ORIGINAL ARTICLE

ABSENCE OF ALLELIC VARIANTS IN THE *BRCA1* GENE OF NORTHERN BRAZILIAN BREAST CANCER PATIENTS WHO MET CRITERIA FOR HEREDITARY PREDISPOSITION: A TRANSVERSAL STUDY

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Highlights: (1) No pathogenic variants were identified. (2) Frequency of pathogenic mutations in the *BRCA1* gene may be low. (3) Provides insights on the Brazilian mutational profile of BRCA genes.

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ABSENCE OF ALLELIC VARIANTS IN THE *BRCA1* GENE OF NORTHERN BRAZILIAN BREAST CANCER PATIENTS WHO MET CRITERIA FOR HEREDITARY PREDISPOSITION: A TRANSVERSAL STUDY

ABSTRACT

Background - It is estimated that about 5 to 10% of all breast cancer cases have a hereditary context, in which tumor progression occurs through the activation or repression of important genes in the germ cell line of an individual. *BRCA1* is the most penetrant gene associated with breast cancer, and the presence of pathogenic mutations in its sequence increases the risk of developing this neoplasm to 45-75%. In the northern region of Brazil, the largest geographical region of the country, only two studies have been conducted to date to detect allelic variants in this gene. *Objectives* - This is a transversal study that aimed to assess pathogenic mutations in the *BRCA1* gene of breast cancer patients treated in a public health reference unit for cancer research and treatment in the western Amazon. *Design, setting and methods*- Genetic testing was performed using polymerase chain reaction (PCR) methods and Sanger sequencing of seven important coding regions of the *BRCA1* gene. *Results* - No variants were found in the sequences studied, which may indicate that the frequency of pathogenic mutations in the *BRCA1* gene in this population is low. *Conclusions* - Although no pathogenic mutations were identified in the analyzed sequences, this study provides epidemiological data for a better understanding of the Brazilian mutational profile of genes associated with breast cancer.

Keywords: mutation; breast neoplasms; genes, BRCA; Brazil.

AUSÊNCIA DE VARIANTES ALÉLICAS DO GENE BRCA1 EM PACIENTES COM CÂNCER DE MAMA COM PREDISPOSIÇÃO HEREDITÁRIA: UM ESTUDO TRANSVERSAL

RESUMO

Introdução: Estima-se que cerca de 5 a 10% de todos os casos de câncer da mama tenham um contexto hereditário, em que a progressão tumoral ocorre através da ativação ou repressão de genes importantes na linha celular germinativa de um indivíduo. O *BRCA1* é o gene mais penetrante associado ao câncer de mama, e a

presença de mutações patogênicas em sua sequência aumenta o risco de desenvolvimento dessa neoplasia para 45-75%. Na região Norte do Brasil, a maior região geográfica do país, apenas dois estudos foram realizados até o momento para detectar variantes alélicas neste gene. *Objetivos* - Este é um estudo transversal que teve como objetivo testar mutações patogênicas no gene *BRCA1* em pacientes com câncer de mama atendidas em uma unidade pública de saúde de referência para pesquisa e tratamento do câncer na Amazônia Ocidental. *Desenho, cenário e métodos*- O teste genético foi realizado utilizando métodos de reação em cadeia da polimerase (PCR) e sequenciamento de Sanger de sete importantes regiões codificadoras do gene *BRCA1*. *Resultados* - Não foram encontradas variantes nas sequências estudadas, o que pode indicar que a frequência de mutações patogénicas no gene *BRCA1* nesta população é baixa. *Conclusões* - Embora não tenham sido identificadas mutações patogênicas nas sequências analisadas, este estudo fornece dados epidemiológicos para uma melhor compreensão do perfil mutacional brasileiro de genes associados ao câncer de mama.

Palavras-chave: mutação; neoplasias da mama; genes, BRCA; Brasil.

