Original Article

Breast Cancer; Genetic factors, Molecular pathways and Diagnostic methods

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ABSTRACT

Breast and ovarian cancers are common among women with high mortality. About 6.6% of global cancer deaths are related to breast cancer. This research a comprehensive review of breast cancer, focusing on its multifactorial etiology, including genetic predispositions, environmental influences, and lifestyle factors. A literature review was conducted using Google Scholar and PubMed, resulting in the selection of 46 articles based on methodological quality, research writing, and results. The review underscores the critical role of BRCA1 and BRCA2 genes in hereditary breast cancer, the deleterious impact of mutations on tumor suppression and DNA repair mechanisms, and the consequent elevated risk of breast cancer in women. The article also explores the association between various factors such as BMI, estrogen levels, breast density, exercise, and alcohol consumption with breast cancer risk. It examines the predictive value of DNA damage repair proteins in assessing sensitivity to neoadjuvant chemotherapy and the imperative for continued research into mitigating common side effects such as chemotherapy-induced peripheral neuropathy. The review stresses the ongoing development of targeted therapies tailored to specific breast cancer subtypes, particularly Triple-Negative Breast Cancer (TNBC), and the continuous advancements in diagnostic technologies. The findings underscore the necessity for interdisciplinary collaboration to enhance breast cancer management and the promising future of genetic screening and personalized medicine in revolutionizing cancer treatment.

Keywords: Breast Cancer, Genetic Factors, Molecular Pathways, Diagnostic Methods, BRCA1/BRCA2 Mutations, Personalized Medicine

Introduction

Among women, breast cancer is one of the most prevalent illnesses. Numerous factors contribute to this cancer [1]. It is vital to understand the pathways that stimulate breast cancer growth, including the role of estrogen and androgen hormones. miRNAs can be positively or negatively regulated for signaling pathways and affect tumorigenesis and cancer progression [2]. GREB1 is one of the crucial genes in the growth of cancer cells. It is regulated by estrogen receptor 1 (ESR1). The deletion of this gene can slow the growth of cancer cells because it plays a critical function in the proliferation of cancer cells. Additionally, data indicates that GREB1 expression is higher in young female patients with breast cancer than in an older patient population [3, 4]. Researching the signalling pathways involved in breast cancer has also demonstrated the role that genes like BRCA1 and BRCA2 play in the disease's dissemination. Additionally, a number of oncogenes linked to this illness have been found, and these genes are important for the development of tumours and the advancement of cancer [3].

Additionally, the association between various factors such as BMI, estrogen levels, breast density, exercise, and alcohol consumption and breast cancer risk has been investigated. This information helps us to provide new approaches to the prevention, diagnosis, and treatment of breast cancer[5]. Lastly, the understanding of these disorders' genetic makeup and how they relate to other variables can aid in improving their diagnosis and course of treatment. It can also improve the health of women suffering from them. In this field, more multidisciplinary research is essential [3]. Important variables in determining a breast cancer patient's vulnerability to neoadjuvant chemotherapy include DNA damage repair proteins. Numerous

investigations are being carried out about the prevalence of breast cancer and its connection to DNA damage [6].

A frequent and dose-limiting adverse impact caused by chemotherapy for individuals with breast cancer is chemotherapy-induced peripheral neuropathy (CIPN). Pain, tingling, and numbness in the hands and feet are clinical indicators of neuropathy. As so, the patient's quality of life can deteriorate [7]. These days, a number of drug regulatory bodies have authorized genotype-based drugs to treat patients with metastatic breast cancer with HER2 amplification and BCR-ABL-positive chronic leukemia myelogenous (CML). These therapies include trastuzumab and imatinib [4]. On the other hand, new approaches are also being used to generate contemporary therapies. For instance, hormone treatment is an effective target for PI3K/AKT/mTOR pathway-positive breast cancer. Another technology that is thought to be suitable for the therapeutic treatment of breast cancer is homologous recombination (HR) in DNA repair [4].

No approved targeted treatment and chemotherapy are used as the standard treatment approach for TNBC breast cancer (Triple-Negative Breast Cancer), which has a poor prognosis compared to other subtypes of breast cancer [4].Thus, providing new and innovative treatment methods for TNBC is vital. To deal with this disease, it is essential to pay attention and follow up on all the key factors and their interactions during the disease's progress [4]. Since rare studies have been conducted on MBCs (Metastatic Breast Cancers) due to their rarity, it is crucial to investigate mutations and targeted treatments for these diseases. Using a panel of CD44v6, EGFR, HER2, IGF1-R, and GLUT1, supplemented by FGFR2 and CAXII, has been proposed as molecular imaging methods to increase sensitivity in the diagnosis of MBCs, and more personalized approaches are needed in the treatment of these diseases. Finally, upgrading the facilities and the technologies used to diagnose and treat breast cancer, especially TNBC, is vital [8]. Continuing studies in this field and paying attention to the genetic and molecular aspects of each of these diseases will improve the treatment and management of this cancer significantly.

