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SCREENING OF BRCA1 AND BRCA2 GENES AND THEIR THERAPEUTIC IMPLICATIONS IN TRIPLE-NEGATIVE BREAST CANCER: A SYSTEMATIC REVIEW OF THE LITERATURE

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ABSTRACT

Background and Objective: Breast cancer represents one of the most prevalent and deadly neoplasms among women, requiring strategic public health interventions to mitigate its social and clinical impacts. This study aims to analyze the biological and epidemiological aspects of breast cancer in Brazil, highlighting the cellular mechanisms involved in tumor progression and the relevance of early screening. **Methods:** This is a narrative literature review focusing on cell cycle regulation, alterations in the synthesis phase (S phase), and regional disparities in access to diagnosis in the Brazilian context. Conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, the searches for this review were performed in the PubMed database, resulting in the selection of 17 articles for analysis **Results:** The literature indicates that tumor progression is closely associated with failures in cell replication checkpoints, favoring the disordered proliferation of atypical cells. From an epidemiological perspective, significant regional inequalities in disease incidence and mortality are observed, influenced by socioeconomic factors and barriers to healthcare access. However, the implementation of systematic screening programs demonstrates high efficacy in detecting subclinical lesions, significantly increasing cure rates and enabling less invasive therapeutic approaches. **Conclusion:** An integrated understanding of cell cycle molecular mechanisms combined with assertive regional screening strategies is essential to reduce mortality, optimize public health resources, and improve patient prognosis and quality of life.

Keywords: Breast cancer; Screening; Early diagnosis.

INTRODUCTION

Breast cancer is a multifactorial disease associated with determinants such as lifestyle, genetic predisposition, reproductive and hormonal history, and age at menopause, among other factors[1]. It is currently one of the leading causes of mortality among women worldwide, which makes it a significant public health challenge in many countries, including Brazil. According to data from the Brazilian National Cancer Institute[2](Instituto Nacional de Câncer), 73,610 new cases of breast cancer were recorded in women between 2023 and 2024, with a higher prevalence in those aged 41 years and older. In the state of Goiás, during the same period, 1,970 new cases were recorded, with a crude rate of 52.75 and an adjusted rate of 45.63. Regarding mortality, the Central-West region has one of the highest mortality rates in the country, followed by the Southeast region. This situation underscores the importance of oncological surveillance as an essential strategy for improving survival rates in the country, particularly in the Central-West region[3].

Cancer arises from genetic and epigenetic alterations that

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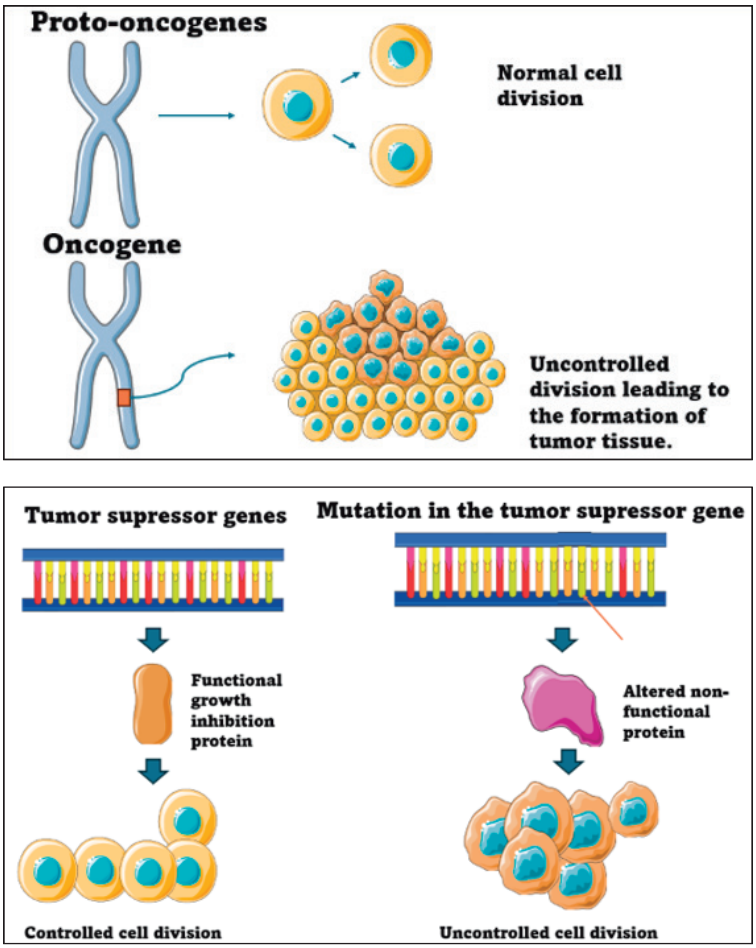
lead to cell cycle dysregulation, resulting in the emergence of abnormal cells that are harmful to the organism. The normal cell cycle comprises three main phases: interphase, mitosis, and G0. Mitosis consists of the division of one cell into two daughter cells. Interphase comprises three subphases: G1, during which the cell grows and verifies the integrity of its genetic material before DNA replication; S, the phase of DNA replication; and G2, in which the cell undergoes further preparation before entering mitosis[4].