INTRODUCTION

Breast carcinoma occupies the position of the most incident neoplasm in the world's population. In the female population of Brazil and the rest of the world, it is considered the leading cause of death from cancer[1,2]. According to data from the National Cancer Institute, the estimated incidence of breast cancer in Brazil in 2020 was 66,280 new cases, and the mortality rate in this year exceeded 27%. Most breast neoplasms have a sporadic character, i.e., they are associated with the accumulation of somatic mutations in the breast tissue. However, it is estimated that about 5 to 10% of all breast cancer cases have a hereditary context, in which tumor initiation and progression occur through the activation or repression of important genes in the germ cell line of an individual. These mutated genes, passed down from generation to generation in a Mendelian pattern of inheritance, increase the risk for hereditary predisposition to breast cancer [3].

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Of the genes associated with breast cancer identified to date, *BRCA1* and *BRCA2* are the most prevalent. Deleterious mutations in one allele of these genes increase the risk of developing breast neoplasia by 45 to 75%, which is four to six times higher when compared to the risk of 10 to 15% in the general population[4]. The *BRCA1* gene, identified more than thirty years ago[5], is located near the centromeric region of chromosome 17 (17q21.31), contains ~100 kb, and has 24 coding sequences (exons). The homonymous protein is composed of 1,863 amino acids and consists of a nuclear localization sequence (NLS) and three functional domains that allow interaction with several other proteins that are part of the genome repair pathway, which leads to a functional variety of this gene in processes such as DNA injury response, cell cycle regulation, ubiquitin-ligase activity, chromatin remodeling, stalled replication forks and homologous recombination[6].

In Brazil, studies conducted aiming at detecting mutations in *BRCA1* genes are mostly concentrated in the southeastern and southern regions. In the PubMed database, when applying the terms (BRCA1) and (Brazil), we found fifteen studies between the years 2004 and 2022, all of them concentrated in the southern hemisphere of the country. We also found two multicenter studies involving populations from several Brazilian states, but once again, the vast majority of the individuals included originated from the southeast and south[7,8]. Regarding the other regions, only one study was identified in the northeast [9] and two studies in the Amazon region, north of the country[10,11].

This study sought to assess for mutations in the *BRCA1* gene by sequencing seven important coding regions of this gene, as well as the characterization of clinical and biological aspects of the tumor in breast cancer patients from northern Brazil who met the criteria for hereditary predisposition.

MATERIALS AND METHODS

Human ethical approval and patient recruitment

This study was approved by the Research Ethics Committee of the *Universidade do Estado do Amazonas* (UEA) № CAAE: 95704617.0.0000.5016. All participants signed an informed consent form (ICF).

Characteristics of study participants

Fifty-three unrelated patients (52 females and one male) with a diagnosis of breast carcinoma were recruited at a reference unit in cancer research and treatment (*Fundação Centro de Controle de Oncologia - FCECON*) in the city of Manaus, northern Brazil.

The inclusion of patients followed the recommendations of the National Comprehensive Cancer Network (NCCN version 3.2014), which presents guidelines for selecting patients diagnosed with breast carcinoma (BC) for testing hereditary predisposition genes. These criteria were as follows: women with a personal history of BC before the age of 45; women with a personal history of BC between 46 and 50 years and first- or second-degree family history for breast, ovarian, or prostate cancer; women with triple-negative BC that were diagnosed before the age of 60; man with BC at any age.

The selected patients were referred to the Human Genetics Laboratory of the UEA. The medical records of each patient were analyzed to collect clinical and biological tumor data, such as age at diagnosis of the primary tumor, histological type and molecular subtype, and histological grade.