According to recent investigations, preventative mastectomy samples from bearers of the BRCA gene mutation have shown precancerous tumors with cytoplasmic lymphoid infiltrate. Research has shown that whereas BRCA2 mutation bearers share the same clinical characteristics as non-mutation patients, they are more likely than non-mutation carriers to develop triple-negative breast cancer [9]. It is believed that BRCA1 and BRCA2 mutations truncate and inactivate the corresponding proteins, which may account for the more robust biology of breast malignancies, including BRCA1 and BRCA2 [4]. Additionally, genetic screening can help identify individuals at higher risk of cancer and identify tumor genomes for appropriate treatment. Additionally, mammography screening reduces mortality and is a more effective technique to identify breast cancer in its early stages, especially in women who have a family history of the illness. Understanding the risk factors for breast cancer, such as age, atypical hyperplasia history, and mammography density, can aid in the diagnosis and treatment of the condition [10].

Generally, studies indicate that epigenetic mechanisms and dysregulation of miRNA are associated with breast cancer development. They can be used as diagnostic and prognostic tools for breast tumors. Extensive studies are being conducted on breast cancer and its development and progress, as one of the most common diseases in women. It is vital to understand the ways of stimulating cancer growth, including the role of estrogen and androgen hormones [11]. The effect of miRNAs on signaling pathways and tumorigenesis is also a significant point in this regard [12].Research has revealed that the estrogen receptor 1 (ESR1)-regulated GREB1 gene is crucial for the growth of cancer cells. The proliferation of cancer cells was slowed down by its elimination. Additionally, research on signaling pathways in breast cancer suggests that the BRCA1 and BRCA2 genes are essential for the disease's spread [13].

The association between various factors such as BMI, estrogen levels, breast density, exercise, and alcohol consumption with breast cancer risk has been investigated. This information can be effective in improving approaches to breast cancer prevention, diagnosis, and treatment [14].Moreover, DNA damage repair proteins and studies related to this field have been considered key factors in predicting the sensitivity of breast cancer to neoadjuvant chemotherapy treatments [15]. The need for more studies in the field of chemotherapy-induced peripheral neuropathy and methods to reduce its side effects is of particular importance [4].

Thanks to recent advances, targeted and innovative therapies are being developed to treat breast cancers, especially TNBC breast cancer. Improving the technologies used in the diagnosis and treatment of breast cancer will play a vital role in improving the treatment and management of these diseases. More interdisciplinary studies will lead to significant improvements in this field and enable better diagnosis and treatment of breast cancer, especially TNBC type [16].

Materials and Methods

The research conducted for this article is based on a meticulous literature review, which is the cornerstone of synthesizing current knowledge on breast cancer. The authors utilized Google Scholar and PubMed as the principal electronic databases for their literature search, employing the search terms "breast cancer" and "diagnosis" to identify pertinent articles. This search strategy was crafted to encompass a wide array of studies that would elucidate the multifaceted nature of breast cancer, including its genetic, epigenetic, hormonal, and environmental underpinnings.The 46 articles selected for the review underwent a stringent evaluation process, with each article being assessed for the robustness of its methodology, the clarity of its research presentation, and the significance of its findings. The authors favored articles that offered substantial data and insights into various facets of breast cancer, such as the pivotal roles of BRCA1 and BRCA2 in hereditary cancers, the consequences of mutations on tumor

suppression and DNA repair mechanisms, and the relationship between modifiable risk factors and the risk of developing breast cancer.

The review also delved into studies examining the molecular pathways of breast cancer, with a particular focus on those pathways that have implications for the creation of targeted therapies. The authors dedicated special attention to the burgeoning field of personalized medicine, which harnesses genetic screening and cutting-edge diagnostic technologies to customize treatment approaches for individual patients. Moreover, the authors incorporated findings from recent genetic studies on breast cancer, exploring the implications of mutations in genes with high and moderate penetrance for cancer risk stratification and screening protocols. The review also contemplates the potential utility of miRNAs as biomarkers for the early detection and prognosis of breast cancer, as well as the role of epigenetic mechanisms in the disease's pathogenesis.

Results and Discussion

Various factors are involved in breast cancer, including social and economic factors, adverse childhood experiences, genetics, and family history [17]. BRCA1 and BRCA2 are the most common causes of hereditary cancers [17]. The capability of these two genes is important in preventing breast cancer [18]. Mutations and changes in these genes prevent the proper functioning of these genes. This means tumor suppression and DNA repair increase the probability of breast cancer in women [17].