The G0 phase is known as the period in which cells enter a stable, non-proliferative state, without growing, until the cell or the organism dies[5]. When a mutation occurs in a parent cell and the organism fails to correct it, thereby preventing daughter cells from inheriting the mutation, the affected genetic material may not function properly, disrupting the cell cycle and leading to cancer[4].

Another mechanism through which this genetic disease can arise is the overexpression of growth factors or the failure of tumor suppressor proteins that regulate the cell cycle. This results in uncontrolled cell proliferation and the emergence of cancer cells that do not undergo apoptosis (programmed cell death) and therefore continue to grow until they infiltrate other tissues. There are also genes known as tumor suppressor genes, such as *BRCA1*, *BRCA2*, and *TP53*, and proto-oncogenes, such as *RAS*, human epidermal growth factor receptor 2 (*HER2*), *BRAF*, *RET*, and *MET*. These genes are responsible for ensuring that cells do not undergo tumorigenic transformation. While tumor suppressors may be inactivated and thus lose their function, proto-oncogenes may acquire mutations that convert them into oncogenes, that is, tumor-promoting genes[4]. Figure 1 illustrates this mechanism, and Table 1 presents the main genes associated with triple-negative breast cancer.

These mutations can affect any region of the body. In the case of the breast, the gene most frequently associated with the hereditary form of this neoplasm is *BRCA1*. Tumors associated with mutations in this gene tend not to express progesterone receptors, estrogen receptors, or human epidermal growth factor receptor 2 (HER2), characterizing the triple-negative subtype. In contrast, *BRCA2* mutations are strongly associated with sporadic breast cancer. When mutations occur in both *BRCA1* and *BRCA2*, patients may develop neoplasms at sites other than the breast, such as the ovaries, a condition known as hereditary breast and ovarian cancer (HBOC) syndrome. Other genes are also implicated in the development of breast cancer, such as *CHEK2*, *ATM*, *BRIP1*, and *PALB2*, although with lower penetrance[6].

Figure 1. Impact of mutations in tumor suppressor genes and proto-oncogenes on cell cycle regulation.



Source: Image modified from Wong et al. 2020[7].

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Table 1. Genes associated with triple-negative breast cancer.

Gene	Full gene name	Location	Gene class	Gene function
BRCA1[8]	Breast cancer gene 1	17q21	Tumor supressor	Plays an important role in maintaining genomic stability by performing DNA repair through homologous recombination.
BRCA2[8]	Breast cancer gene 2	13q12.3	Tumor supressor	Plays an important role in maintaining genomic stability by performing DNA repair through homologous recombination in conjunction with BRCA1.
TP53[9]	Tumor protein p53	17p13.1	Tumor supressor	Responsible for regulating the expression of target genes, inducing cell cycle arrest, apoptosis, senescence, DNA repair, or metabolic alterations.
BARD1[8]	BRCA associated RING domain 1	2q35	Tumor supressor	Forms a heterodimer with BRCA1, acting in the DNA damage response, particularly in homologous recombination repair and cell cycle regulation.
PALB2[8]	Partner and localizer of BRCA2	16p12.2	Tumor supressor	Acts as a mediator of BRCA1 and BRCA2 in DNA repair by homologous recombination.
RAD51D[8]	RAD51 paralog D	17q12	DNA repair	Acts in DNA repair via homologous recombination as one of the RAD51 paralogs.
RAD51C[8]	RAD51 paralog C	17q22	Reparo de DNA	Acts in DNA repair via homologous recombination as one of the RAD51 paralogs.
BRIP1[8]	BRCA1 interacting DNA helicase 1	17q23.2	DNA repair	Acts in DNA repair through interaction with BRCA1, contributing to genomic stability.
MYC[9]	MYC proto-oncogene	8q24.21	Oncogene	Encodes a transcription factor that controls the expression of genes related to the cell cycle.
PTEM[9]	Phosphatase and tensin homolog	10q23.31	Tumor supressor	Encodes a lipid phosphatase that negatively regulates the PI3K/AKT pathway, inhibiting cell proliferation and promoting genomic stability.
rb1[9]	Retinoblastoma 1	13q14	Tumor supressor	Encodes the pRb protein, which acts as a negative regulator of the cell cycle by binding to E2F factors, preventing progression from the G1 to the S phase.

