REVIEW ARTICLE
https://doi.org/10.29289/2594539420230046

The influence of germline mutations on breast cancer

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ABSTRACT

The ability to evade protection mechanisms and uncontrolled cell growth can lead to the development of mutations, whether somatic or germline, and consequently to the dreaded diagnosis of cancer. Breast cancer is considered the most common type of cancer in women in several regions of Brazil, mainly in the South and Southeast, second only to non-melanoma skin cancer. Approximately 5% to 10% of neoplasms are related to germline alterations that lead to hereditary predisposition. There is evidence of an association with mutations in nine genes, the highest risk being breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2). Due to its epidemiological importance, in this narrative review we observed the main genetic mutations and syndromes associated with breast carcinoma, the recommendations for screening in high-risk patients, and the indication for genetic counseling. Bibliographic research on the PubMed and Cochrane databases and analysis of the *Guidelines Breast Cancer Risk Reduction* and *Breast Cancer Screening and Diagnosis*, from June 2022 to September 2023. In this review, we observed a greater influence of germline mutations on breast cancer related to the genes BRCA1, BRCA2, PALB2, PTEN, CDH1, STK11 and, in Brazil, considered a country of ethnic-racial diversity, to TP53. As cancer screening in the country is opportunistic, knowledge of germline mutations associated with breast cancer offers specific screening recommendations for high-risk patients, indications for genetic counseling, and guidelines for prophylactic surgery, in addition to impacting the formulation of public screening policies.

KEYWORDS: genetic predisposition to disease; germ-line mutation; breast neoplasms; genes; genes, BRCA1; genes, BRCA2.

INTRODUCTION

The human genome is composed of approximately 20 to 25 thousand genes, capable of producing functional molecules, and are considered the units of genetic information. This production results from the processes of transcription and translation[1].

Exposure to various endogenous and exogenous factors can generate changes in DNA, causing the so-called mutations[2], which can occur in somatic or germline cells. There are protective mechanisms capable of correcting them, but when these mechanisms are ineffective, they lead to the development of malignant cells[3].

Female breast carcinoma is prevalent in all regions of the country, mainly in the Southeast and South, second only to non-melanoma skin cancer. An estimated 73,610 new cases were reported each year in the 2023–2025 triennium. The risk increases with age, but it has been observed that the number of young patients diagnosed with the disease has exponentially increased[4].

Researchers indicate that between 70% and 80% of breast carcinomas are related to environmental factors and 5% to 10% to germline genetic alterations[5].

When a pathogenic germline variant alone is associated with a significantly increased risk of cancer, it is a hereditary predisposition syndrome. Most of these syndromes result from a mutation in one of the two alleles of a given gene present in the genome. Therefore, they present an autosomal dominant inheritance pattern, with a 50% risk of transmission to offspring[6].

Risk stratification for the development of breast cancer in a consultant depends on a detailed anamnesis, starting from personal history, analyzing factors such as age, habits, sedentary lifestyle, smoking, alcohol use, gynecological and obstetric history, personal and family history of cancer in first-degree relatives. In addition, there are mathematical models that quantify the risk of breast cancer, the most widely used being those of Gail and Tyrer-Cuzick[7].

Authors of a recent publication by the Breast Cancer Association Consortium found strong evidence for the association of pathogenic variants in nine genes with breast cancer risk. The genes considered high risk are TP53, BRCA1, BRCA2, PALB2, and ATM; BARD1, CHEK2, RAD51C, and RAD51D are moderate risk. ATM

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Conflict of interests: nothing to declare. Funding: none.
Received on: 11/19/2023. **Accepted on:** 07/03/2024

and CHEK2, in turn, are related to estrogen receptor-positive breast cancer, and the others, to hormone receptor-negative[8].

Pathogenic variants in BRCA1 and BRCA2 are the most common, being associated with almost 50% of the risk attributable to the family component for the development of the disease. These patients have a cumulative increase in the risk of invasive breast cancer, from 55% to 85%, up to the age of 70 years and a 15% to 65% increase in the risk of developing ovarian cancer[8].

It is worth familiarizing oneself with other hereditary diseases, such as Li-Fraumeni syndrome (mutation in the TP53 gene), Cowden syndrome (PTEN), and those in which other sites of involvement are more common, but which also present a risk for breast cancer such as Peutz-Jeghers syndrome (STK11) and hereditary diffuse gastric cancer (CDH1)[9].

Due to their epidemiological importance, in this study we described the main genetic mutations and syndromes associated with breast cancer and the risks of developing the disease as well as screening recommendations, strategies for early diagnosis, classification of high-risk patients, and genetic counseling.

