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# BREAST CANCER: HARMFUL CHANGES IN THE BRCA 1 AND BRCA 2 GENES

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**Abstract:** Breast cancer, like many other types of tumors, is associated with genes whose main function is to repair errors in DNA, helping to maintain the genetic stability of cells. When for some reason these genes are affected and are unable to correct errors in genetic recombination with the chromosomes, it can lead to uncontrolled cell growth, causing genetic mutation, a problem that is relevant to the creation of tumors. This is a bibliographical review, which used Google Academic, PubMed and INCA as a research database, with the intention of demonstrating research related to genetic mutations in the BRCA1 gene, which is located on chromosome 17 and following mutations in this gene increase the risk of ovarian cancer, breast cancer and prostate cancer, and BRCA2 located on chromosome 13, mutations in this gene increase the risk of cancer, especially in women. This study shows the relationship between these genes in the formation of breast cancer, through readings based on existing published articles from 2012 to 2023 (except those relevant to the article). An understanding of the BRCA1 and BRCA2 genes and their role in predisposing to breast and ovarian cancer is essential for identifying high-risk individuals through tests to identify mutations in these genes, especially people with a family history of cancer, as well as developing appropriate prevention and management approaches.
**Keywords:** Genetic mutations. Breast cancer. BRCA 1 and BRCA 2.

## INTRODUCTION

Breast cancer is a disease caused by the disordered multiplication of abnormal cells, a neoplasm, and is one of the most common types of cancer affecting women in 2023, where 73,610 new cases were estimated, and in 2021 there were 18,139 deaths. Its origin is linked to various factors, environmental, genetic, age, gender; genetic factors, mutations in genes, are the most studied and relevant in its formation (INCA, 2023).

The *Breast Cancer gene* (BRCA), normally tumor suppressor genes, are essential for maintaining genetic stability, and when they are mutated they lose their protective capacity, increasing the propensity to develop tumors. In other words, they are responsible for correcting errors in the DNA, and when an alteration occurs there is a genetic mutation. These mutations can be hereditary, with a 50% chance of transmission to offspring, regardless of gender. Knowledge of these mutations is vital for the screening and early diagnosis of breast cancer. It is important to note that the BRCA1 and BRCA2 genes are responsible for ensuring a correction in cases of DNA errors, including during gene recombination between homologous chromosomes (CASTRALLI, BAYER, 2019).

The high risk of cancer associated with alterations in the BRCA1 and BRCA2 genes is based on their tumor suppressor function, their impact on the cell cycle, their heritability, their association with specific types of cancer and consistent epidemiological evidence. This justification highlights the importance of identifying and managing these mutations to reduce the risk of developing cancer in affected individuals (FURINI, 2018).

Mutation in the BRCA1 and BRCA2 genes is associated with a significant increase in the risk of developing breast and ovarian cancer in women, as well as increasing the risk of prostate cancer in men and other types of cancer

in both sexes. Recognizing these alterations is crucial for early identification and cancer risk management (ESTEVES, 2019).

Heredity to these mutations means that individuals with affected family members have an increased risk of carrying these mutations. Identifying these alterations in families with a history of cancer allows for preventive interventions and risk management strategies in relatives likely to develop the disease (DESTRO, 2019).

Therapeutic decisions are made after knowing the *status of* the BRCA1 and BRCA2 genes, which is crucial for determining treatment options in cancer patients. For example, patients with mutations in these genes may be candidates for targeted therapies, such as PARP (Poly ADP-Ribose) inhibitors, which are a family of enzymes involved in DNA repair. PARP is one of the first enzymes recruited when DNA is damaged, so its function is to facilitate proper repair, ensuring the genetic integrity of cells. These inhibitors have been shown to be effective in cancers associated with these mutations. With prevention and early detection Individuals with mutations in the BRCA1 and BRCA2 genes can benefit from preventative measures, such as more intensive surveillance and even prophylactic surgery, to reduce the risk of developing cancer or enable early detection, when the cancer is more treatable (SOARES, 2012).

Raising awareness about the importance of alterations in the BRCA1 and BRCA2 genes is key to ensuring that people understand their personal cancer risk and are aware of the options available for genetic testing, risk management and prevention. This can lead to better adherence to screening programs and preventive interventions. As a result, alterations in the BRCA1 and BRCA2 genes have great relevance, from the increased risk of cancer to implications for risk management, therapeutic decisions, prevention and early detection of cancer, as well as the need for awareness and education about these alterations (PEREIRA, 2020).