Source: Author's compilation (2026), based on Shimelis et al. (2018) [8], Wang et al. (2019) [9], and NCBI Gene database[10].

Breast neoplasia exhibits high biological heterogeneity and can be classified into distinct subtypes based on the expression of immunohistochemical markers, such as human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER), and progesterone receptor (PR). This classification is essential for therapeutic management, since certain subtypes, such as triple-negative breast cancer, are associated with low survival rates[11].

Triple-negative breast cancer (TNBC) comprises a group of tumors characterized by distinct transcriptional profiles, biological composition, and immune microenvironment. This subtype does not express estrogen receptors, progesterone receptors, or HER2, which makes its treatment a major challenge. At the molecular level, TNBC can be classified into basal-like (1 and 2), luminal androgen receptor (LAR), immunomodulatory (IM), and mesenchymal (MES) subtypes[12]. Currently, the main therapeutic approaches include systemic chemotherapy and immune checkpoint blockade, a

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strategy that inhibits regulatory proteins of the immune system, allowing T cells to recognize and eliminate tumor cells more effectively.

To optimize treatment and prognosis, early diagnosis is of fundamental importance, given that poor prognosis is frequently correlated with detection at advanced stages and diagnostic failures[13]. Mammography is currently one of the most widely used techniques, as it facilitates early detection, reduces the need for more invasive medical interventions, and guides appropriate therapeutic management[14]. Another method considered the gold standard for the evaluation of breast nodules is core needle biopsy, which, despite its invasive nature, allows a definitive histological diagnosis[15].

However, these methods show high rates of false positives (56%) and false negatives (22%) in women under 50 years of age, especially those with dense breast tissue. This highlights the need to develop new diagnostic methods that can reduce the discomfort associated with traditional approaches and provide better sensitivity and specificity across all breast tissue types[16]. Accordingly, a study of patients' genetic profiles may contribute to improved treatment, since this profile is individual and understanding the mechanism of action of tumor suppressor genes and proto-oncogenes may help guide the selection of appropriate therapy.

Among the several genes reported in the literature as associated with the prognosis of this neoplasm, mutations in the BRCA1 and BRCA2 proteins, mainly deleterious ones, are strongly linked to hereditary susceptibility and early onset of TNBC[17]. The *BRCA1* and *BRCA2* genes play a crucial role in maintaining genomic stability and are heavily involved in the repair of DNA double-strand breaks through homologous recombination. In addition to acting directly in the repair of lesions, these proteins also function in preventing the formation of gaps during DNA replication. Loss of function of these proteins results in genomic instability, which may lead either to cell death or to the survival of mutant clones with oncogenic potential[18].

Although BRCA1 or BRCA2 deficiency renders tumor cells more sensitive to chemotherapy, since chemotherapy induces the very lesions that these genes normally repair, TNBC remains a neoplasm with an unfavorable prognosis, marked by a high rate of early recurrence, frequent metastases, and low overall survival compared with other breast cancer subtypes[17]. In Brazil, studies have focused on the evaluation of germline variants in patients with a family history of breast cancer, leaving research on molecular and histological characteristics limited[20].

Therefore, this study aims to review the available scientific literature on the impact of *BRCA1* and *BRCA2* mutations on the prognosis of patients with triple-negative breast cancer, highlighting the importance of genetic classification as an essential tool for therapeutic decision-making and individualized clinical management.