BRCA1 gene mutation diagnostic tests are performed in certain groups of people to prevent cancer [3]. BRCA1 primarily contributes to the HR mechanism, which starts the DNA damage response and repairs double-strand breaks, preserving genomic integrity [3]. In addition to the genes listed, there are additional high- or medium-penetrance genes linked to an increased risk of breast cancer [9]. Medium-penetrance mutations include ATM, NF1, CHEK2, and RAD51C, and high-penetrance mutations like TP53, PTEN, PALB2, STK11, and CDH1 (3), BRCA1&2 genes, and high-penetrance genes TP53 and PTEN account for 20% of breast cancers and the other 80% are unknown genetic factors and moderate-penetrance gene mutations [9, 19].

Research has demonstrated that individuals with medium-penetrance mutations are 2-4 times more likely to develop breast cancer (3). 55–65 percent of women with a BRCA1 mutation and 45 percent of women with a BRCA2 mutation will get breast cancer before the age of 70 [3]. Research has shown that individuals with BRCA1 mutations had a higher chance of receiving a triple breast cancer (TN) diagnosis than those without the gene, whereas those with BRCA2 mutations have the same pathological characteristics as those without the mutation [20].

Most BRCA1 and BRCA2 mutations found in breast cancer truncate the protein product, and thus BRCA1 and BRCA2 proteins are truncated and inactive [12]. Scientists revealed that the BRCA1 phosphorylation depends on ATM in response to IR radiation and it is independent of ATM in response to UV treatment [3]. Among the P53 (Ser-15) phosphorylations induced by IR and UV irradiation, only IR irradiation can induce G1/S arrest [20].

Triple-negative breast cancer is the most common type of breast cancer in women. It includes estrogen and progesterone receptors HER2 negative and HER2 positive [3]. Gefitinib and SF1126 together cause TNBC cells to undergo cell apoptosis, which is mediated by the EGFR-P12K-AKT-mTOR-P70S6K pathway [20]. Genetic screening for people at risk of cancer and identifying the tumor genome for appropriate treatment are very helpful for patients [21, 22]. Mammography is the most efficient method to detect cancer in the early stages and specific genetic diagnosis of cancer types [23]. The mammography time is crucial. It should be done when the risk of infection is high enough in a healthy population. Mammography also has disadvantages, such as the risk of over-diagnosis and unnecessary treatment. It affects a person's quality of life and physical performance [14]. It can even increase the risk of infection in people with BRCA1&2 mutations after exposure to radiation and radiotherapy [14, 23] . Evidence links P/Lp variations in ATM and CHEK2 to a higher risk of cancer. It is amenable to MRI examination [13]. Mammography density, SNP, and family history all have an impact on P/Lp variations in moderate-penetrance genes relative to high-penetrance genes [23]. The mammography effectiveness in reducing mortality is higher in young women than in the 70-year-old group [14]. It was found that the GREB1 gene plays a significant role in the proliferation of cancer cells and the expression of this gene is higher in young women [24, 25].

In postmenopausal women, obesity increases the incidence of breast cancer, and there is a correlation between breast cancer and oestrogen levels. Elevated oestrogen levels raise the risk of breast cancer and increase body weight. Compared to patients with a moderate or high BMI (obesity), those with a normal BMI had a significantly higher overall survival and disease-free survival [26, 27]. The results revealed that the P53 signaling pathway plays a significant role in cancer risk [16]. Upstream regulators are overexpressed when the P13K/AKT/mTOR pathway is oncogenously activated [28]. The treatment of cancer requires this mechanism .The cell nucleus contains BRCA1 and BRCA2, which encode large proteins that are widely expressed in several tissues throughout the S and G2 stages [28, 29]. Mutations or changes to the BRCA1 gene impede the production of the separate and unrelated A1 and BRCA2 proteins, which either inhibit the formation of tumours or inadequately carry out the DNA repair function [29].This issue increases the possibility of breast and ovarian cancer in women. This mutation may be genetically inherited from parent to child. The following groups are suitable candidates for BRCA1 gene mutation detection tests.

1: People diagnosed with breast cancer before the age of 50.

2: Women who have cancer of both breasts.

3: People who experienced both breast and ovarian cancer

4: People whose family members have both breast and ovarian cancer

5: People who have several people in their family with breast cancer

6: Men diagnosed with breast cancer [3].

The breast cancer development risk is multifactorial and sometimes changeable. However, the risk caused by family history and types of genetic diseases in a person's genetic code is currently a significant constant variable [5].