Genomic DNA extraction and molecular analysis

A 5 ml sample of peripheral blood was collected from each participant. Genomic DNA was extracted using the cetylmethylammonium bromide (CTAB) 2% method and quantified in a spectrophotometer (Nanodrop 1000®, Thermo Fisher). Exons 5, 6, 12, 15, 17, 18, and 24 of the *BRCA1* gene were amplified by polymerase chain reaction (PCR), using seven pairs of flanking primers [12]. The selection of the specific regions of

the *BRCA1* gene for sequencing in this study was guided by the results of previous research conducted in Brazil[7,8,13–15]. The PCR reaction was performed using 50 ng of genomic DNA, 1x amplification buffer, 0.6 mM $MgCl_2$, 0.2 mM dNTPs, 0.6 µM of both forward and reverse primers, and 1 U of Platinum Taq DNA polymerase (Invitrogen). The following thermocycling conditions were used: initial denaturation at 94°C for 5 minutes, 40 cycles of denaturation at 94°C for 45 seconds, specific annealing temperature of each primer for 40 seconds, and extension at 72°C for 45 seconds. PCR products were purified and subjected to the Sanger direct sequencing reaction using the BigDye™ Terminator v3.1 Cycle Sequencing kit (Applied Biosystems) and the same PCR primers. The sequences were read using an automatic sequencer (ABI 3130xl Genetic Analyzer, Applied Biosystems). The reference version of the human genome for identification of variants was the GRch38 version, which was obtained from the NCBI (National Center for Biotechnology Information) database. The transcript sequence NM_007294.3 served as a reference for alignment in BioEdit (v7.2.6), enabling comparison of similarities and detection of nucleotide variants in each studied exon.

RESULTS

Specific regions of the *BRCA1* gene (exons 5, 6, 12, 15, 17, 18 and 24) of 53 breast cancer patients were PCR amplified and sequenced for mutations. No pathogenic mutations or any other form of allelic variants was detected in the seven coding regions of this gene analyzed in this study. Invasive carcinoma of a non-special type was the predominant histological type (n=36), and the luminal B type was the most observed molecular subtype. Table 1.

Table 1. Histological types and molecular subtypes observed in patients in this study.

Histological types	
Invasive carcinoma - non-special type (NST)	36
Invasive carcinoma - special type	3
ductal carcinoma i*n situ* (DCIS)	3
Core biopsy unavailable	11
Molecular subtypes	
Luminal B	15
Luminal A	9
Triple-negative	6
Luminal hybrid	5
HER2-*enriched*	3
Unclassified	3
Without IMQ*	12

*Immunohystochemistry test.

DISCUSSION

The absence of pathogenic mutations or any other type of variants (benign or variant of unknown significance) is an unexpected result since these regions were chosen because pathogenic mutations have already been found in previous studies conducted in Brazil [7,8,13–17].

Other Brazilian studies have already conducted only partial investigation of mutations in the *BRCA1* gene either by selecting only specific coding regions for sequencing or by searching for specific variants[18]. Rocha et al. (2020) selected eight *BRCA1* exons (2, 3, 8, 9, 13, 16, 19 and 20) and detected a single pathogenic variant in a sample of fifty-three individuals from northern Brazil. Dufloth et al. (2005) also reported a single variant in thirty-one breast cancer patients, searching for mutations in only five exons (2, 3, 5, 11 and 20). Other authors searched for specific variants in the gene sequence. Ewald et al. (2011) aimed at determining the frequency of c.68_69del and c.5266dupC mutations in a sample of 137 Brazilian patients.

In this present research, the choice of exons was directed according to the methodology performed by Palmero et al. (2018), who aimed to map the most recurrent *BRCA1* variants throughout Brazil. This strategy was adopted to increase the probability

of identifying significant mutations within the limitations of the resources at hand. The sequencing method used was Sanger direct sequencing, a conventional technique that, although dependable, has considerable drawbacks for large-scale genetic analysis. Sanger sequencing machines produce DNA reads that are comparatively short - less than one kilobase in length - which means that each exon, or even a fragment of an exon, must be individually amplified by PCR and then sequenced. As a result, investigating the presence of mutations in multiple of exons, or even the entire gene, becomes a highly labor-intensive and technically demanding process[19]. A promising alternative is provided by the development of next-generation sequencing (NGS) platforms, which allow for the simultaneous analysis of several coding regions or even the entire *BRCA1* gene sequence. However, despite NGS's obvious benefits in terms of coverage and efficiency, major financial obstacles prevent it from being implemented. The high cost of purchasing and using NGS technology continues to be a significant barrier, especially for labs linked to Brazilian universities and public institutions. The majority of these facilities are unable to adopt this innovative methodology in routine practice because they lack the funding required to integrate NGS into their research and diagnostic workflows[20] .