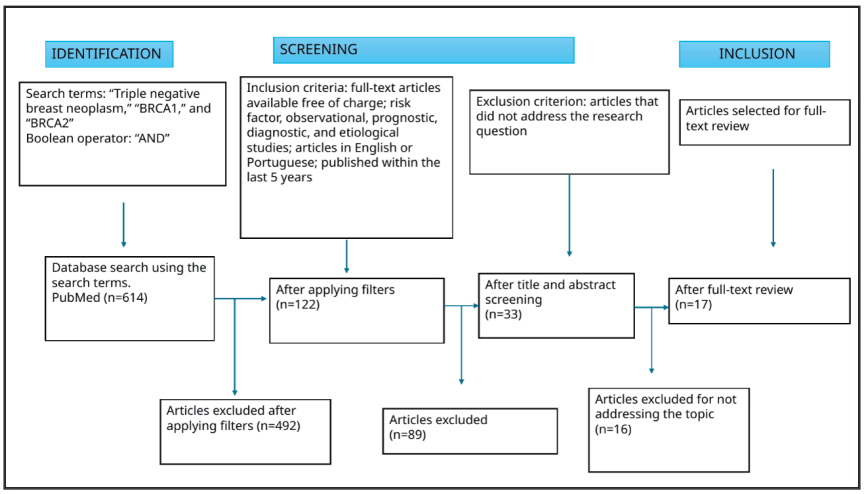
METHODS

This systematic review was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. Searches were conducted in the PubMed database for articles published within the last five years. The search terms were selected from the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH) and combined using the Boolean operator AND. The descriptors were used as follows: "Triple Negative Breast Neoplasms" AND "BRCA1" AND "BRCA2".

The inclusion criteria were as follows: full-text articles available free of charge, and studies addressing risk factors, observational designs, prognosis, diagnosis, and etiology. Only articles published in English or Portuguese were considered. Any article that did not meet these criteria was excluded. Figure 3 outlines the study workflow.

The figures were created in PowerPoint using icons available on the Bioicons platform.

Figure 3. Flow diagram of the methodological selection of articles included in the systematic literature review.



Source: Adapted from PRISMA (2020).

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RESULTS

Initially, according to the flow diagram in Figure 1, 614 articles were identified in the databases without the application of filters. After applying the inclusion criteria filters, 122 articles remained. Subsequently, through title and abstract screening, 89 articles were excluded because they did not address triple-negative breast cancer or the genes investigated in this study. After full-text reading of the remaining 33 articles, only 17 were retained.

Table 2 summarizes the findings from the scientific literature regarding the impact of *BRCA1* and *BRCA2* mutations on the prognosis of patients with triple-negative breast cancer.

Table 2. Results obtained from systematic searches in scientific literature databases.

Authors/Year	Title	Objetive	Main findings
Richters, Lisa, et al. 2025[21]	Genetic Alterations, TherapyResponse, andSurvivalAmongPatients WithTriple-Negative BreastCancer.	To analyze the effect of tumor pathogenic variants (tPVs) in *BRCA1* and/or *BRCA2* on pathological complete response (pCR), invasive disease-free survival (IDFS), and overall survival (OS) in patients with early-stage triple-negative breast cancer (TNBC), comparing two intensified neoadjuvant treatment regimens.	Patients harboring pathogenic variants in *BRCA1/2* showed higher pathological complete response rates.
Li, Ruo Qi, et al. 2024[22]	Genomic characterization reveals distinct mutational landscapes and therapeutic implications between different molecular subtypes of triple-negative breast cancer.	To identify the specific molecular characteristics of each TNBC subtype and their clinical relevance using next-generation sequencing.	Mutations in *BRCA1* and *BRCA2* were more frequently found in patients with the MES and IM subtypes, respectively. Moreover, each subtype showed a better prognosis with specific therapeutic management that differed among subtypes.
Telli, Melinda L. et al 2024[23]	Neoadjuvant talazoparib in patients with germline BRCA1/2 mutation-positive, early-stage triple-negative breast cancer: exploration of tumor BRCA mutational status.	To study alterations in *BRCA1* and *BRCA2* in order to better understand the outcomes of talazoparib treatment in patients carrying mutations.	The presence of hereditary mutations in *BRCA1* and *BRCA2* strongly influences the pathological biology of TNBC and is a strong aid in deciding on neoadjuvant treatment. It is also associated with a higher degree of aggressiveness.
Mutai, Raz et al. 2024[24]	The impact of germline BRCA pathogenic variants in locally advanced, triple negative breast cancer treated with platinum-based neoadjuvant chemotherapy.	To investigate the impact of germline *BRCA* pathogenic variants on outcomes of patients with advanced TNBC treated with platinum-based neoadjuvant chemotherapy.	Although previous studies had not explicitly reported better outcomes in patients with germline *BRCA* mutations, carriers showed better survival than patients with wild-type *BRCA*. The article reinforces that knowing *BRCA* status aids early diagnosis.
Moreno, Marcelo et al. 2023[25]	Risk of metastasis in BRCA2 carriers diagnosed with triple-negative breast cancer.	To examine patterns of metastasis in TNBC patients with a *BRCA2* pathogenic variant, comparing them with patients with and without a *BRCA1* variant.	The study demonstrated an increased frequency of central nervous system (CNS) and bone metastases in patients with germline *BRCA2* mutations, although this is not an independent factor for prognosis or overall survival.

