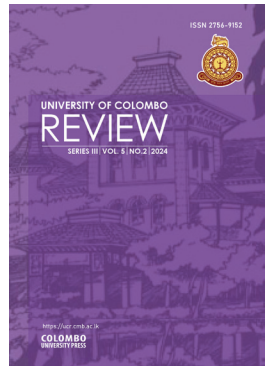

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Genetic Predisposition to Breast Cancer: Understanding the role of Susceptible Genes and the impact of Hereditary Mutation

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ABSTRACT

Breast cancer is the most frequently diagnosed cancer in women worldwide. In 2018, there were 2.1 million [2.0–2.2 million] recorded cases of breast cancer, resulting in 626,679 deaths (Sharma, 2021), while by 2020, an additional 2.26 million new cases were reported. Both benign and malignant tumors can develop in the breast. However, the vast majority of breast lumps are benign. Benign tumors are less life-threatening and less likely to spread, while malignant tumors can invade tissues and spread through the bloodstream or lymphatic system. Among several risk factors of breast cancer, heredity plays a main role and accounts for 5-10% of breast cancer cases. Positional cloning and genome-wide linkage analysis are techniques used to identify genes associated with specific traits or diseases. Positional cloning focuses on specific regions of DNA, while genome-wide linkage analysis examines the DNA of entire families. Both methods are used to narrow down the search for genes involved in inherited diseases. Based on the positional cloning and genome-wide linkage analysis, the two main breast cancer risk genes, *BRCA1* and *BRCA2*, were identified together with other breast cancer susceptibility genes including *CDH1, TP53, PTEN, NF1, STK11, PALB2, CHEK2,* and *ATM*. This review discusses the ten major or commonly known breast cancer susceptible genes and how variations in these genes could lead to breast carcinogenesis. Although progress has been made in identifying genes linked to breast cancer risk, more research is necessary to fully understand these genetic factors and improve prevention and treatment strategies.

KEYWORDS:

BRCA1 gene, *BRCA2* gene, Breast Cancer, Classification, Common breast cancer susceptible genes, High-risk susceptibility genes

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Introduction

Breast cancer ranks as the second most common cause of cancer-related deaths among women (American Cancer Society, 2016) and it is the most frequently diagnosed cancer globally, primarily affecting women, though men can also be diagnosed, and accounting for 2.3 million new cases each year. Among all cancer diagnoses, one in eight cases is breast cancer, with a quarter of all female cancer patients being affected by it. In 2020, breast cancer was the leading cancer diagnosis in women, with its prevalence on the rise in many regions. Tragically, breast cancer claimed the lives of 685,000 women in the same year, making up 16% of all cancer-related deaths among women, equivalent to 1 in every 6 cancer fatalities in women (Arnold et al, 2022). In Sri Lanka, breast cancer remains the most common cancer among women, with approximately 3,000 new cases diagnosed annually (Balawardena et al, 2020).

Breast cancer development is influenced by factors like risky alcohol use, genetic history, radiation exposure, aging, reproductive history, smoking, estrogen, and postmenopausal hormone treatment (Sun et al., 2017). Genetic mutations, particularly in *BRCA1* (Breast Cancer Gene 1) and *BRCA2* (Breast Cancer Gene 2), significantly contribute to familial breast cancer (Zubair et al., 2021). Population-based studies on *BRCA1* and *BRCA2* mutation screening in breast cancer patients support the existence of additional susceptibility genes such as *PALB2, CHEK2,* and *TP53* (Palmero et al., 2016). In addition, there are some other genes involved with the development and progression of breast cancer including *CDH1, PALB2, ATM, PTEN, NF1, STK11, CHEK2,* and *TP53* (Hu et al., 2021, Gage et al., 2012).

Some genetic mutations are linked to an increased risk of various cancers. For example, mutations in the *CDH1* gene can elevate the risk of hereditary diffuse gastric cancer, a rare form of stomach cancer, as well as invasive lobular breast cancer. Similarly, mutations in the *STK11* gene can cause Peutz-Jeghers syndrome, which heightens the risk of multiple types of cancer, including breast cancer. This syndrome can be associated with more than one type of breast cancer(Sun et al., 2017). Known susceptibility genes can account for about 15-20% of the family aggregation of breast cancer. This indicates that environmental as well as genetic variables may influence heredity, and more investigation is required to find these variables and understand their role in the development of breast cancer (Wendt & Margolin, 2019). This review explores the ten most common breast cancer susceptibility genes and the genetic mutations leading to hereditary breast cancer predispositions. This review provides a foundation for future research to identify specific genetic changes involved in breast cancer development within common breast cancer susceptibility genes.

Prevalence of Breast Cancer: World and Sri Lankan Statistics

Global Prevalence

In 2020, breast cancer was the most frequently diagnosed cancer globally, with an incidence of approximately 11.7%. Colorectal, lung, prostate, and stomach cancer incidence rates were also reported to be 10%, 11.4%, 7.3%, and 5.6%, respectively. Lung cancer accounted for the highest percentage (Sung et al., 2021) of cancer fatalities among them (18.0% of all cancer deaths), as shown in Figure 1.

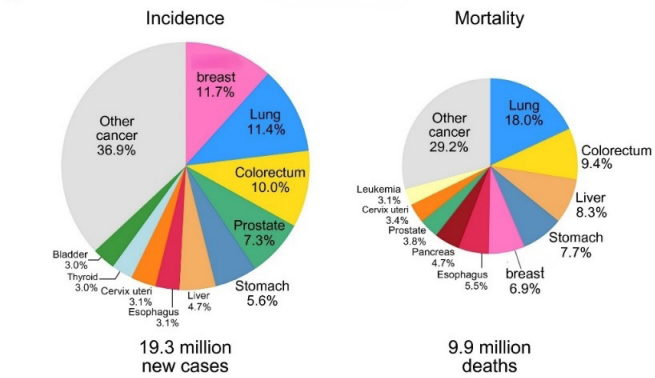

Figure 1: Global distribution of cancer cases and deaths for the most common types of cancers in 2020 (Sung et al, 2021).