The main objective of the study was to identify the importance and influence of germline genetic mutations on breast cancer in the literature. As secondary objectives, we sought to outline strategies for tracking the disease in the high-risk population.

METHODS

For this narrative review, the bibliographic research was based on the described objectives. The starting point consisted of the questions: what is the importance of the hereditary component in the risk of breast cancer? What syndromes are most associated with breast cancer? What are the risks of a person with a hereditary predisposition developing breast cancer? What are the screening strategies for patients classified as high risk? Searches were conducted on the PubMed and Cochrane databases and analysis of the *National Comprehensive Cancer Network Breast Cancer* (NCCN), *Guidelines Breast Cancer Risk Reduction*, and *Breast Cancer Screening and Diagnosis*, from June 2022 to September 2023.

RESULTS AND DISCUSSION

The human genome is composed of DNA, and we are exposed daily to several endogenous and exogenous factors capable of affecting and changing our genetic code, giving rise to somatic or germline mutations[10]. Somatic, or acquired, mutations occur during DNA replication, preceding a mitotic division, and are generally limited to a specific tissue. They affect all cells generated from the mutated cell, and this mechanism is one of the hallmarks of cancer. Germline cells occur during DNA replication, preceding meiosis. The mutation affects gametes and all cells that originate from them and are transmitted to offspring[10].

Breast cancer is categorized into subtypes based on molecular identification from immunohistochemical evaluation. In this process, the presence or absence of hormone receptors (estrogen and progesterone) and overexpression of the HER2 protein are identified. Perou and Sorlie (2000) developed *in situ* hybridization techniques for detecting HER2 amplification, leading to greater accuracy in dividing breast cancer into four subgroups[11]:

- Luminal A (KI 67, which corresponds to a cell proliferation index<10%);
- Luminal B (KI 67>10%);
- HER2 overexpressed (3+);
- Triple-negative (tumor without all three standard molecular markers).

Although most neoplasms are the result of complex interactions between the genetic component and the environment, a percentage of cases can be attributed to inherited genetic alterations, which lead to a greater predisposition to the development of tumors. Currently, it is estimated that approximately 5% to 10% of carcinomas are associated with hereditary predispositions such as breast, prostate, colorectal, and pancreatic cancer. Furthermore, certain tumors that occur predominantly in childhood may be hereditary, as is the case with retinoblastoma, considered the paradigm of familial cancer[12].

There are support tools, such as mathematical models, that can be used to numerically predict the risk of breast cancer. The most widely used are the Gail, Claus and Tyrer-Cuzick models. The Gail model is the best known and focuses primarily on personal background, but is limited to family background. The Claus model focuses almost exclusively on family background. Conversely, the Tyrer-Cuzick model is the one that covers information the most[13].

Gail assesses the risk of breast cancer occurring in the next five years, reaching the age of 90 (lifetime risk). Using this method, eligibility for the use of tamoxifen is calculated (greater than 1.67% in five years). The Claus model assesses the lifetime risk of breast cancer and determines eligibility for breast MRI (greater than 20%). Tyrer-Cuzick assesses the ten-year risk of breast carcinoma and polygenic genetic inheritance and guides genetic counseling in patients with a lifetime risk above 20%.

Genes associated with hereditary breast cancer are subdivided into high-risk genes (relative risk – RR>or equal to 5), moderate-risk genes (RR>or equal to 1.5 and<or equal to 5), and low-risk genes (RR<or equal to 1.5)[8,14].

In the last decade, significant advances have been made in the knowledge of molecular mechanisms that give rise to cancer, identifying several genes directly involved in the development of neoplasias, including oncogenes (which predispose to cancer when overexpressed), tumor suppressor genes (which can give rise to a tumor when inactivated), and genes of the DNA repair system (inactivation leads to the accumulation of mutations). This culminated in the identification of genes associated with specific hereditary cancer predisposition syndromes[15].

The most frequently mutated genes are BRCA1 (27.4%), BRCA2 (20.3%), TP53 (10.5%), ATM (8.8%), CHEK2 (6.2%), and PALB2 (5.1%) (Figure 1). BRCA1 and BRCA2 account for approximately 50% of all pathogenic/likely pathogenic germline variants. The multigene panel was responsible for doubling the identification of germline variants in predisposition genes other than BRCA1 and BRCA2 as well as increasing the chance of finding a variant of unknown significance (VUS) by 12 times[16].

Genes considered moderate risk, which increase the risk of breast cancer by at least two times, are identified in 2% to 3% of women diagnosed with breast carcinoma and in approximately 1% of the general population. ATM, CHEK2, and PALB2 are the most common in this subgroup[17].