Therefore, the aim of this study is to review the contribution of the BRCA1 and BRCA2 genes to breast cancer, with the aim of demonstrating the identification of people with a greater predisposition to hereditary genetic alterations that can lead to breast cancer. As well as demonstrating the contribution of the BRCA1 and BRCA2 genes in breast cancer, which can include identifying mutation carriers, i.e. identifying individuals who have mutations in the BRCA1 and BRCA2 genes, especially those with a family history of breast cancer. Provide information on the significance of the mutations, the risks associated with breast and ovarian cancer and risk management options, show the importance of the BRCA1 and BRCA2 genes in breast cancer, highlighting the relevance of genetic testing, prevention strategies and treatment options for individuals with mutations in these genes.

## MATERIALS AND METHODS

A descriptive literature review was carried out on the subject, selecting recent articles from the years to the present day (2012-2023), in Portuguese and English, searched in the following databases: Google Academic, PubMed and INCA. The aim was to demonstrate research related to BRCA1 and BRCA2 genetic mutations and what they have to do with the formation of breast cancer, by reading published articles.

Inclusion criteria included papers published in English and Portuguese, articles on genetic mutations linked to breast cancer and articles selected between 2012 and 2023 (except those relevant to the article).

Exclusion criteria were articles dealing with types of cancer other than breast cancer and articles published before 2012.

In the end, 23 articles were selected out of 25 that met the proposed inclusion criteria.

## THEORETICAL FRAMEWORK

### LINKING GENES WITH BREAST CANCER

In cancer, the cells go into a mode of dividing uncontrollably and aggressively, forming a tumor that can spread to any other region of the body. The ability of these cells to also and the speed at which they migrate to other regions is known as metastasis (INCA, 2019).

Breast tumors are the most common type of cancer in women and are caused by the growth of breast cells, which may or may not develop rapidly. In Brazil, the incidence of breast cancer has been rising sharply, with an estimated 74,000 new cases per year, representing approximately 10.5% of all cancer cases and being one of the main causes of cancer death in women (INCA, 2021).

It is known that tumors such as breast cancer are linked to the BRCA 1 and BRCA 2 genes, which function as repairers in that they produce tumor suppressor proteins, and when for some reason these genes suffer mutations or alterations, their protein does not function correctly. As the protein in these genes is what repairs DNA, any intervention can affect cell production, causing uncontrolled cell production and damage without the possibility of repair, as the genes have been mutated or altered throughout the cell cycle. Hereditary predisposition plays a significant role in breast cancer, with 5% to 10% of cases related to hereditary genetic mutations. This can be achieved through genetic tests that assess the presence of mutations in these genes (PEREIRA et al, 2023).

A family history of breast cancer, especially involving genes such as BRCA1 and BRCA2, increases the risk of the disease. BRCA1, located on chromosome 17, is involved in DNA repair and cell cycle regulation and is expressed in situations of estrogen-mediated genomic instability. Meanwhile, BRCA2, located on chromosome 13, interacts with the RAD51 protein to repair breaks in the DNA double strand. The loss of function of these genes in germ cells can result in carcinogenic effects when both alleles of the BRCA1 and BRCA2 genes are affected by mutations. As a result, there is an increased risk of breast cancer due to hereditary mutations in BRCA 1 and BRCA 2 (figure 1). Rates of breast cancer in women are high due to mutations in these genes (MARQUES; MATTOS, 2023).

### TUMOR SUPPRESSOR GENES (BRCA 1 AND BRCA 2)

The BRCA1 and BRCA2 genes are essential for cell function and are located in the cell nucleus. They encode proteins responsible for DNA repair, controlling cell divisions and maintaining genomic stability (VEIGA, 2013).

BRCA1, located on chromosome 17, has 24 exons that code for 1,863 amino acids in different domains. BRCA2 is on chromosome 13 and also acts in tumor suppression, repairing DNA damage to maintain genomic integrity. Both genes present duplicated information, inherited from both the father and the mother (RBAC, 2018).

If BRCA1 is positive for a mutation, it means that one part of the gene is not working properly, making the cell dependent on the other allele to maintain its health. Mutations in BRCA1 increase the likelihood of developing diseases throughout life, while mutations in BRCA2 increase the risk for a wider variety of organs (FIGURE 1) (FURINI, 2018).