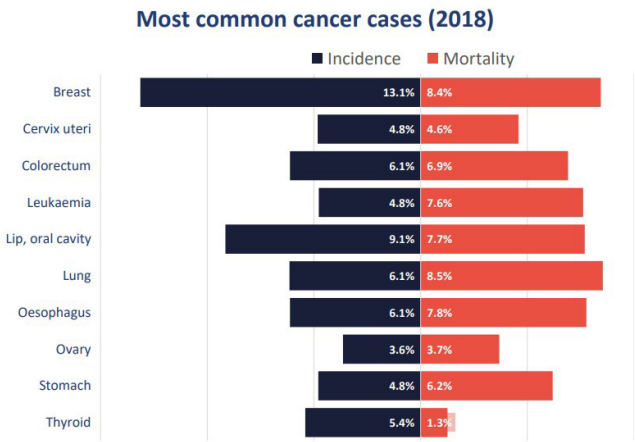

Figure 2: Distribution of cancer cases and deaths in Sri Lanka for the top 10 most common cancers in 2018 (World Health Organization, 2020).

Sri Lankan Prevalence

In Sri Lanka, there were an estimated 14,013 cancer deaths and 23,530 newly diagnosed cases in 2018. As in Figure 2, breast cancer accounted for 13.1% of all cases of cancer that have been reported, followed by cases of the lip/oral cavity (9.1%), esophagus (6.1%), colorectal cancer (6.1%), lung cancer (6.1%), thyroid cancer (5.4%), cervix uteri (4.8%), leukemia (4.8%), stomach (4.8%), and ovarian cancer (3.6%).

Moreover, the data also provide insight into the specific locations within the breast where cancer occurred in females. While the majority of cases were categorized as "breast, unspecified (C509)" with 4,592 cases (accounting for 83.7% of all female cases), other areas are worth noting. The upper-outer quadrant (C504) saw 353 cases (6.4% of female cases), and the lower-outer quadrant (C505) had 107 cases (2.0% of female cases) (Cancer Incidence & Mortality Date Sri Lanka 2021, n.d.).

Etiological factors of breast cancer

Several factors have been identified as etiological causes of the illness. These elements fall into three broad categories.

Genetic or familial factors

The 1990s saw the discovery of more breast cancer genes with a medium to considerable chance of producing breast cancer. Advancements in genomic technology have enabled genome-wide association studies to identify numerous low-penetrance genetic regions linked to breast cancer. High-risk genes, including *BRCA1, BRCA2, TP53, CDH1, STK11*, and *PTEN*, account for approximately 20% of familial breast cancer risk. Moderate penetrance, in risk can account for up to 5%. Over 180 low-risk gene locations, accounting for 18% of the overall family risk, have been identified. Those genetic and low-risk loci that made a significant contribution to the remaining percentage are likely to be found, even though the genetic occurrence of breast cancer is still unknown and is familial (Wendt & Margolin, 2019).

Endocrine factors

Factors influencing breast exposure to estrogen and progesterone include age at menarche and menopause, pregnancy and breastfeeding history, postmenopausal obesity, adult weight gain, exogenous hormone use, and physical activity. Estrogen promotes ductal development and accelerates cell division, both of which might raise the risk of random genetic mistakes (Calaf et al., 2020). Genes involved in DNA repair, hormone metabolism and transport, tumor suppressor genes, and oncogenes are among those that are regarded as significant in this model. Hormone-induced cell proliferation can alter sensitivity to mitogens or carcinogens, while genes involved in carcinogen metabolism may influence breast cancer development (Zubair et al., 2021).

Environmental factors

Laboratory and human studies support the role of genotoxic chemicals, which alter mammary gland growth, hormonal response, and promote tumor formation. Genotoxic substances alter a cell's genetic makeup, which may result in cancer-causing mutations. Ionizing radiation increases the risk of breast cancer in both men and women, serving as a model for carcinogenic mechanisms similar to those of conventional carcinogens. The greatest risk factor for breast cancer is early-life exposure to ionizing radiation (Rodgers et al., 2018). Hormonal changes and lifestyle habits like alcoholism and obesity are possible risk factors for breast cancer (Sun et al., 2017).

Etiological factors of breast cancer

Classifying tumors is essential for understanding their nature, treatment options, and potential outcomes. Proper classification enables healthcare professionals to determine the best course of action for patients, ultimately impacting prognosis and survival rates (Feng et al., 2018a).

Main classifications of tumors

Tumors can primarily be classified into two categories; benign and malignant. Understanding these classifications helps in assessing the behavior of the tumors and the necessary interventions.

Benign tumors are defined by several distinct characteristics. Their cell composition consists of cells that closely resemble healthy tissue. In terms of growth behavior, benign tumors grow at a slow rate and are localized in their development. Furthermore, these tumors do not invade adjacent tissues or organs, and they do not metastasize, meaning they do not spread to other regions of the body. Conversely, malignant tumors exhibit a different profile. Their cell composition includes abnormal cells that diverge significantly from normal cells. Malignant tumors demonstrate uncontrolled growth and division, indicative of aggressive proliferation. Additionally, they possess the ability to invade surrounding tissues and organs and can metastasize, spreading throughout the body via the lymphatic or circulatory systems(Punitha et al, 2018).