Genetics, mutation, and cancer

There is a genetic predisposition due to mutations in genes with high and moderate penetrance in both breast and ovarian cancers [9], Harmful mutations, mutations in TP53, PTEN, PALB2, CDH1, and STK11 are classified as high-penetrance mutations. More genes with medium penetrance mutations for breast cancer risk have been identified in recent years. Some of them are ATM, CHEK2, NF1, RAD51C, RAD51D, and BARD1 [19]. Generally, medium-penetrance mutations increase the breast cancer risk by two to four times. RAD51C, RAD51D, ATM, CHEK2, BRCA1, BRCA2, PALB2, BARD1, and RAD51C were shown to have a substantial association (3) [19]. DNA damage repair requires the RAD51 and XRCC2 protein families as vital components. Loss of sensitivity to DNA damage is the consequence of placental mutations of XRCC2, which substitute or eliminate 188 amino acids from the XRCC2 gene [19].

XRCC1 R399Q polymorphism also shows the hereditary breast cancer risk [3]. However, no significant correlation was observed for TP53 and PTEN primarily due to the low frequency of mutations (3). Breast cancer is a heterogeneous disease that is challenging to diagnose and cure due to its attractiveness. BRCA1 or BRCA2 mutation-carrying women may also be at risk for multiple other causes. There are a number of other genes that have been found, such as PTEN, ATM, TP53, CHEK2, CASP8, PBRL, and BRIP1 [3, 30]. The risk of breast cancer has not yet been established for a large number of genes found in current polygenic cancer panels, including RAD50, BRIP1, XRCC2, and MRE11A. Furthermore, results indicate that a sizable portion of the population who do not fit the screening risk criteria may be included in the estimated risk range for carriers of P/LP variations in ATM and CHEK2 [13, 30].

According to the research, BRCA1 is mainly responsible for repairing double strand breaks via the HR mechanism. It also triggers the DNA damage response, which helps to preserve genomic integrity. In early diffuse breast cancer, a complicated system that inactivates BRCA1 and other DNA repair genes that promote tumour growth counteracts genetic instability [3]. Compared to BRCA-negative or diffuse instances, carriers of the BRCA1/BRCA2 mutation had a worse overall survival (OS). In triple-negative breast cancer, bearers of the BRCA1/2 mutation had a better overall survival (OS) than carriers of the BRCA-negative mutation. Fifty-five to sixty-five percent of women with a BRCA1 mutation and forty-five percent of women with a BRCA2 mutation will each develop breast cancer before the age of seventy [31]. Particularly prevalent in ER-and/or PGR-positive breast cancers are mutations in the ATM gene, which codes for the major adaptor involved in DNA double-strand break (DSB) repair. Furthermore, tumours treated with ATM have a higher chance of becoming positive [31].

Little frameshift insertions or deletions, nonsense mutations, or changes affecting the binding site that result in the whole or partial loss of exons or complicated sequence insertions are the most frequent mutations in the BRCA1/2 gene. Nonetheless, a large number of BRCA1 and BRCA2 gene mutations are known as variations of unknown significance (VUS) [12]. Due to substantial rearrangements in the BRCA1 and BRCA2 genes, less than 1% of cases of breast and ovarian cancer have been linked to a hereditary cause. These are necessary ingredients for DNA damage repair as well as transcription repair. Thus, fast cell proliferation can result from mutations in one of the mediators. Numerous new breast cancer subtypes have been discovered that are connected to BRCA interactions in addition to BRCA1 and BRCA2 mutations [3]. Non-BRCA mutations are thought to be uncommon and potentially invasive [12].

Mammography and Screening

Recent research has revealed that preventive mastectomy tissues from BRCA gene mutation carriers have precancerous lesions with substantial cytoplasmic lymphoid infiltration. According to studies, people without a BRCA1 mutation have a lower chance of receiving a triple-negative (TN) breast cancer diagnosis. On the other hand, patients without a BRCA2 mutation appear to share pathological characteristics with carriers of the gene. According to predictions, most BRCA1 and BRCA2 mutations found in families with breast and ovarian cancer would truncate the protein product, making the BRCA1 and BRCA2 proteins shorter and inactive [12].

A high rate of bilateral mastectomy in breast cancer patients with VUS has been reported following BRCA1/2 sequencing [13]. By integrating somatic mutations to determine the tumor genome for appropriate therapy and germline mutations to identify individuals at increased risk of cancer, cross-sectional genetic screening may easily improve patient care [12]. The most effective method of reducing mortality and early detection of breast cancer is serial mammography screening. When population-based mammography screening is available in high-income nations, women between the ages of 50 and 69 make up the majority of the at-risk group [3]. Screening at the population level may have less detrimental effects if it is known who should be screened. Breast cancer screening should ideally be carried out in a healthy population when the likelihood of contracting the illness is high enough to offset the negative effects of overdiagnosis and overtreatment.