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Samusieva, Anastasiia et al. 2022[26]	Contribution of BRCA1 5382insC mutation to triple-negative and luminal types of breast cancer in Ukraine.	To estimate the frequency of the *BRCA1* 5382insC mutation in patients with TNBC and to compare it with its frequency in patients with luminal breast cancer in Ukraine.	*BRCA1* is highly mutable, and the prognosis of TNBC patients tends to vary according to this mutation, reinforcing the need to test for such mutations in patients with this breast cancer subtype.
Menghi, Francesca et al. 2022[27]	Genomic and epigenomic BRCA alterations predict adaptive resistance and response to platinum-based therapy in patients with triple negative breast and ovarian carcinomas.	To investigate the causes of inconsistencies in the clinical predictive value of *BRCA* status and homologous recombination deficiency (HRD) scores in defining chemotherapy response in TNBC and ovarian cancer (OvCa).	Tumors with pathogenic *BRCA1* and *BRCA2* mutations, tumors with silencing of these genes by promoter methylation, and tumors proficient for both genes are distinct clinical-therapeutic entities and respond differently to chemotherapy.
Ji, Gang et al. 2021[28]	Germline and tumor BRCA1/2 pathogenic variants in Chinese triple-negative breast carcinomas.	To investigate the prevalence of germline and tumor pathogenic variants (PVs) in *BRCA1/2* according to age-based screening in Chinese patients with TNBC.	The study suggests that *BRCA1/2* pathogenic variant testing is more cost-effective for patients and allows better therapeutic targeting, since these patients are more sensitive to chemotherapy.
Glodzik, Dominik et al. 2020[29]	Comprehensive molecular comparison of BRCA1 hypermethylated and BRCA1 mutated triple negative breast cancers.	To analyze the occurrence of *BRCA1* promoter hypermethylation in a population-based cohort of early-stage TNBC, its signature in the tumor genome and immune microenvironment, and its implications for patient prognosis after standard adjuvant chemotherapy in the context of *BRCA1*-null tumors.	The study implies that *BRCA1* hypermethylation accounts for the increased incidence of TNBC in patients without a family history of the disease.
Zhu, Xiuzhi et al. 2024[30]	Stability and variability of molecular subtypes: comparative analysis of primary and metastatic triple-negative breast cancer.	To investigate, through a longitudinal study, the clinical characteristics of each molecular subtype of TNBC.	Subtype classification proved extremely important for guiding appropriate treatment. Among the four subtypes, the basal subtype had the worst prognosis and is one of the predominant subtypes in both early-stage and metastatic TNBC.
Eras, Nazan et al. 2024[31]	Clinicopathological Characteristics and BRCA1/BRCA2 pathogenic variants of patients with breast Cancer.	To analyze the relationship between *BRCA1/2* pathogenic variants and the clinicopathological features of breast cancer patients in Turkey.	Patients with pathogenic variants in *BRCA1* and *BRCA2* tended to present with high histological grade, the triple-negative subtype, and a high cell proliferation rate.
Muhammad, Noor et al. 2023[32]	Contribution of constitutional BRCA1 promoter methylation to early-onset and familial breast cancer patients from Pakistan.	To investigate the frequency of *BRCA1* promoter methylation in patients with TNBC in Pakistan and its correlation with the clinicopathological characteristics of the disease.	The study found a high frequency of *BRCA1* promoter methylation in TNBC patients, supporting its investigation as a good predictor of triple-negative breast cancer.