Early detection and treatment of malignant tumors are crucial for improving patient prognosis and managing outcomes effectively. Understanding the distinctions between benign and malignant tumors aids in providing appropriate medical care (Chaurasia et al, 2018).

Breast cancer can be categorized in several ways. Diagnoses, prognoses, and forecasts regarding the condition are all goals of classification. According to the World Health Organization (WHO), breast cancer has been classified based on several categories: invasive breast carcinoma, epithelial tumors, neuroendocrine

neoplasms, rare and salivary gland-type tumors, epithelial-myoepithelial tumors, fibroepithelial tumors, papillary neoplasms, mesenchymal tumors, metastatic tumors, tumors of the nipple, as well as precursors, malignant lymphoma, and tumors of the male breast (Sinn & Kreipe, 2013). Breast cancer types are further classified based on tumor characteristics and behavior, crucial for accurate diagnosis, treatment, and prognosis. Additionally, ongoing research aims to identify new subtypes and refine existing classifications to improve patient outcomes (Zubair et al., 2021).

Breast cancers are generally classified into three main categories: histological classification, functional classification, and molecular classification, as shown in Figure 3. Histological classification focuses on the microscopic structure and appearance of tissues, allowing for the identification of various diseases, particularly cancers, based on their cellular composition and arrangement. Functional classification is based on the specific roles and functions of the tissues or organs within a biological system. It typically includes categories such as epithelial (covering), connective (supportive), muscular (movement), and nervous (signal transmission) tissues. The molecular classification approach categorizes tissues or tumors based on their molecular and genetic characteristics. It involves analyzing the expression of particular genes, proteins, or biomolecules, facilitating insights into the underlying mechanisms of diseases, and guiding the development of targeted therapies (Schmitt, 2016).

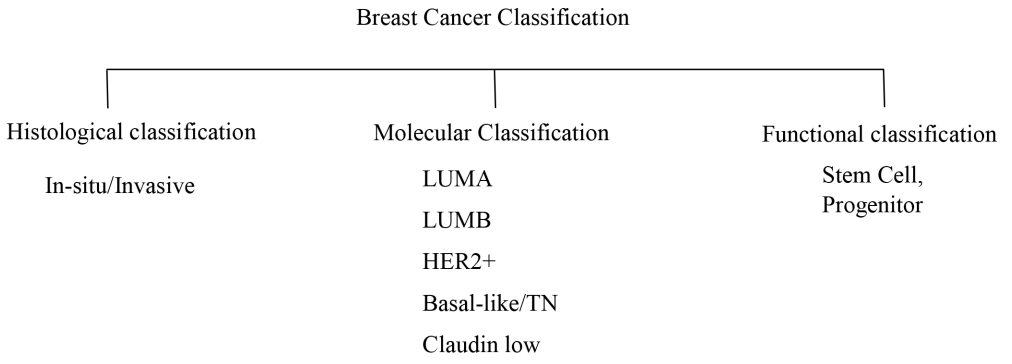

Figure 3: Breast cancer classification (Schmitt, 2016).

As shown in Figure 4, breast cancer is divided into two categories depending on the histological appearance of the breast tissue: in situ carcinoma and invasive (infiltrating) carcinoma. Based on cytological traits and development patterns, in situ breast cancers are also classified as ductal and lobular subtypes (Malhotra et al., 2010).

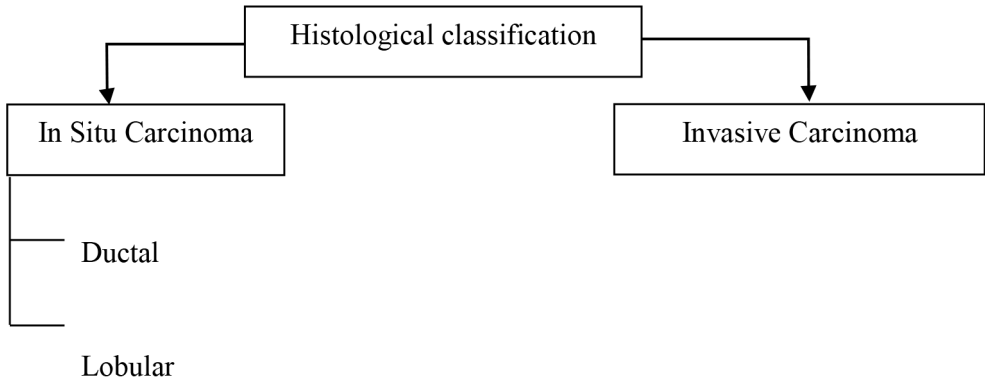

Figure 4: Histological classification of breast cancers (Malhotra et al., 2010).

The functional classification of breast cancer depends on breast cancer stem cells that reveal molecular subtypes as shown in Figure 5. Cancer stem cells (CSCs) are identified as tumor-initiating cells in various cancers with limited tumorigenic potential, but a small number are responsible for tumor initiation and development. CSCs' origin is unclear; two theories suggest normal or common stem cell origin; isolation and identification techniques are uncertain due to rapid field expansion (Stingl & Caldas, 2007).

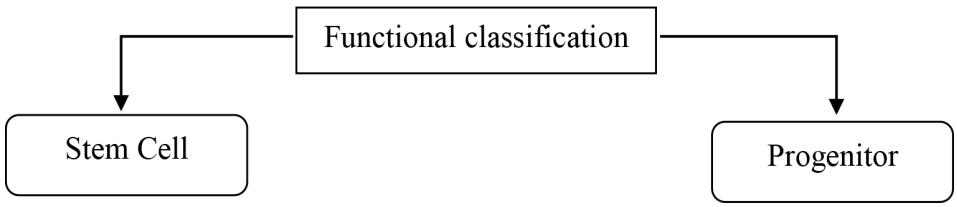

Figure 5: Functional classification of breast cancers (Malhotra et al., 2010).