It is more done on types of breast cancer that are often more aggressive and have a worse prognosis [14]. At the moment, information on the degree of invasiveness of breast cancer is utilised to direct treatment after a favourable result (i.e., determining the type of P/LP). Advanced screening or RRM for genes with the highest penetrance may be part of the monitoring process. By comparison, only some moderately penetrant genes that above the 20% lifetime risk threshold are indicated for

advanced screening (but not for RRM). Strong evidence points to a 25–30% higher cancer risk in the range of P/LP in ATM and CHEK2. The screening threshold for breast magnetic resonance imaging (MRI) is met with this degree of risk. However, based just on P/LP polymorphisms that do not provide this kind of risk, there is no evidence to support RRM [13].

Furthermore, relative to high-penetrance genes, P/LP variations in moderate-penetrance genes are probably influenced by risk factors such as mammography density, numerous single nucleotide polymorphisms (SNPs), and family history [13]. It is also expected that younger women would have fewer comorbidities and live longer. Given that non-cancer illnesses comprise a greater proportion of fatalities in the older age group (over 70), there is debate on the effectiveness of mammography screening in reducing mortality. Regular screening may not be very beneficial for older women. Mammography can lead to overdiagnosis and unnecessary therapy, which can be harmful to one's physical functioning and quality of life. For women who are not currently in the at-risk group, personal risk assessments may change the screening mammography risk-benefit ratio, improving patient outcomes [14].

Mammography density, determined by the appearance of breast tissue on mammography, is another risk factor for breast cancer. It may be used to identify if a certain genetic susceptibility, such as rare variants of BRCA1 or BRCA2 loss of function, increases an individual's chance of getting breast cancer [9]. People who have a family history of breast cancer are more likely to be screened for the illness using a risk-based approach [14]. Several studies have demonstrated that after being exposed to medical radiation through radiotherapy or mammography, women with BRCA1 or BRCA2 mutations are more likely to develop breast cancer. Additional results suggest that there is a higher risk of breast cancer associated with mammography when there are multiple alleles in genes relevant to DNA repair processes.

Furthermore, epigenetic processes resulting from exposure to chemicals and radiation, including changes in DNA methylation, histone modifications, and differential expression of miRNAs, have a significant effect on the structure. Histone acetylation, DNA methylation, differentially expressed miRNAs, and increased lncRNA synthesis are the primary epigenetic processes associated with breast cancer [12]. An imbalance in hormones and deregulation of miRNAs are associated with the development of breast cancer [3]. Nevertheless, it is unclear if miRNAs can be used to diagnose or predict the prognosis of breast cancers [12].

Breast cancer growth stimulation pathway

Breast cancer is stimulated by estrogen and the proliferation of breast cancer cells by androgen hormones [12]. miRNAs have the ability to either favourably or negatively control signalling pathways, which has an impact on carcinogenesis and many elements of cancer progression. Since GREB1 transcription is induced independently of protein synthesis, oestrogen receptor 1 (ESR1) directly regulates GREB1 rather than one of its transcriptional targets [32]. The original name of the GREB1 gene was KAA0575. Eventually, it was dubbed GREB1, for growth regulator in breast cancer 1 [32]. The GREB1 gene is an essential mediator in the development of cancer cells, as its deletion prevents cancer cells from growing in cancer models in vitro. GREB1 expression was substantially higher in younger breast cancer patients than in older ones [32].

Cancer signaling

Breast cancer frequently has BRCA1 and BRCA2 identified. In a research including 500 breast tumors, the oncogenes with the highest frequencies of 41%, 30%, 20%, 16%, 16%, 13%, 11%, and 10%, respectively, were TP53, PIK3CA, MYC, PTEN, CCND1, ERBB2, FGFR1, and GATA3. Further AKT2, ARID1B, CASP8, CDKN1B, MAP3K1, MAP3K13, NCOR1, SMARCD1, and TBX3 mutations have been found. Cell cycle progression is regulated by CDKN1A, a cyclin-dependent kinase inhibitor. It is important for the p53 and PI3K/AKT signaling pathways [3]. Our pathway analysis found 221 genes associated with breast cancer risk (Supplementary Methods and Table S16). Several signaling pathways were shown to be strongly correlated with the incidence of breast cancer in FDR.

Remarkably, ER-negative breast cancer is more strongly associated with at-risk locations for MDM4 and CCNE1 than ER-positive breast cancer. Furthermore, MDM4 expression was solely linked to a higher risk of ER-negative breast cancer, according to our TWAS. These findings suggest that breast cancer risk, particularly that of ER-negative breast cancer, is significantly influenced by the p53 signaling pathway [16]. Because driver mutations affect important mechanisms governing carcinogenesis, such as cell destiny, cell survival, and genome maintenance, they are linked to a selective growth advantage, which facilitates the development of cancer [33]. BMI had a negative correlation with non-dense tissue (NDA) and a positive correlation with PMD. We found that the age of menarche influences the link between DA and ER-positive breast cancer differently. There was an interaction between alcohol intake and physical exercise and PMD in cases with ER-negative breast cancer [33].