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Mahtani, Reshma et al. 2023[33]	Real-World Study of Regional Differences in Patient Demographics, Clinical Characteristics, and BRCA1/2 Mutation Testing in Patients with Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer in the United States, Europe, and Israel.	To compare demographic data, clinical characteristics, and genetic counseling practices in a real-world population of adult patients diagnosed with locally advanced or metastatic HER2-negative breast cancer who underwent *BRCA1/2* mutation testing across different geographic regions.	Among TNBC patients tested for any *BRCA1/2* mutation, there were fewer significant regional differences in patient characteristics.
Feng, Cong et al. 2023[34]	Relationship between homologous recombination deficiency and clinical features of breast cancer based on genomic scar score.	To analyze the relationship between homologous recombination deficiency and the clinical characteristics of Chinese patients with breast cancer.	The study found that the rate of homologous recombination deficiency is higher in TNBC patients, highlighting the importance of screening for this alteration to improve treatment of patients with this subtype.
Guzmán-Arocho, Yaileen D. et al. 2022[35]	Clinicopathological features and BRCA1 and BRCA2 mutation status in a prospective cohort of young women with breast cancer.	To investigate the clinical and pathological differences among young breast cancer patients in the study population.	Among TNBC patients aged ≤30 years, *BRCA1* mutations predominated, whereas among those aged 36 to 40 years, *BRCA2* mutations predominated.
Boddicker, Nicholas J et.al 2021[36]	Risk of Late-Onset Breast Cancer in Genetically Predisposed Women.	To assess the prevalence of breast cancer caused by germline pathogenic variants in older women and the risks these variants may pose in this age group.	Even with a low prevalence of pathogenic variants at older ages, genetic screening for *BRCA1* and *BRCA2* mutations remains necessary. The study also highlights the importance of magnetic resonance imaging for diagnosis.
Chávarri-Guerr, Yanin et al. 2021[37]	Breast cancer associated pathogenic variants among women 61 years and older with triple negative breast cancer.	To characterize the profile of germline mutations and pathogenic variants in *BRCA* genes in women older than 60 years with TNBC.	The study showed a higher prevalence of pathogenic variants in *BRCA2* among women older than 60 years and reinforced that genetic screening in this age group remains crucial.

Source: Adapted from PRISMA (2020).

DISCUSSION

The analysis of the 17 included articles revealed the relevance of pathogenic variants and epigenetic alterations of these genes in the pathogenesis, prognosis, and therapeutic response of this neoplasm. In addition, the findings demonstrated how the presence of germline or somatic mutations can directly impact the aggressiveness of this oncological disease.

The association between *BRCA1/2* mutations and the triple-negative phenotype was consistently demonstrated across the analyzed studies. Samusiieva et al.[26] showed, in a Ukrainian population, that 10% to 20% of breast cancer cases correspond to the triple-negative subtype and that approximately 20% of these cases are associated with germline *BRCA1* mutations, highlighting the crucial role of this gene in the development of TNBC. This pattern was observed in different geographic contexts, as shown by Mahtani et al.[33], who compared data from European, North American, and Israeli patients and found that 3% to 6% of all breast cancer cases are caused by *BRCA1/2* mutations, with few significant regional differences in the characteristics of TNBC patients tested for these pathogenic variants.

Although Samusiieva et al.[26] observed a higher frequency of TNBC in patients older than 40 years in their cohort, whereas Mahtani et al.[33] included a younger population starting at 18 years of age, both studies reinforce that testing for *BRCA1/2* mutations should be considered regardless of age group, given the relevance of these alterations to the development and characteristics of TNBC.

The clinical manifestation of this association is reflected in features of greater tumor aggressiveness. Telli et al.[23] and Eras et

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al.[31] consistently showed that *BRCA1/2* mutations are associated with tumors of high histological grade, high proliferative index, and greater biological aggressiveness. This aggressiveness has a clear molecular basis, as *BRCA1/2* play a fundamental role in homologous recombination repair, a mechanism essential for maintaining DNA integrity. Feng et al.[34] corroborated this by demonstrating a significantly elevated rate of homologous recombination deficiency in TNBC patients. Thus, mutations in these genes result in genomic instability, which translates clinically into the aggressive phenotype observed.

However, it is important to recognize that *BRCA1* and *BRCA2* mutations should not be considered clinically equivalent entities. Li et al.[22] demonstrated, through next-generation sequencing, that *BRCA1* mutations are more frequently associated with the mesenchymal (MES) subtype of TNBC, whereas *BRCA2* mutations predominate in the immunomodulatory (IM) subtype. This distinction has relevant prognostic implications, since different molecular subtypes respond differently to specific therapeutic approaches and show distinct clinical outcomes. Zhu et al.[30] complement these findings by showing, in a comparative longitudinal study, that the IM subtype has a higher survival rate and a lower risk of recurrence than the MES and luminal androgen receptor (LAR) subtypes, reinforcing that molecular classification is essential for prognostic stratification and therapeutic decision-making.