Figure 6 shows the molecular classification of breast cancer which includes subgroups such as luminal A, luminal B, triple-negative, HER-2, and claudin-low (Herschkowitz et al., 2007). Luminal A breast cancers are characterized by the expression of estrogen receptor (ER) and progesterone receptors (PR), low proliferation, and a better prognosis (Höller et al., 2023). Luminal B tumors have ER and PR positivity and express the HER-2 gene in younger female patients, but have worse prognoses due to lower-grade tumors, larger diameters, and lymph node involvement (Jin et al., 2017). Triple-negative breast cancers do not express ER, HER-2, or PR, are often basal-like, and account for 15%–20% of cases, commonly affecting younger women. Most *BRCA1*-associated breast cancers are basal-like and triple-negative (Malhotra et al., 2010). *HER-2* breast cancer is characterized

by negative ER and PR status, lymph node involvement, lower tumor grade, poor prognosis, and higher recurrence and spread rates. It is often diagnosed earlier than luminal A or B cancers (Jin et al., 2017). Claudin-low tumors have reduced adhesion proteins, lymphocyte infiltration, stem cells, and mesenchymal cell characteristics (Herschkowitz et al., 2007). Normal-like tumors, which represent 6%–10% of breast cancer cases, are typically small and have a favorable prognosis (Jin et al., 2017).

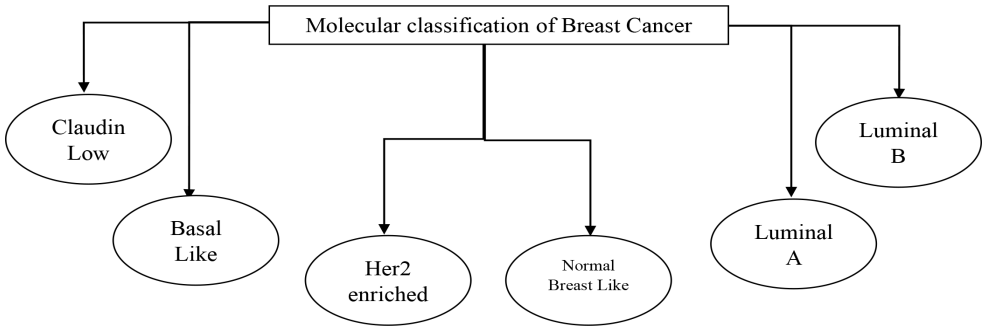

Figure 6: Molecular classification of breast cancers (Malhotra et al., 2010).

Breast cancer susceptibility genes

The likelihood of developing breast cancer increases with the number of affected relatives and the early onset of the disease (Lalloo & Evans, 2012). Around 5–10% of all cases of breast cancer cases follow an autosomal dominant Mendelian inheritance pattern, classifying them as hereditary. Women with two or more first- or second-degree relatives diagnosed with breast cancer are considered to have familial breast cancer, which accounts for an additional 15–25% of cases. At least 30% of familial breast cancer cases are thought to result from germline mutations in the highly penetrant *BRCA1* and *BRCA2* genes (Economopoulou et al., 2015). Advancements in sequencing technology have enabled the simultaneous testing of multiple genes, allowing the identification of both high- and moderate-risk genes linked to breast cancer. It is crucial to identify the newly discovered hereditary breast cancer syndromes so that those who are afflicted can get genetic counseling, testing, screening, and preventative efforts (Kwilas et al., 2015).

Breast cancer susceptibility genes have been discovered using a variety of methods. These risk alleles may generally be categorized into three groups based on their frequency and level of risk (Wendt & Margolin, 2019). They are high-risk breast cancer susceptibility genes, moderate-risk breast cancer susceptibility genes, and low risk breast cancer susceptibility genes (Turnbull & Rahman, 2008). High-risk variants are extremely rare, with a minor allele frequency of less than 0.005, and they carry a relative risk of breast cancer greater than four. In contrast, moderate-risk variants have a minor allele frequency ranging from 0.005 to 0.01 and confer a

relative risk between two and four. Finally, low-risk variants are more common, with a minor allele frequency exceeding 0.05, and they are associated with a relative risk of less than 1.5 (Wendt & Margolin, 2019).

High-risk breast cancer susceptibility genes

Specific familial breast cancer syndromes, which result from mutations in a single gene that carries a significant risk, lead to clustering of breast cancer cases within families. *BRCA1* and *BRCA2* are the most well-known high-risk breast cancer susceptibility genes, each conferring a lifetime risk greater than fourfold (Wendt & Margolin, 2019). Mutations in these genes are rare, with *BRCA1* mutations occurring in 1 in 800 individuals and *BRCA2* mutations in 1 in 500. However, carriers face a 10- to 30-fold increased risk of developing breast cancer compared to non-carriers (Ghoussaini et al., 2013). These alleles also predispose to other cancer types, including ovarian and prostate cancers. Deleterious alleles in other genes conferring a similar risk to *BRCA1* and *BRCA2* may exist, but they are likely to be rare because approximately 84% of families with four or more cases of breast cancer diagnosed at age younger than 60 years can be explained by mutations in *BRCA1* or *BRCA2* (Ghoussaini et al., 2013). A high risk of 40–60% for breast cancer has been linked to several other rare disorders. Such as, mutations in *PTEN, STK11*, and E-Cadherin (*CDH1*) which causes Cowden syndrome; Peutz-Jeghers syndrome, and hereditary diffuse gastric cancer, respectively (Lalloo & Evans, 2012). Therefore, the mutations in the *BRCA1* and *BRCA2* genes significantly increase the risk of breast cancer and are found in a small percentage of individuals, while other rare genetic disorders also contribute to elevated breast cancer risks.