For ATM and CHEK2 variants, odds ratios were higher for breast cancer with estrogen receptor-positive disease than for hormone receptor-negative disease. For BARD1, BRCA1, BRCA2, PALB2, RAD51C, and RAD51D variants, odds ratios were higher for estrogen receptor-negative than for hormone receptor-positive disease[18].

Among the high-risk syndromes, we can mention hereditary breast and ovarian cancer (HBOC), related to BRCA1 and BRCA2. Female patients with a BRCA1 mutation have a risk of approximately 70% of developing breast cancer by the age of 80 and a 9% to 20% risk of developing a second breast cancer. In patients with a BRCA2 mutation, the risk remains the same until the age of 80, but the risk of developing a second cancer within five years is reduced by 3% to 12%. The risk of developing ovarian cancer by the age of 70 in patients with a BRCA1 mutation is approximately 44% and with a BRCA2 mutation, 17%[9].

Li-Fraumeni syndrome is also mentioned, associated with a germline mutation in the TP53 gene, in which international case studies estimate a risk of up to 90% of carriers developing cancer by the age of 60. When developing breast cancer, the risk would be approximately 85% by the age of 70. The syndrome is considered to be at high risk for the development of multiple primary tumors[16].

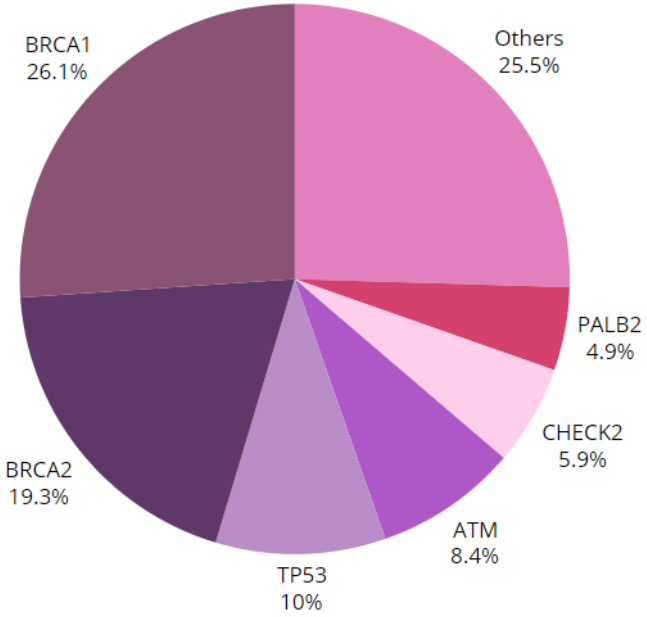


Figure 1. Graph with the main genes related to breast cancer and their frequency.

In Brazil, special attention should be given to the p.(Arg337His) variant in the TP53 gene. It is estimated that it is found in around 2.7 out of a thousand individuals born in the Southern region of the country. Researchers associate a more aggressive phenotype of Li-Fraumeni, with a mutation in an expression-modifying gene, XAF1. As a consequence, the high prevalence of this variant in TP53 significantly impacts screening strategies and risk reduction in the country[19].

Knowledge of genetic mutations related to breast cancer predisposition has a strong impact on the creation of screening and early diagnosis strategies.

According to the NCCN, screening for patients with BRCA1 and BRCA2 mutations begins at the age of 25, with a biannual clinical examination and annual breast MRI, and at age of 30, with annual mammography and MRI. According to the North American organization, risk-reducing mastectomy or prophylactic tamoxifen should be considered; salpingo-oophorectomy should be indicated as of the age of 35 in BRCA1 and as of the age of 40 in BRCA2; and, above the age of 75, management should be individualized.

For men, an annual clinical breast exam is recommended as of the age of 35 and mammography should be considered at the age of 50 or ten years before the earliest diagnosis in the family. For patients with TP53 mutation, breast screening is recommended as of the age of 20, with biannual clinical examination and annual MRI, and as of the age of 30, annual breast MRI and mammography[20,21].

Genetic testing to assess susceptibility to breast cancer has been an important aspect of disease prevention. Since the 1990s, with the description of the BRCA1 and BRCA2 genes, there has been a continuous improvement in guidelines for screening for breast cancer and reducing the risk for high-risk women and their families[22].

Genetic counseling is a fundamental part of the national cancer policy, being responsible for identifying individuals at high risk of developing tumors. This is the communication process that deals with the problems associated with the occurrence or possibility of a genetic disorder occurring in a family. Families with multiple cases of cancer, bilateral tumors, or tumors diagnosed at very early ages compared to the average age of diagnosis in the general population should be referred to genetic counseling. Among the foundations of this counseling are:

- voluntary use of services;
- informed decision-making;
- nondirective and noncoercive counseling;
- protection of privacy and confidentiality of genetic information;
- attention to psychosocial aspects associated with the impact and management of genetic information[9].