High levels of physical activity decreased the incidence of ER-negative breast cancer associated with high DA, while alcohol intake had a negative interaction with the protective effect against ER-negative breast cancer associated with high NDA [34]. According to Clemons and Goss, there is a correlation between estrogen exposure and the risk of breast cancer in specific female demographics [34]. According to Berclaz et al., bone mineral density, serum estrogen levels, and mammography breast density are helpful indicators of obesity in relation to tumor load and breast cancer. Overall survival (OS), disease-free survival (DFS), and body mass index (BMI) were all substantially higher in patients with normal BMIs than in those with intermediate or obese BMIs. Research indicates that in women who have gone through menopause, obesity increases the risk of breast cancer.

Increased body weight and breast cancer risk are associated with high estrogen levels [3].

BRCA at the molecular level

In order to repair double-strand breaks, BRCA 2 is essential. In particular, it is able to regulate the bacterial eukaryotic Rec RAD51 recombinase. a homolog necessary for repairing double-strand breaks. A BRCA 1 shortage can harm DNA, which inhibits cell division and death [3]. Abnormalities in spindle checkpoint, G2/M checkpoint, Sphase checkpoint, and centrosome replication are caused by BRCA 1 lack. BRCA1 interacts with hypophosphorylated RB protein (retinoblastoma) to cause G1 phase arrest. RB is a phosphoprotein and recognised tumour suppressor. Hypophosphorylated RB inhibits cell proliferation by repressing the transcription of genes downstream through its interaction with the transcription factor E2F. Chk1 aids in DNA damage-induced cell cycle arrest in the S phase. G2 phase arrest, however, occurs independently of Chk1 and Chk2. To halt development, BRCA1 maintains RB in a hypophosphorylated state [34].

Along with two RB-binding proteins, RbAp46 and RbAp48, and histone deacetylases 1 and 2 (HDAC1 and HDAC2), the BRCA terminal 1 domain (BRCT) also forms a complex. In terms of the G1/S phase, p53 is linked to the BRCA1-activated G1/S cell cycle checkpoint. It is thought that RB suppresses E2F-responsive transcription and further promotes RB-induced growth suppression through the histone deacetylase complex (HDCR). BRCA1 can control the generation of p21 and stop the cell cycle from entering the S phase. Global BRCA1 phosphorylation in response to infrared light is regulated by the ataxia telangiectasia mutant (ATM) gene product [35].

As demonstrated by Tibetso et al., BRCA1 phosphorylation is UV treatment-independent and IR-dependent, depending on ATM. ATM/ATR-related BRCA1-BARD1 complex (Rad3-related mutant disease) controls p53 phosphorylation and DNA damage under UV or IR light. G1/S arrest when p53 (Ser-15) is phosphorylated can only be caused by IR light, not UV radiation. ATM is the mediator of IR-induced phosphorylation, while ATR is responsible for rapid UV-induced phosphorylation. The BRCA1-BARD1 complex is catalyzed by p53 phosphorylation (Ser-15), and these results imply that ATM mediates this complex. G1/S arrest brought on by IR is mediated by p21 and p53 [36].

Further evaluation of genomic integrity, DNA damage response (DDR), and tumor growth is necessary to comprehend the processes behind BRCA1-related carcinogenesis and to open the door to the development of novel therapeutics for the BRCA1 function in cell cycle checkpoints [36]. BRCA 1 can facilitate Rad5 assembly and repair damage to DNA. Deviations in the PI3K/AKT/mTOR pathway are frequently linked to an increased risk of breast cancer. Two essential elements of the DNA damage checkpoint signaling cascade are the checkpoint kinases Chk1 and Chk2 [3]. A family of enzymes known as phosphoinositide 3-kinase (PI3K) is involved in intracellular transport, differentiation, proliferation, and development of cells. Comprising catalytic (p110) and regulatory (p85) subunits, it is a heterodimer. The signalling cascade is started by receptor tyrosine kinase stimulation, which phosphorylates AKT and mTOR complex 1 (mTORC1), and then PI3K is activated [3]. The growth factor receptor pathway, in particular the tyrosine kinase receptor, has a major impact on the biology of breast cancer [12].

The p53, RAS/MAPK, and PI3K/AKT pathways are, respectively, mediated by MDM4, PLA2G6, and RIT1. Potentially helpful treatment targets are these recently identified probable genes linked to breast cancer risk. Upstream regulators like the epidermal growth factor receptor (EGFR) are overexpressed in triple-negative breast cancer (TNBC) due to the oncogenic activation of the PI3K/AKT/mTOR pathway. The pathway EGFR-PI3K-AKT-mTOR-p70S6K mediates the cell death that gefitinib and SF1126 together elicit in TNBC cells [3].The association between FGFR2 (fibroblast growth factor receptor 2) and familial breast cancer is confirmed by SNP analysis. Breast cancer and infection are substantially correlated at the gene level [2]. Moreover, it includes mutations in the PI3K catalytic α subunit (PIK3CA), proline-rich inositol polyphosphate, and loss of function or expression of phosphatase and tensin homolog (PTEN).