Moderate-risk breast cancer susceptibility genes

Four moderate-risk breast cancer genes have been identified via mutational screening: *CHEK2, ATM, BRIP1*, and *PALB2* (Turnbull & Rahman, 2008). Linkage analysis of a large non-BRCA family allowed for the localization of the first moderate-risk gene, *CHEK2* (1100delC) (Meijers-Heijboer et al., 2002). As moderate-risk genes exhibit unclear inheritance patterns as a result of their intermediate penetrance, linkage analysis, and an association study were coupled to quantify the transferred risk. Therefore, for discovering moderate-risk genes, the candidate gene technique is more useful (Wendt & Margolin, 2019). Genes with moderate susceptibility have been discovered through resequencing in cases from families with high penetrance, and these genes have subsequently been tested in case-control association studies.

Moderate-risk breast cancer genes; *CHEK2, ATM, BRIP1*, and *PALB2*, show unclear inheritance due to intermediate penetrance. *CHEK2* was identified through linkage analysis in a non-BRCA family. The candidate gene technique and case-control studies have helped discover these genes from high-penetrance families.

Low-risk breast cancer susceptibility genes

Approximately 25% of breast cancer heritability can be attributed to harmful mutations in high- and moderate-penetrance genes. The remaining heritability is likely due to a mix of common and rare genetic risk variants with varying degrees of penetrance and population frequency. Common low-risk variants, defined by a minor allele frequency (MAF) greater than 0.05%, generally confer a small increased risk of breast cancer, typically less than 1.5-fold, and because of their low penetrance, these variants are difficult to detect using traditional pedigree-based linkage studies. As a result, during the past ten years and more, population-based genetic association studies to find these risk variations have become increasingly important (Dalivandan et al., 2021). Several low-risk breast cancer susceptibility genes and chromosomal loci have been identified through genome-wide association studies (GWAS), including FGFR2, LSP1, MAP3K1, TGFB1, TOX3, and loci on chromosomes 2q and 8q (Ripperger et al., 2009).

About 25% of breast cancer heritability is linked to harmful mutations in high- and moderate-penetrance genes, while the rest is attributed to a mix of common and rare genetic variants with low risk, identified through recent population-based genetic association studies(Shiovitz & Korde, 2015).

Most common breast cancer susceptibility genes

BRCA1, BRCA2, and several other genes associated with breast cancer susceptibility, such as *ATM, PTEN, NF1, STK11, CHEK2*, and *TP53*, play a crucial role in understanding hereditary risks and cancer development. These genes are important for cellular repair mechanisms and the normal functioning of breast, ovarian, and other tissues. When mutations occur in *BRCA1* and *BRCA2*, often passed down through generations, the genes lose their ability to repair cellular damage effectively. This impairment significantly increases the likelihood of developing breast cancer, ovarian cancer, and other malignancies(Sokolova et al., 2023).

Research shows that *BRCA1* and *BRCA2* mutations account for approximately 10% of breast cancer cases, illustrating their impact on genetic susceptibility (Jin et al., 2017). Women carrying these mutations not only face a heightened risk of developing breast cancer but are also likely to encounter it at an earlier age compared to those without such genetic variations.

In addition to *BRCA1* and *BRCA2*, other less common inherited mutations contribute to breast cancer risk, though these atypical gene alterations are significantly rarer (Feng et al., 2018b). The implications of these mutations extend beyond breast and ovarian cancers; they are also linked to increased risks for other cancers, including colon, prostate, pancreatic, melanoma, and gastric cancers. For women with *BRCA1* or *BRCA2* germline mutations, the probability of developing breast cancer can be

as high as 60% to 80%, with a similarly elevated risk for ovarian cancer in women and prostate cancer in men. Mutations in *BRCA1* and *BRCA2*, though rare, often involve small insertions, deletions, nonsense mutations, missense mutations, or splicing errors, all of which can lead to the production of truncated or non-functional proteins. These mutations frequently result in the production of a truncated, non-functional protein, which impairs the cell's ability to repair DNA, thereby increasing cancer risk (Jin et al., 2017). In addition to *BRCA1* and *BRCA2,* other high-risk genes associated with breast cancer include *PALB2*, *ATM, TP53, CHEK2, PTEN, CDH1, NF1,* and *STK11*, all of which are involved in processes like DNA repair, cell growth regulation, and tumor suppression (Wendt & Margolin, 2019). The causative genes along with the estimated lifetime risk of breast cancer are presented in Table 1.

Table 1: Causative gene and the estimated lifetime risk of breast cancer (Kwong et al., 2016)

Gene	Estimated lifetime risk of breast cancer
BRCA1	55-65%
BRCA2	45-47%
CDH1	39-52%
PALB2	33-58%
ATM	15-52%
PTEN	25-50%
NF1	25-30%
STK11	30-50%
CHEK2	20-44%
TP53	49-60%

Breast Cancer gene 1 (BRCA1) and Breast Cancer gene 2 (BRCA2)