During a genetic evaluation, the patient's ancestry and region of origin must be taken into account. Individuals with *Ashkenazi* Jewish ancestry, for example, have a higher prevalence of mutations in the BRCA1 and BRCA2 genes, given that one in every 40 patients (2.5%) carries the mutation compared to one in every 400 patients (0.25%) in the general population[9].

In genetic counseling, risk-reducing surgeries, traditionally known as prophylactic surgeries, are considered prevention strategies. This term should be used with caution, as it suggests the false idea that mastectomy guarantees total prevention against breast cancer. This procedure may be indicated for high-risk patients, however, its role is better defined in women carrying deleterious mutations, especially BRCA1 and BRCA2. These surgeries are highly complex and have a considerable risk of complications, and should therefore be reserved for special situations and after careful assessment of risks and benefits in a multidisciplinary environment[23].

In the guideline published in 2024 by the American Society of Clinical Oncology (ASCO)[24], germline genetic testing is recommended for any patient up to 65 years of age who is newly diagnosed with breast cancer or has a history of this neoplasia, regardless of family history. This will allow patients to seek genetic counseling, allowing changes to be made in the way they and their families are monitored. It is also recommended that all patients with a history of breast cancer diagnosed over the age of 65 with any of the following criteria be tested:

1. Personal or family history suggesting the presence of a pathogenic variant;
2. Patient with triple-negative breast cancer histology;
3. Male patient;
4. Patient of *Ashkenazi* Jewish descent or member of a population with a higher prevalence of founder mutations.

In Brazil, Bill No. 265/2020 is currently being processed in the National Congress, which amends Law No. 11.664/2008, which provides for the implementation of health actions that ensure prevention, detection, treatment, and follow-up of cervical and breast cancers within the scope of the Brazilian Unified Health System (SUS), to also ensure tests for detecting genetic mutations[25].

The right has already been assisting women in the supplementary system operated by health insurance plans since 2014. In 2015, through the law known as the "Angelina Jolie Law," an agreement was signed between the government of Rio de Janeiro and the SUS for tests to detect genetic mutations of the BRCA1 and BRCA2 genes in women with a family history of neoplasia diagnosis. In 2019, Minas Gerais was the second Brazilian state to formulate legislation with the same purpose, followed by the states of Goiás, the Federal District, and Amazonas.

The NCCN 2024 includes the possibility of risk-reducing mastectomy for women carrying mutations in other genes, such as TP53, PTEN, PALB2, and salpingo-oophorectomy for those with mutations in RAD51C, RAD51D, and BRIP1. The first consistent data regarding the benefit of risk-reducing surgery in women at high risk for breast cancer come from the study by Hartmann et al., which showed a risk reduction after 14 years of follow-up in 90% of cases[26].

A study published in the Breast Cancer Research and Treatment in 2019 evaluated 2,857 asymptomatic women carrying a BRCA1 or BRCA 2 mutation and the benefit of risk-reducing surgery. At the end of the average follow-up of ten years, there were 268 cases of breast cancer in the BRCA1 group, which did not undergo surgery, and a higher mortality rate compared to those patients who underwent surgery (99.7% *vs* 93.2%, p=0.002)[21].

In view of the complexity of hereditary cancer in public health programs in 1996, in the USA, the National Cancer Institute (NCI) proposed the creation of a national cancer genetics network through the joint effort of doctors and researchers from various health institutions. The Cancer Genetics Network (CGN) was officially announced in September 1998 as a network of eight centers specializing in the study of hereditary predisposition to cancer[27].

CONCLUSIONS

The Brazilian population has unique ethnic characteristics. The miscegenation observed in the country offers an opportunity to advance in the understanding of the genetic characteristics of cancer without the bias of studies with isolated populations[28].

Identifying individuals with a higher genetic susceptibility to developing neoplasms is important, considering that there are education, screening, and risk reduction measures that can be indicated for this specific group[12]. Screening strategies should be followed with clinical and imaging tests in patients of all social conditions.

In Brazil, there are still few public or private actions aimed at identifying, guiding, and monitoring individuals and families at high risk for hereditary cancer. Larger and more prospective studies are necessary to observe and measure more effective interventionist — or even observatory — methods with greater certainty of execution.

AUTHORS' CONTRIBUTION

MFSVG: Conceptualization, Literature review, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. LLSC: Data curation, Formal analysis, Writing – review & editing. CA: Formal analysis, Investigation, Writing – original draft. JPCA: Validation, Writing – review & editing. HRG: Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. ADS: Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. JTCA: Conceptualization, Project administration, Methodology, Visualization, Writing – original draft.

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