In cancer therapy, the PI3K/AKT/mTOR pathway has become a vital tool [3]. Oestrogen and progesterone receptors as well as HER2 are not present in triple-negative breast cancer. For women, this is the most prevalent kind of breast cancer. The mutation in BRCA 1 is the cause. Oestrogen and progesterone receptors are negative and HER2 is positive in HER2-rich breast cancer [3]. Patients who test positive for HER2 still develop breast cancer even when new anti-HER2 compounds are developed by research [12]. Family history and fertility may not provide an accurate assessment of each woman's risk. However, it is a better way to understand the estrogen role in breast cancer pathogenesis. Lack of expression of HER2, estrogen, and progesterone receptors is another cause of breast cancer [3].

Currently, there are four primary molecular classifications for breast cancer, based on the expression profile of the receptor gene. Among them are luminal A, luminal B, and HER2 positive. Positive luminal A and B hormone receptors, sometimes referred to as HR, oestrogen, and/or progesterone receptors, are the most common subtypes. Approximately 50-60% and 15-25% of all instances of breast cancer are represented by them, respectively [37].

HER2-targeted therapy, chemotherapy, and endocrine gland treatment are among the pharmacological treatments for HR-positive breast cancer that vary according to the risk of recurrence [38]. Primarily, the expression of progesterone receptor (PgR), estrogen receptor (ER), and human epidermal growth factor receptor (HER) or its amplification is used to determine the molecular subtypes. The four molecular subtypes are as follows: 1- Lumen A, which is HER2-negative, PgR-positive, and ER-positive; 2- Lumen B, which is HER2-positive, PgR-positive; 3-HER2 negative or triple HER2 positive, which is HER2-positive (especially aggressive); and 4- Triple breast cancer baseline negative (TNBC), which is HER2-negative, and

PgR-negative. In addition to lacking HER2 amplification, ERBB2, ERBB3, TBX3, and FOXOA1 mutations, as well as a greater frequency of CDH1 and PTEN loss, lobular tumors frequently express ER. GATA3 gene mutations are seen in fallopian tube cancers that are ER-positive. In response to DNA alterations, ER-positive breast cancer modifies the transcript in two distinct ways [12].

Tumours that express Tbx3 are known to be ER-positive. Thus, special consideration should be given to the ER-FGF-Tbx3 pathway [3]. Breast and ovarian tissues contain BRCA-deficient cells, which can evade apoptosis and lose their capacity to repair damage. Breast tissues also react to oestrogen. The reduction of cyclin D1 and cdc2 in HCC and BEL-7402 cells leads to phase arrest and apoptosis. Cyclin has a strong correlation with the risk of breast cancer. Cyclin D1 null resistance in breast carcinomas resulting from neu and ras oncogenes suggests that cyclin D1 plays a critical role in the development of some breast cancers. Primarily, overexpression of cyclins D1 and E1 is seen in breast cancer. The overexpression of cyclin E in breast cancer cells largely impacts the course of the cell cycle, whereas cyclin D1 focusses on transcriptional regulation [3, 39]. It ascertains the induction of p21waf1/Cip1, p27Kip1, and p53 concurrently with the extinction of cyclin A, D1, D3, and cycline kinase-dependent protein expression (CDKs) associated with breast cancer [39]. The G1-S phase's rate-limiting phases include cyclin D1, c-Myc production and function, and cyclin E-Cdk2 complex activation. All of these processes are regulated by oestrogen. The production of macromolecules is aided by the activation of cyclin E-Cdk2 by oestrogen. With the weight complex, the CDK p21 inhibitor is absent [39].

Single nucleotide polymorphism (SNP)

Studies connected to genomics have effectively identified over 170 loci linked to the risk of breast cancer [40]. Single nucleotide polymorphisms (SNPs) are particular genetic alterations that involve several nucleotides and happen in a particular region of the genome [2]. These SNPs are associated with risk but are not usually responsible for the studied phenotype; however, they are in high LD with functional SNPs that are responsible for the studied phenotype [40]. The "cancer phenotype" is determined by the expression of the cancer genome. A group of traits that arise from the interaction of a gene with its environment are categorised as cancer phenotypes. Stated differently, all phenotypic manifestations, including cancer, result from the interaction of inherited genes with external stimuli, also known as gene-environment interactions [12].