The *BRCA1* and *BRCA2* genes are the two most frequently found genes in breast cancer and ovarian cancer that are autosomal dominant and have high penetrance variants. *BRCA1* and *BRCA2* are classified as tumor suppressor genes (TSGs) because they produce proteins that help repair damaged DNA, preventing uncontrolled cell growth and tumor development. Cancer researchers have spent years figuring out how genes called tumor suppressors (TSGs) prevent cancer. According to the two-hit hypothesis, both copies of a tumor suppressor gene must be altered or silenced before it can lead to cancer development. One mutation in a TSG is not enough because its effects are recessive within a cell. However, the discussion

indicates that the implications extend beyond mere mutations. Sometimes, these TSGs get turned off without any changes to their DNA code, or they get broken down or misplaced inside the cell. Additionally, problems with how these genes get turned on and off can also play a role. To summarize, there are numerous mechanisms through which tumor suppressor genes (TSGs) may lose their function, each of which can contribute to cancer development (L. H. Wang et al., 2019). Mutations in the *BRCA1* and *BRCA2* genes significantly increase the risk of certain cancers. The *BRCA1* gene, located on chromosome 17q, is primarily associated with an elevated risk of breast and ovarian cancer. Similarly, alterations in the *BRCA2* gene, found on chromosome 13q, also heighten the risk for breast and ovarian cancers, as well as prostate cancer. Both genes play a crucial role in maintaining genomic stability, and their mutations can lead to the development of these malignancies (Kwong et al., 2016). These two genes create TSG proteins and function as cell growth inhibitors. There are 1,863 amino acids in the *BRCA1* protein, and three hundred disease-causing mutations have so far been identified in this gene. There are 3,418 amino acids in the *BRCA*2 protein. These proteins, also known as anti-oncogenes, support cellular DNA repair and genetic material preservation. As a result, if a single of these two genes is broken, damaged DNA would not be repaired, which may also result in further alterations and mutations in cell DNA that ultimately result in cancer (Kwong et al., 2016). Up to 72% of women who carry a *BRCA1* or *BRCA2* mutation (or both) throughout their lifetimes may get breast cancer (Kuchenbaecker et al., 2017). When compared to breast tumors in women without these genetic abnormalities, those linked with *BRCA1* or *BRCA2* tend to manifest in younger patients and more frequently affect both breasts. Ovarian, pancreatic, colon, and melanoma cancers are also more prevalent in women with *BRCA1* or *BRCA2* mutations. At the age of 80, men with *BRCA2* mutations have an 8% lifetime risk of developing breast cancer, which is significantly higher than in the general population, and an elevated risk of prostate cancer (Feng et al., 2018b). Men with either a *BRCA1* or *BRCA2* mutation may also have modestly increased risks for other cancers, such as skin or digestive system cancer (Tai et al., 2007).

In the 1990s, researchers uncovered the *BRCA1* and *BRCA2* genes as key factors in hereditary breast cancer. Women with a *BRCA1* mutation have a lifetime risk of breast cancer between 57% and 60%, while those with a *BRCA2* mutation face a risk of 49% to 55%. Women with *BRCA1* mutations have a 39-46% lifetime risk of ovarian cancer, compared to 10-27% for *BRCA2* mutation carriers (Kwong et al., 2016).

Cadherin 1 (CDH1)

The *CDH1* gene, located on chromosome 16q22.1, encodes the protein E-cadherin, which is crucial for maintaining cell-to-cell adhesion and tissue integrity.

It plays a key role in regulating cell maturation, migration, and gene activity (Sengupta & Banerjee, 2021).

As a tumor suppressor, E-cadherin prevents uncontrolled cell growth by maintaining proper cell adhesion. Loss of E-cadherin due to *CDH1* mutations leads to cell proliferation and tumor development. At the mRNA level, *CDH1* is one of the genes with the greatest differences in expression among ductal and lobular carcinomas (Economopoulou et al., 2015). Mutations in the *CDH1* gene, which impair E-cadherin function, are strongly associated with invasive lobular breast cancer (ILBC). Women with *CDH1* mutations face a lifetime risk of developing ILBC ranging from 39% to 52% (Liu & Chu, 2014).

Breast cancer risk among *CDH1* carriers ranges from around 40% to 60% throughout a woman's lifetime. Interestingly, these mutations, while significant in their potential impact, are quite rare, occurring in fewer than 1% of pathogenic variants. This highlights the unique challenge of addressing breast cancer risk in this specific group of individuals (Frey et al., 2017).

Families with *CDH1* germline mutations have significant aggregation for lobular breast cancer (LBC) (Kaurah & Huntsman, 2019). The criteria for *CDH1* genetic testing were broadened after germline mutations were found in individuals with early-onset diffuse gastric cancer (DGC) and lobular breast cancer (LBC) without a family history of DGC (van der Post et al., 2015).

Partner and localizer of BRCA2 (PALB2)

PALB2, which partners with *BRCA2*, plays a crucial role in DNA repair, specifically in homologous recombination and the repair of double-strand breaks. Loss-of-function mutations increase the incidence of familial breast cancer by 2–4 times compared to non-mutation carriers (Kwong et al., 2016). Women with a *PALB2* mutation face a 14% risk of breast cancer by age 50, which increases to 35% by age 70. In addition, 58% of those with a family history of breast cancer will develop it by the age of seventy (Thomas & Brown, 2015). For comparison, women with *BRCA1* mutations have a 50-70% chance of developing breast cancer by age 70, while those with *BRCA2* mutations have a 40-60% chance.

The risk of breast cancer in *PALB2* mutation carriers is further increased in those with a family history of breast or ovarian cancer, highlighting the strong genetic component of the disease (Antoniou et al., 2014, Kwong et al., 2016).

Ataxia Telangiectasia Mutated (ATM)

The Ataxia-telangiectasia mutated (*ATM*) gene, a crucial onco-suppressor located on chromosome 11q23, encodes a 350-kDa protein essential for DNA double-strand break (DSB) repair. As a member of the phosphatidylinositol 3-kinase-related protein kinase (PIKK) superfamily, *ATM* plays a pivotal role in maintaining genomic

stability. In response to DNA damage, *ATM* is activated through autophosphorylation and subsequently phosphorylates a cascade of proteins involved in DSB repair, including *BRCA1, TP53*, and various DNA repair enzymes (Moslemi et al., 2021).