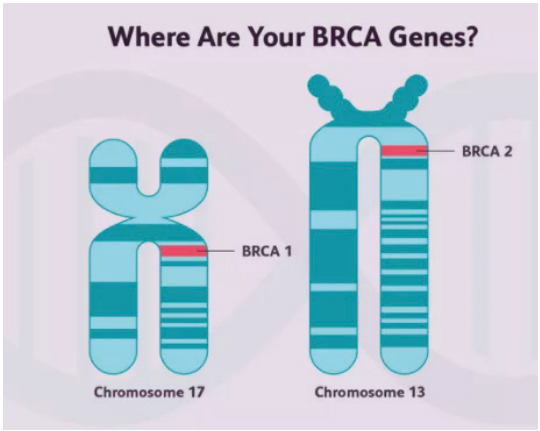


Figure 1 Chromosomes 17 and 13 showing the BRCA1 and BRCA2 genes, respectively. Source: Genera Blog (2020).

Individuals heterozygous for these genes are more likely to develop tumors, especially in the breast, ovary, pancreas and prostate. Although mutation in the BRCA gene is commonly linked to breast and ovarian cancers, it can affect both sexes. In addition, a mutation in the BRCA genes significantly increases the risk of developing tumors in the prostate and pancreas. In the case of prostate cancer, the BRCA2 mutation can result in more aggressive tumors compared to cancers unrelated to this mutation (JÚNIOR, 2016).

## BRCA1 AND BRCA 2 GENES

The BRCA1 gene encodes the BRCA1 protein, which has several functional domains, including RING (*Really Interesting New Gene*, at the N Terminal), BRCT (BRCA1 C Terminal), a superhelix-like structure (*coiledcoil*) and Nuclear Localization Signals (NLS). The RING and BRCT domains interact with proteins such as BARD1 (BRCA1-associated RING domain 1) and ABRAXAS (The ABRAXAS gene encodes a protein that interacts with BRCA1 (breast cancer 1), playing an essential role in maintaining genomic integrity and repairing double strand breaks by homologous recombination. (SILVER; LIVINGSTON, 2012).

During the S and G2 phases of the cell cycle, the essential function of restoring the integrity of damaged genetic material takes place, where an intact sister chromatid acts as a template for repair. This process is crucial for maintaining the accuracy of DNA replication. It is during this period that the highest concentrations of BRCA1 proteins are identified within the cell (ROY et al., 2017).

The BRCA2 gene encodes the BRCA2 protein, which contains different binding domains, including PALB2, RAD51, DNA and Nuclear Localization Signals (NLS). The BRCA2 protein regulates the assembly of the RAD51 recombinase, which is essential for invasion and the search for homologous DNAs. In addition, BRCA2 is involved in mediating cellular resistance against mutagens such as UV radiation (FURINI, 2018).

As mentioned, the BRCA2 protein plays a crucial role in DNA repair, interacting with BRCA1 to activate homologous recombination and repair double strand DNA breaks. Its interaction with the RAD51 protein is fundamental to this process, as evidenced by the similar phenotype between cells deficient in RAD51 and BRCA2. Mutations in the BRCA2 and TP53 genes in tumor cells influence the survival and initial development of the tumor. Loss of BRCA2 function can trigger genetic instability and affect cell cycle regulatory genes, such as TP53, leading to uncontrolled cell proliferation and invasive growth (SALEEM, 2018).

## RELEVANCE GENETIC TESTING

The field of biomedical science is increasingly allowing early diagnosis with the advancement of technologies, and genetic testing is highly relevant since it maps the human genome, exploring the constitution of DNA and thus making it possible to predict pathologies. The main benefit of carrying out a genetic test is to guide screening, recommendations and

prevention, followed by obtaining more accurate estimates of the risk of developing cancer and confirming whether breast cancer is hereditary (NEVES, 2022).

For some years now, we have been talking about Genetic Counseling, a service that aims to provide detailed information about a certain condition that is or may be genetic, with the aim of preventing or detecting genetic diseases at an early stage. Once the risk has been detected, a multidisciplinary team decides on the treatment to be applied to the patient on a case-by-case basis. In the case of breast cancer, there is the possibility of prophylactic surgeries that have a major impact on the patient, such as mastectomy (removal of the breast unilaterally or bilaterally) or oophorectomy (removal of the ovary unilaterally or bilaterally). These surgical procedures are traumatic for the patient and, for this reason, the team needs diversified and highly qualified professionals. It is important to emphasize that the final decision is always up to the patient, and the doctor can only explain the possibilities (NELSON, 2019).

The existing genetic tests are BRCA1 and BRCA2, which analyze the sequences of these two genes and whether or not they show any alterations, since errors in the information contained in these genomic sequences can be risk factors for some types of cancer, such as breast and ovarian cancer. This procedure makes it possible to identify alterations in the DNA sequences contained in these genes, compared to those observed in a reference genome. The methodology used to analyze the BRCA1 and BRCA2 genes is *Next Generation Sequencing* (NGS). This technology is also used in panels with multiple genes, such as the "Breast and Ovarian" panel or the "Hereditary Cancer" panel. The test is recommended for all people with a history of breast, ovarian or metastatic prostate cancer (NCI, 2018).