The functional significance of most risk-associated SNPs is difficult to understand since they are localized to non-coding areas. Despite this, a number of investigations have hypothesized that breast cancer may be predisposed by single nucleotide polymorphisms (SNPs) in homologous recombination genes [3]. There is limited clinical insight gained from GWAS results [12]. PALB2 genes are known as a factor in increasing susceptibility to breast cancer. SNPs in PALB2 (rs249954 and rs152451) are associated with breast cancer risk [3]. We examined linkage disequilibrium and haplotypic diversity in breast cancer susceptibility genes with high and moderate penetrance in Tunisia by analyzing 387 SNPs identified in BRCA1, BRCA2, STK11, PTEN, TP53, ATM, BRIP1, CHEK2, and PALB2 gene [38]. The syndrome caused by the STK11 gene mutation is called Peutz-Jeghers syndrome. One of the symptoms of this syndrome is the presence of spots on the lips and mouth and the formation of polyps in the urinary and digestive systems. This syndrome also increases the possibility of hereditary breast cancer [2].

miRNAs

The use of miRNAs as BC biomarkers has been extensively studied. Using c-myc in a mouse model of B-cell lymphoma, it has been shown that mir groups 17 to 91 promote the formation of tumors. Targeting the tumor suppressor genes associated with the G2-M checkpoint is how Mir 27 applies its oncogenic activity. The possibility of using miRNAs as breast cancer biomarkers and their involvement in carcinogenesis offers hope for the early detection and treatment of breast cancer. Breast cancer subtypes exhibit different patterns of mRNA expression, and there are 133 miRNAs found in both tumor and normal breast cells. The mir 21 gene will someday be an oncogenic and therapeutic target, according to a TaqMan real-time polymerase chain reaction study of miRNA expression. By controlling the proto-oncogene EST 1 of invasive breast cancer cells, miR125b functions as a tumour suppressor. Even more diagnostically, the expression of miRNA can be used to ascertain whether or not the tumour has spread. Such a scenario is indicated by high levels of miR-21 and miR-155 and low levels of miR200. Visible in invasive carcinoma is miR-21 [3, 41].

Adjacent to the BRCA1 gene is the non-protein coding gene NBR2. Even though the endogenes only differ by 218 base pairs, their transcriptions are very different. According to multiple studies, the NBR2 and BRCA1 genes may be cooperatively controlled. In some cell lines, there is a relationship between decreased BRCA1 levels and increased NBR2 expression. RNA polymerase II promoter competition may be the cause of this. It also indicates that the NBR2 promoter proposal might reduce BRCA1 expression [40]. A noteworthy variation has been identified in the BRCA1 gene, rs8176318. It is related to the NBR2 gene's expression in breast tissue. It should alter the manner in which various miRNAs attach. Numerous miRNAs are dysregulated in human breast cancer cells, as shown by northern blot and microarray analysis. Pathological characteristics of breast cancer, such as the expression of the progesterone and estrogen receptors, vascular invasion, and proliferation index, are associated with the expression of mir-125 b, mir-145, mir-21, mir-155, and miRNA [41].

Conclusion

The convergence of genetic screening and personalized medicine, combined with the ongoing enhancement of diagnostic

technologies, is set to transform the management of breast cancer. The critical role of interdisciplinary research is underscored, as it is indispensable for unraveling the intricacies of breast cancer and for developing more effective preventive, diagnostic, and therapeutic strategies.This study lays a solid foundation for future research aimed at reducing the impact of breast cancer. By capitalizing on the latest discoveries in the genetic and molecular aspects of the disease, alongside a profound understanding of risk factors and innovative treatment modalities, the potential for improved patient outcomes and a better quality of life for breast cancer survivors is within reach.The research also emphasizes the importance of early detection through mammography screening, which has been demonstrated to lower mortality rates, especially in women with a family history of the disease. However, it also recognizes the potential drawbacks of screening, such as overdiagnosis and unnecessary treatment, which can affect a person's quality of life and physical well-being. Striking a balance between the benefits and risks of screening is a critical aspect of cancer management.Moreover, the research highlights the role of genetic mutations beyond BRCA1 and BRCA2, including those in genes like TP53, PTEN, and PALB2, which are associated with an increased risk of breast cancer. Identifying these genetic markers through multigene panel testing and studying variants of uncertain significance are essential for risk stratification and personalized treatment planning.The research also addresses the impact of obesity in postmenopausal women, which is associated with a higher incidence of breast cancer, and the correlation between breast cancer and estrogen levels. It suggests that elevated estrogen levels not only increase the risk of breast cancer but also contribute to weight gain, potentially exacerbating the disease in a vicious cycle.The research presented in this article provides an in-depth examination of breast cancer, covering its genetic foundations, risk factors, and innovative treatment methods. The findings underscore the need for ongoing research and collaborative efforts to advance the field and enhance patient care. The potential of genetic screening and personalized medicine to revolutionize breast cancer management is significant, and with continuous progress in diagnostic technologies and targeted therapies, the prognosis for breast cancer patients is becoming increasingly hopeful.

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