Beyond differences in molecular subtypes, *BRCA1* and *BRCA2* mutations are also associated with distinct patterns of metastatic dissemination and age distribution. Moreno et al. observed an increased frequency of central nervous system and bone metastases specifically in carriers of germline *BRCA2* mutations, although this gene was not shown to be an independent prognostic factor for overall survival.

Additionally, Guzmán-Arocho et al.[35] identified age-related differences in mutation predominance, with *BRCA1* prevailing in younger patients (≤30 years) and *BRCA2* in patients aged 36 to 40 years. Taken together, these findings show that the heterogeneity of TNBC associated with *BRCA1/2* mutations is manifested not only in molecular characteristics but also in patterns of disease progression and age at onset, reinforcing the need for personalized approaches that take into account the specific mutated gene.

Epigenetic alterations, in addition to germline and somatic mutations, have emerged as a relevant mechanism in the inactivation of *BRCA* genes, particularly *BRCA1*. Glodzik et al.[29] identified that *BRCA1* promoter hypermethylation accounts for a significant proportion of TNBC cases in patients without a family history of the disease, broadening the spectrum of individuals who could benefit from targeted therapies. Muhammad et al. consolidate this finding by demonstrating a high frequency of *BRCA1* promoter methylation in Pakistani patients with early-onset breast cancer, no germline mutation, and a high-grade triple-negative phenotype, proposing *BRCA1* hypermethylation as a useful biomarker for screening and early diagnosis of the disease.

Although *BRCA1* hypermethylation is associated with aggressive tumors, Glodzik et al.[29] observed a good prognosis after standard adjuvant chemotherapy in patients with this alteration, suggesting that epigenetic silencing may confer therapeutic sensitivity similar to that observed in carriers of germline mutations. These findings highlight the need to evaluate not only genetic mutations but also the epigenetic profile, establishing *BRCA1* hypermethylation as a relevant biomarker for both risk stratification and prediction of therapeutic response in TNBC.

In the therapeutic context, alterations in *BRCA1/2*, whether through genetic mutation or epigenetic silencing, proved to be a robust predictor of response to neoadjuvant chemotherapy. The findings of Richters et al. showed that pathological complete response (pCR) in triple-negative patients carrying a *BRCA1/2* pathogenic variant was associated with a favorable prognosis after neoadjuvant treatment, particularly with carboplatin combined with nab-paclitaxel. In turn, Telli et al. suggested that patients with germline mutations could benefit from treatment with talazoparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, since this enzyme is essential for DNA repair and its inhibition is lethal to cancer cells harboring such mutations.

Additionally, the study by Mutai et al.[24] showed that the presence of germline *BRCA* mutations is associated with better overall survival compared with patients with wild-type *BRCA*, that is, patients whose *BRCA* genes are not mutated and whose tumors arise from alterations in other genes. The study therefore reinforces that, with knowledge of *BRCA* mutation status, patients may benefit from neoadjuvant platinum-based chemotherapy in particular. Supporting these studies regarding the chemosensitivity of patients with *BRCA* mutations, Ji et al. demonstrated that screening for *BRCA1* and *BRCA2* pathogenic variants may be more cost-effective: in their retrospective study, patients who underwent such screening derived substantial benefit from chemotherapy owing to its high efficacy, thereby avoiding additional treatments that would have increased costs.

It is important to emphasize, however, that breast cancers caused by a pathogenic variant, those with gene silencing through methylation, and those proficient for both genes represent distinct clinical and therapeutic entities. Menghi et al. demonstrated this in a translational study that analyzed groups of patients with a pathogenic variant, with methylation, and with neither alteration. They concluded that, although both the pathogenic variant and methylation result in homologous recombination deficiency, patients with methylation did not benefit as much from platinum-based chemotherapy as those with the pathogenic variant, owing to the lower sensitivity of these tumors. In contrast, patients without *BRCA* alterations benefited more from immunotherapy. Thus, genetic screening of patients with triple-negative breast cancer appears to offer both economic and prognostic benefits.