Another reason for the divergence in mutation frequencies observed among populations from different regions of Brazil may be attributed to the significant ethnic diversity present within the groups selected for study. Brazil, due to its history, is a very ethnically diverse country and is composed of miscegenation between Indigenous peoples, Portuguese, and Africans. These groups came to Brazil from the nineteenth century onwards[18]. When comparing peoples from different Brazilian geographical regions, it is observed that African ancestry is predominant in the northeast region, while European ancestry is more frequent in the south and southeast of the country [21,22]. In northern Brazil, it has been estimated that white-skinned individuals constitute 22.7% of the population, while brown-skinned (with a varied ethnic ancestry) constitute 72.1% of the population. In the south and southeast of the country, for example, the percentage of whites is 83.3 and 62.3, respectively (IBGE, 2012). Considering the ethnic disparity between the northern and southern regions of the country and adding to this the fact that

the vast majority of molecular studies of the *BRCA1* gene have been carried out with the population of the southern and southeastern regions (the majority white), the non-observation in this work of mutations already detected by other Brazilian studies could be due to the difference in ancestry between these populations.

The mean age at diagnosis of the patients in this study was 44.5 years. Of the fifty-three participants in this study, fifty-one are native to northern Brazil (50 from the state of Amazonas and one from the state of Pará). The self-declaration of ethnicity (white, brown, Black, Indigenous, or others) was not found in the medical records of most patients.

The predominant histological type in this sample was invasive carcinoma of a non-special type (n=36), which is usually observed in about 50 to 80% new breast cancer diagnoses [23]. The other histological types were invasive carcinoma of special type (n=3) and *in situ* ductal carcinoma (n=3). In the other eleven cases, the result of the core biopsy was unavailable in the medical record. Regarding the classification by the immunohistochemical standard (IMQ), the luminal B subtype was the most observed (n=15), followed by luminal A (n=9), triple-negative (n=6), hybrid luminal (n=5), HER2-enriched (n=3), unclassified (n=3), and twelve other cases without immunohistochemical test results in their medical record. Among the hormone-positive tumors, luminal B tends to present the highest histological grade and the worst prognosis [24].

Even though this study did not identify deleterious mutations or any other polymorphism in the sequences studied, it provides molecular epidemiological data for a broader understanding of the Brazilian mutational profile in genes associated with the development of breast cancer. Verifying the presence of pathogenic mutations in an individual with breast neoplasia has implications for the clinical and therapeutic management of the disease since new personalized drugs have been developed [25]. The detection of variants in an individual also directly affects their family members, who may carry the same mutation and be at increased risk for breast cancer or other related neoplasms such as ovarian, pancreatic, or prostate cancer [26]. The asymptomatic carrier can therefore adopt prophylactic measures such as lifestyle changes, more frequent

surveillance for early detection (clinical breast examination and annual magnetic resonance imaging from the age of 30, mammography from the age of 25), preventive chemotherapy, or even surgical methods such as mastectomy or prophylactic salpingo-oophorectomy [27,28].

CONCLUSION

The *BRCA1* gene is one of the main genes associated with hereditary breast cancer tumorigenesis, but there are still other genetic components that contribute to the increased risk of this type of neoplasm. The gene panel with the greatest clinical importance to be requested for the investigation of the hereditary predisposition of breast cancer is composed of nine other genes, besides *BRCA1* (*ATM, BARD1, BRCA2, BRIP1, CHEK2, PALB2, RAD51D, RAD51C,* and *TP53*)[29]. In the present study, the sequences of seven of the twenty-four coding regions of this extensive gene were analyzed. The remaining exons are being studied in parallel by another team from UEA's Human Genetics Laboratory, to obtain the complete sequence of this gene.

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