Hereditary mutations in *ATM* have been linked to increased susceptibility to various cancers, including breast cancer. Carriers of *ATM* mutations have a higher lifetime risk of developing breast cancer compared to the general population. Studies have shown that *ATM*-associated breast cancers often exhibit specific clinical and histopathological features. For instance, *ATM*-mutant tumors frequently present as luminal B subtype with higher rates of estrogen receptor (ER) and progesterone receptor (PR) positivity (Kankuri-Tammilehto et al., 2023).

While significant advances have been made in understanding *ATM's* role in DNA repair and cancer risk, ongoing research is focused on identifying novel *ATM*-interacting proteins and developing targeted therapies based on *ATM* inhibition. Furthermore, large number of variants of uncertain significance and likely pathogenic variants associated with *ATM* complicates genetic counseling and risk assessment (Ünsal et al., 2023).

Phosphatase and tensin homolog (PTEN)

PTEN, located on chromosome 10q23.3, encodes a protein consisting of 403 amino acids. This phosphatase plays a crucial role in tumor suppression by inhibiting the PI3K/AKT signaling pathway. By dephosphorylating the lipid products of phosphatidylinositol 3-kinase (PI3K), *PTEN* helps to modulate cell growth and survival, thereby preventing excessive cell proliferation that can lead to tumor development. *PTEN* can become inactivated through various mechanisms, including somatic mutations, gene deletions (monoallelic or biallelic), epigenetic modifications like promoter methylation, protein degradation, and post-translational modifications. Around 50% of breast tumor cases show *PTEN* site loss of heterozygosity upon diagnosis (Yari et al., 2023). Loss of *PTEN* function leads to an inability to activate cell cycle arrest and apoptosis, resulting in unchecked cell survival. This disruption plays a significant role in various cancerous processes, allowing cells to proliferate uncontrollably (Q. Wang et al., 2021). Several diseases, including *PTEN* hamartoma tumor syndrome and Cowden syndrome (CS), have been linked to inherited *PTEN* mutations. Multiple hamartomas are present in a range of tissues, and the risk of malignant transformation is higher in affected individuals. The most frequent type of malignancy connected to CS is breast cancer. Women with CS have a 25% to 50% lifetime risk of developing breast cancer and are more likely to experience an early onset, despite the fact that CS accounts for less than 1% of all breast cancers (Razack & Prabhuswamimath, 2024). Moreover, benign breast disease, which is characterized by numerous bilateral mammary hamartomas, is more common (67%) in women with CS (Pîrlog et al., 2024).

Neurofibromatosis type 1 (NF1)

NF1, located on chromosome 17, encodes neurofibromin, a 2,818-amino acid protein that acts as a tumor suppressor. The gene comprises 61 exons, with 4 subject to alternative splicing, which influences the protein's function (Frayling et al., 2019). The Cancer Genome Atlas (TCGA) analysis suggests that roughly 25% of breast cancers are characterized by somatic mutations or deletions in the *NF1* gene (Dischinger et al., 2018). These mutations and deletions are prevalent in the HER2 (human epidermal growth factor receptor 2)-amplified and basal tumor subtypes of breast cancer (Uusitalo et al., 2017). According to several research, women who carry the *NF1* mutation are five-fold increased risk, especially before the age of fifty (Madanikia et al., 2012). Moreover, breast tumors with two to six *NF1* alterations may have inferior prognostic indicators and worse survival rates. In addition to breast cancer, individuals with *NF1* mutations are also at elevated risk for other cancers, including ovarian cancer, pheochromocytoma, intestinal tumors, and sarcomas. While early breast cancer screening is recommended for women with *NF1* mutations, there are currently no universal screening guidelines. Surgical prophylaxis is generally considered only for those with additional personal or family risk factors (Uusitalo et al., 2017).

Serine/threonine kinase 11 (STK11)

The gene *STK11*, also known as Liver Kinase B1 (*LKB1*), is a serine-threonine kinase that was first discovered by Chugai Pharmaceuticals in 1996 (Laderian et al., 2020). It is situated on the short arm of chromosome 19 and is made up of nine coding exons and one noncoding exon. Liver Kinase B1, which is widely expressed in all tissues, is comprised of 433 amino acids and plays a crucial role in cellular energy metabolism. When adenosine triphosphate (ATP) levels are low, *LKB1* forms a heterotrimeric complex with the pseudokinase STE20-related adaptor alpha and the scaffolding protein MO25α, resulting in allosteric activation of its kinase domain. *LKB1* can then phosphorylate and activate 5' AMP-activated protein kinase (AMPK) (Laderian et al., 2020). In breast cancer, germline mutations in *STK11* are primarily associated with Peutz-Jeghers syndrome (PJS), a hereditary condition caused by high-penetrance mutations in the *STK11* tumor suppressor gene. PJS is linked to an increased risk of multiple cancers, including breast cancer (Frey et al., 2017). Women with *STK11* mutations have a lifetime risk of 30–55% for breast cancer development. These *STK11* mutations represent a small fraction of all harmful mutations in breast cancer, accounting for less than 1%. With a typical diagnostic age of 30–40 years, this risk grows throughout the course of the patient's life. Moreover, patients are more likely to develop lung, pancreatic, gastrointestinal, and ovarian cancers (Van Lier et al., 2010). By the time they reach the age of seventy, women with Peutz-Jeghers syndrome are thought to have a 45% lifetime chance of developing breast cancer (Van Lier et al., 2010).

