA1 and BRCA2 as targets in canine oncology: A comprehensive review of their role in cancer development and treatment. International Journal of Molecular Sciences **26**(4), 1768.

Peleg Hasson S, Menes T, Sonnenblick A. 2020. Comparison of patient susceptibility genes across breast cancer: Implications for prognosis and therapeutic outcomes. Pharmacogenomics and Personalized Medicine **13**, 227–238.

Pezzoli P, McCrory EJ, Viding E. 2024. Shedding light on antisocial behavior through genetically informed research. Annual Review of Psychology **76**.

Podralska M, Sajek MP, Bielicka A, Żurawek M, Ziółkowska-Suchanek I, Iżykowska K, Kolenda T, Kazimierska M, Kasprzyk ME, Sura W, Pietrucha B. 2024. Identification of ATM-dependent long non-coding RNAs induced in response to DNA damage. DNA Repair **135**, 103648.

Pourmasoumi P, Moradi A, Bayat M. 2024. BRCA1/2 mutations and breast/ovarian cancer risk: A new insights review. Reproductive Sciences **31**, 1–1.

Qian H, Ali H, Karri V, Low JT, Ashley DM, Heimberger AB, Godley LA, Sonabend AM, Dmello C. 2025. Beyond DNA damage response: Immunomodulatory attributes of CHEK2 in solid tumors. Oncotarget **16**, 445.

Rahmati M, Ebrahimi E, Shirkoohi R, Mahmoodzadeh H, Mohammanjad A, Malekisarvar H, Valizadeh Z, Dehghani M, Haghighat S, Marzban M, Zendehdel K. 2023. Study of CDH1 germline mutation in hereditary diffuse gastric cancer and lobular breast cancer: A multicenter study in Iran. Basic & Clinical Cancer Research **15**(2), 130–139.

Rameshkumar A, ArunPrasanna V, Mahalakshmi V, Raja MR, Gopinath K. 2024. Recent advancement of analytical approaches for assessing Ataxia telangiectasia mutated kinase inhibitors in Ataxia telangiectasia: An overview. Process Biochemistry **144**, 142–159.

Razack NA, Prabhuswamimath SC. 2024. Exploring high-penetrance genes in breast cancer associated genetic syndromes: Insights into genetic predisposition and clinical implications. International Journal of Health and Allied Sciences **13**(1), 6.

Reid S, Pal T. 2020. Update on multi-gene panel testing and communication of genetic test results. The Breast Journal **26**(8), 1513–1519.

Rocca V, Lo Feudo E, Dinatolo F, Lavano SM, Bilotta A, Amato R, D'Antona L, Trapasso F, Baudi F, Colao E, Perrotti N. 2024. Germline variant spectrum in southern Italian high-risk hereditary breast cancer patients: Insights from multi-gene panel testing. Current Issues in Molecular Biology **46**(11), 13003–13020.

Rodrigues LM, Maistro S, Katayama ML, Rocha VM, Lopez RV, Lopes EF, Gonçalves FT, Fridman C, Serio PA, Barros LR, Leite LA. 2024. Prevalence of germline variants in Brazilian pancreatic carcinoma patients. Scientific Reports **14**(1), 21083.

Saundarya LA, Gunathilaka MD. 2024. Genetic predisposition to breast cancer: Understanding the role of susceptible genes and the impact of hereditary mutation. University of Colombo Review **5**(2).

Shumilova S, Danishevich A, Nikolaev S, Krasnov G, Ikonnikova A, Isaeva D, Surzhikov S, Zasedatelev A, Bodunova N, Nasedkina T. 2024. High- and moderate-risk variants among breast cancer patients and healthy donors enrolled in multigene panel testing in a population of central Russia. International Journal of Molecular Sciences **25**(23), 12640.

Swaminathan H, Saravanamurali K, Yadav SA. 2023. Extensive review on breast cancer: Its etiology, progression, prognostic markers, and treatment. Medical Oncology **40**(8), 238.

Valentini V, Bucalo A, Conti G, Celli L, Porzio V, Capalbo C, Silvestri V, Ottini L. 2024. Gender-specific genetic predisposition to breast cancer: BRCA genes and beyond. Cancers **16**(3), 579.

Varadhan V, Manikandan MS, Nagarajan A, Palaniyandi T, Ravi M, Sankareswaran SK, Baskar G, Wahab MR, Surendran H. 2024. Ataxia-Telangiectasia Mutated (ATM) gene signaling pathways in human cancers and their therapeutic implications. Pathology - Research and Practice **260**, 155447.

Wang L, Jin Z, Master RP, Maharjan CK, Carelock ME, Reccoppa TB, Kim MC, Kolb R, Zhang W. 2022. Breast cancer stem cells: Signaling pathways, cellular interactions, and therapeutic implications. Cancers **14**(13), 3287.

Wong SM, Apostolova C, Ferroum A, Alhassan B, Prakash I, Basik M, Martel K, Meterissian S, Fleiszer D, Wong N, Sadinsky MB. 2025. Chemotherapy receipt in affected BRCA1/2 and PALB2 carriers with operable breast cancer: The impact of early detection and pre-diagnostic awareness on clinical outcomes and treatment. Hereditary Cancer in Clinical Practice **23**(1), 14.

Xu Z, Xie H, Song L, Huang Y, Huang J. 2025. BRCA1 and BRCA2 in DNA damage and replication stress response: Insights into their functions, mechanisms, and implications for cancer treatment. DNA Repair **118**, 103847.

Zulfiqar A, Rauf A, Rasool E, Yousaf F, Nudrat A, Farooq M, Munawar A. 2024. Assessing long-term non-genetic risk factors for breast cancer. In: Asad M, Hussain R, Toor SI, Mughal MAS, Ahmad M (eds), Complementary and Alternative Medicine: Non-Conventional Therapies. Unique Scientific Publishers, Faisalabad, Pakistan, 122–129.