It is extremely important that biomedical professionals recognize this area of activity and get involved with the necessary training so that they can take ownership of this practice with quality and ethics, contributing to universal health care for people throughout the country. Biomedical professionals will certainly contribute to the organization of a network of services to carry out promotion, prevention, diagnosis, counselling and the necessary therapy for congenital anomalies or genetic diseases, which will enable comprehensive care in Clinical Genetics and improve the population's access to this specialized care. (CRUZ, 2019).

## PREVENTION AND TREATMENT

For people with mutations in the BRCA 1 and BRCA 2 genes, there are prevention strategies such as genetic testing, which is recommended for women with a family history of ovarian cancer or breast cancer; genetic mapping, which allows tests to be individualized and properly sequenced, guaranteeing early detection of the disease using a sample containing genetic material; and genetic counseling, where people at high risk of developing the disease should be referred for genetic testing, to clarify doubts, reduce possible anxiety and be prepared for the possible results of genetic tests (MATTOS, 2023).

Intensive screening measures and prophylaxis (prophylactic surgery and chemoprophylaxis) tend to significantly reduce the risk of cancer in mutation carriers, otherwise bilateral mastectomy is indicated for people who test positive for the BRCA mutation (COELHO, 2018).

Once the mutation of the BRCA 1 and 2 genes has been found, she and her medical team can proceed with measures that will reduce the risk of developing the disease or discovering it in the early stages, such as regular monitoring, screening, prophylactic surgery and preventive chemotherapy (MARQUES, 2023).

## CONCLUSION

It was concluded that mutations in the BRCA1 and BRCA2 genes play a significant role in breast cancer predisposition. These genes are involved in important DNA repair pathways and cell cycle regulation, and their mutations can substantially increase the risk of developing this type of cancer. Mutations in the BRCA1 and BRCA2 genes are associated with a higher incidence of breast cancer at an early age. In addition, these mutations are also linked to an increased risk of other types of cancer, such as ovarian cancer and cancer of the fallopian tube.

Breast cancer risk assessment in BRCA1 and BRCA2 mutation carriers must take into account genetic factors, as well as additional risk factors such as family history, age and hormone exposure. This information is essential for targeting preventive interventions and appropriate screening programs for high-risk individuals. The clinical management of patients with mutations in the BRCA1 and BRCA2 genes is complex and must be personalized, taking into account individual characteristics and family histories of cancer. Management options may include intensive surveillance, risk-reducing surgery and chemoprevention.

Understanding the BRCA1 and BRCA2 genes and their role in predisposition to breast and ovarian cancer is fundamental for identifying high-risk individuals and developing appropriate prevention and management approaches.

In order to identify the presence of germline mutations in the BRCA1 and BRCA2 genes, genetic testing is necessary. Currently, all the major international research and technological development centers advocate genetic counseling as an obligatory part of the investigation of abnormalities in the BRCA1 and BRCA2 genes, which are related to the development of hereditary breast cancer. The great challenge of anti-cancer therapy is cell or tissue specificity, i.e. getting the treatment to specifically target cancer cells. Agents that cause DNA damage play an important role in non-surgical anti-cancer treatments. In order to combat DNA damage and thus allow cells to function and replicate properly, cells have developed various mechanisms to detect and repair lesions in their genome.

DNA repair is a critical process to ensure the formation of intact proteins at the right time and in the right quantity. The balance between DNA damage and repair determines the success of the therapy. A high DNA repair capacity in tumor cells can lead to resistance and limit the effectiveness of these agents. For this reason, the study of DNA repair has become a very important aspect of anticancer therapy.

The development of specific therapies for patients with mutations in the BRCA1 and BRCA2 genes is already a reality. The therapies developed are based on agents capable of causing double strand breaks in the DNA, which will be repaired by homologous recombination, a pathway in which the BRCA1 and BRCA2 proteins participate.

Genetic testing offers the possibility of cancer prevention and early detection, but it also has other advantages. These include the possibility of more specific treatment, based on the genetic profile of the tumour, individualized clinical follow-up and testing for at-risk family members.

Biomedical geneticists can work in the performance, analysis and interpretation of genetic tests, including being the technical manager of laboratories specializing in this area. They can also offer consultancy and courses on this innovative subject to other professionals who want to implement or optimize their care and services with genetics and genomic medicine innovations. In all these cases, it is important to work in a multi-professional manner so that genetic information can be used in practice in different professional areas, providing better results for the patient.

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