Two studies in this review focused specifically on genetic screening in older women with TNBC, a population frequently neglected in molecular testing protocols. Boddicker et al.[36] showed that, in a cohort of women older than 65 years, the prevalence of TNBC associated with *BRCA1/2* mutations was 4.79%, underscoring that genetic screening remains necessary in this age group, in addition to diagnosis by magnetic resonance imaging. Chávarri-Guerra et al.[37] corroborated this need by identifying a

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high prevalence of mutations specifically in *BRCA2* in women older than 60 years with TNBC, reinforcing that genetic screening in this population should not be overlooked. These findings challenge the notion that genetic testing is less relevant in older patients, demonstrating that age criteria should not limit access to molecular screening and appropriate therapeutic targeting.

The evidence presented in this review has direct practical implications for the clinical management of TNBC. Testing for *BRCA1/2* pathogenic variants should be performed routinely in patients with this cancer subtype, regardless of age or family history, since mutational status has a direct impact on therapeutic decisions, allowing the use of PARP inhibitors and platinum-based regimens, which are more likely to elicit a response. In parallel, the assessment of epigenetic factors, such as *BRCA1* hypermethylation, should also be considered, as it may influence the patient's response to the chosen therapy, as may the molecular classification of the subtypes of this neoplasm.

Genetic screening also has fundamental preventive implications, enabling the identification of at-risk relatives and the implementation of intensified surveillance strategies. The systematic incorporation of *BRCA* testing into clinical practice, ideally complemented by molecular classification of the tumor and assessment of epigenetic alterations, has the potential to significantly improve outcomes for patients with this disease and should be considered an essential component of the contemporary management of this neoplasm.

Despite the robust findings and the consistency observed across multiple studies, some limitations should be considered when interpreting this review. Methodological heterogeneity among the studies, including differences in mutation detection methods, patient selection criteria, and therapeutic regimens, limits the direct comparability of the results. In addition, the studies were conducted in populations of different ethnic backgrounds, including China, Turkey, Pakistan, Ukraine, the United States, and Israel, which may reflect geographic variations in the prevalence of specific mutations and differences in access to diagnostic and therapeutic resources.

Most of the included studies had a retrospective or cross-sectional design, with few prospective clinical trials, which introduces potential selection and information biases. Furthermore, few studies simultaneously evaluated germline mutations, somatic mutations, and epigenetic alterations in the same cohort, limiting the understanding of the relative contribution of each *BRCA* inactivation mechanism. These limitations, however, do not invalidate the consistent findings observed, but rather reinforce the need for additional prospective studies with standardized methodologies to confirm and expand the results of this review.

The gaps identified in this review point to important directions for future research. First, new prospective studies are urgently needed to report the outcomes of each patient group according to their mutations, in order to substantiate the various prognoses associated with the wide range of possible *BRCA1* and *BRCA2* mutations. Additionally, research on targeted therapies is still needed for patients with *BRCA* hypermethylation, since these patients respond differently to chemotherapy compared with those carrying pathogenic variants. The inclusion of populations underrepresented in the literature, particularly from Latin America, is essential for understanding the global variability of *BRCA* mutations and their clinical implications. Finally, studies integrating genetic, epigenetic, and transcriptomic data into multivariate predictive models may significantly improve risk stratification and the personalization of TNBC treatment.

Accordingly, the findings in the literature make it evident that analysis of *BRCA1* and *BRCA2* status is a crucial biomarker for the management of TNBC. This is further supported by the heterogeneity of mutations arising from ethnic variability, as shown by European, American, Asian, and African studies. The systematic incorporation of *BRCA* testing into clinical practice, complemented by molecular classification and epigenetic assessment, has the potential to significantly improve outcomes and should be considered an essential component of the contemporary management of TNBC.

CONCLUSION

This systematic review considers that the marked heterogeneity of *BRCA1* and *BRCA2* mutations results in distinct prognoses and varied responses to conventional treatments in patients with TNBC. Furthermore, based on the European, African, and American articles included, these mutations appear to be strongly influenced by ethnic factors. Thus, given that Brazil has a highly heterogeneous population, the need for genetic screening of patients is reinforced.

Accordingly, clinical research on both genes is clearly necessary, aiming to define personalized treatment and improved prognosis for patients with breast cancer, with an emphasis on the triple-negative subtype.

ETHICS APPROVAL

Approval from a Research Ethics Committee (Comitê de Ética em Pesquisa – CEP) was not required for this study, as it is a systematic review based exclusively on previously published studies and does not involve human participants or identifiable personal data.

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