Checkpoint kinase 2 (CHEK2)

CHEK2 is a vital tumor suppressor gene that aids in DNA repair and cell cycle regulation. It encodes a protein that detects DNA damage and pauses the cell cycle, allowing time for repairs. This function is crucial for maintaining genomic stability and preventing tumor formation. Mutations in *CHEK2* can compromise its protective abilities, increasing the risk for cancers like breast and colon cancer. By facilitating DNA repair and regulating cell division, *CHEK2* serves as a key defense mechanism against cancer. The 1100delC mutation, a common variant in *CHEK2,* is associated with a two- to three-fold increased risk of breast cancer, particularly in individuals with a family history of the disease (Meijers-Heijboer et al., 2002). Moreover, it may raise the risk of prostate and colorectal cancer. The lifetime risk of breast cancer for women with *CHEK2* mutations and a family disease history is predicted to be between 28% and 37%. Yet, the risk might be higher based on how many members of the family have the disease (Gage et al., 2012).

Genetic predisposition to breast cancer is connected with defective DNA double-strand break repair. The *BRAC1*-associated genome surveillance complex includes the Ataxia Telangiectasia Mutant (*ATM*), a crucial repair-sensing mechanism (BASC) (Jalilvand et al., 2017). *CHEK2* is phosphorylated and voluntarily activated by *ATM* kinases in response to double-strand break repair. *CHEK2* is crucial for activating proteins involved in DNA repair and cell cycle regulation. Upon DNA damage, *CHEK2* phosphorylates key substrates, including the Cdc25 family, which helps control cell cycle progression. It also phosphorylates *BRCA1* at serine 988, enhancing its role in repairing double-strand breaks. Additionally, *CHEK2* stabilizes and activates P53, promoting cell cycle arrest or apoptosis in response to severe DNA damage. Through these actions, *CHEK2* plays a vital role in maintaining genomic integrity and preventing tumorigenesis. On chromosome 22q12.1, the *CHEK2* gene is prone to mutation, which can result in cancer (Zannini et al., 2014).

Tumor protein p53 (TP53)

TP53 is a high-penetrance tumor suppressor gene that encodes the p53 transcription factor, a crucial protein for maintaining genomic stability. It controls a number of functions, including metabolism, DNA repair, apoptosis, and cell division (Shahbandi et al., 2020). It has been demonstrated to contribute to the emergence of a number of cancer types, such as colon cancer, lung cancer and osteosarcomas. A mutant *TP53* gene is carried by 60% to 80% of Li-Fraumeni syndrome (LFS) families, which is an uncommon but very aggressive familial cancer disease (Kappel et al., 2015). Autosomal dominant inheritance describes genetic variations in the gene sequence that are transmitted from parents (Kwong et al., 2016). LFS families are more likely to have an early onset pattern and a variety of primary malignancies, including soft-tissue sarcomas and osteosarcomas in addition to breast, brain, and

adrenocortical cancers. It is estimated that LFS4 is responsible for 1% of all breast cancers (McCuaig et al., 2012). A *TP53* mutation is present in around 1% of breast cancer patients under the age of forty. Up to one-third of all cancer cases in LFS families are female *TP53* mutation carriers, and breast cancer is the most common malignancy among them. Even though LFS only contributes to a tiny portion of breast cancers, it is responsible for a 60-fold rise in the probability of breast cancer that develops early when compared to the general population. The breast cancer risk for women with LFS is 56% by the age of 45 and more than 90% by the age of 60. In women with breast cancer associated with LFS, very early disease onset (the 20s or 30s) and moderately advanced disease staging have been described. Studies show that 3% to 8% of women under the age of 30 who are diagnosed with breast cancer and do not have a significant family history of the illness also have a *TP53* mutation (Valdez et al., 2017).

Benefits of NGS-based testing in families with genetic predisposition to cancer

Modern genetic techniques, such as next-generation sequencing (NGS), revolutionize the field by enabling the analysis of multiple genes simultaneously, providing deeper insights into complex diseases like familial cancers(Yadav et al., 2023).

Researchers are particularly interested in figuring out which genes cause these familial cancers. These genes, known as germline mutations, are present from birth and encompass inherited alterations in the DNA sequence. Variations within these genes can significantly enhance an individual's susceptibility to cancer by potentially disrupting normal cellular functions or impairing the body's ability to repair damaged DNA. Gaining a comprehensive understanding of these genetic factors is essential for accurately assessing cancer risk and developing targeted strategies for prevention and treatment. Identifying these new genes is crucial because it allows doctors to better predict a person's cancer risk. This knowledge can then be used to develop strategies to prevent cancer altogether.

For example, in families with a history of breast and ovarian cancer, mutations in *BRCA1* and *BRCA2* account for many cases, but not all. Other, less commonly known genes, such as *ATM* and *PALB2,* also contribute to cancer risk, but much remains unknown about their exact roles. This is where next-generation sequencing (NGS) becomes essential. By rapidly analyzing many genes at once, NGS can help us discover these new factors that contribute to familial breast and ovarian cancer. This will ultimately lead to better diagnosis, risk assessment, and potentially even prevention methods for these cancers (Zelli et al., 2020).

Conclusion

Breast cancer is a multifaceted disease influenced by both genetic and lifestyle factors. Approximately 15-20% of breast cancer cases are hereditary, with *BRCA1* and *BRCA2* mutations significantly elevating the lifetime risk to 55-72% and 45-69%, respectively. Lifestyle choices play a crucial role in risk management. Individuals with *BRCA* mutations can reduce their risk by 25-30% through regular physical activity, a balanced diet, moderate alcohol consumption, and avoidance of smoking. Additionally, environmental factors such as hormone replacement therapy and high-fat diets have been associated with increased breast cancer risk, with studies indicating that high saturated fat intake may elevate risk by up to 30%. A comprehensive understanding of these factors is essential for effective risk assessment and early detection, facilitating the development of targeted prevention and treatment strategies.

Conflict of interest

The authors declare no conflict of interest.

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