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Prevalência de Mutações nos Genes *BRCA1* e *BRCA2* e a Predisposição ao Câncer de Mama Hereditário em Brasileiros: Revisão Sistemática

Prevalence of Mutations in BRCA1 and BRCA2 Genes and Predisposition to Hereditary Breast Cancer in Brazilians: Systematic Review

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RESUMO

Os fatores genéticos hereditários são responsáveis por 5% a 10% dos casos de câncer de mama (CM) no mundo. Os genes *BRCA1/2* estão entre os mais frequentemente analisados para CM hereditário. O presente estudo objetivou revisar a prevalência de mutações nos genes *BRCA1/2* em pacientes brasileiros com/ou candidatos a desenvolver CM hereditário. A pesquisa foi realizada através de bases de dados *Pubmed*, *ScienceDirect*, *Medical Literature Analysis and Retrievel System Online* (*MedLine*) e Literatura Latino-americana e do Caribe em Ciências da Saúde (LILACS), de artigos publicados entre 2011 e 2019. Doze artigos foram incluídos no presente estudo. A taxa de mutação para *BRCA* variou de 0,65 a 27,3%. Na região Sudeste foi realizada a maioria dos estudos. A mutação fundadora mais prevalente encontrada foi da população judaica *Ashkenazi*, c.5266dup (5382insC) em *BRCA1*. Poucos estudos brasileiros sobre a prevalência de *BRCA* foram publicados até hoje, o que dificulta traçar o perfil mutacional da população. Foi possível verificar uma grande variação da prevalência de mutações nos genes *BRCA*, porém, esses dados podem não refletir no Brasil como um todo, já que a população brasileira é bastante heterogênea e com altos índices de imigração.

Palavras-chave: Brasil. *BRCA1. BRCA2*. Câncer de mama hereditário. Prevalência.

ABSTRACT

Hereditary genetic factors are responsible for 5% to 10% of breast cancer (BC) cases worldwide. The *BRCA1/2* genes are among the most analyzed for hereditary BC. The present study aimed to review the prevalence of mutations in the *BRCA1/2* genes in Brazilian patients with/candidate or developing hereditary BC. Researches were conducted through Pubmed, ScienceDirect, Medical Literature Analysis and Retrievel System Online (MedLine) and Latin American and Caribbean Literature in Health Sciences (LILACS) databases, with articles published between 2011 and 2019. Twelve articles were included in this study. The *BRCA* mutation rate ranged from 0.65 to 27.3%. Most studies were carried out in the Southeast region. The most prevalent foundational mutation found was c.5266dup (5382insC) in *BRCA1*, from the Jewish population Ashkenazi. Few Brazilian studies on *BRCA* prevalence have been published to this date, which makes it difficult to trace the mutational profile of the Brazilian population. It was possible to verify a wide variation in the prevalence of mutations in the *BRCA* genes, however, these data may not reflect throughout Brazil, since the Brazilian population is quite heterogeneous and has high rates of immigration.

Keywords: Brazil. *BRCA1*. *BRCA2*. Hereditary breast cancer. Prevalence.

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1. INTRODUCTION

Cancer is a group of genetic diseases that originate from the abnormal and unregulated proliferation of body cells. For cancer to develop, a cell undergoes genetic mutation and spreads uncontrollably, forming a population of mutated cells. This population suffers additional mutations that result in tumor progression, increasing malignancy (ROSANE, 2014). According to Alberts *et al*. (2017), the altered genes are classified into two groups: proto-oncogenes and tumor suppressor genes. According to Ewald *et al*. (2011), germline mutations in tumor suppressor genes, such as *BRCA1* and *BRCA2* (breast cancer 1 and 2), helps hereditary breast cancer (BC) development.

The most recent global estimate, from 2018, shows that there were 2.1 million new cases of BC in the world, which is equivalent to 11.6% of all estimated cancers, and, by sex, BC was the most frequent in women (24.2%). In Brazil, it is estimated that from 2020 to 2022 there will be 625,000 new cases of cancer each year, with non-melanoma skin cancer being the most incident (177,000), followed by BC with 66,000 cases per year (INCA, 2019). Among the factors that contribute to the increased risk of developing the disease are hereditary genetic factors, accounting for 5% to 10% of BC cases worldwide (BRAY et al., 2018). That is, people who have germline gene mutations have a higher risk of developing BC (TUNG *et al*., 2015).

Molecular biology helps to identify people susceptible to develop the disease, acting through genetic tests to detect a mutation (TUNG *et al*., 2015). According to Castéra *et al*. (2014), *BRCA1* and *BRCA2* genes are among the most frequently analyzed for BC. In contrast, Tung *et al*. (2015) report that other genes may also have germline mutations, such as ATM, TP53, CDH1, PALB2 and PTEN, however, mutations in these genes are rarer.

Genetic counseling groups recommend the genetic tests to women at increased risk, as the result can have an impact on the clinical management of patients and their families, presenting preventive interventions that have been shown to significantly increase the patients' chance of survival (MOYER, 2014).

This work is a systematic literature review, which aims to describe the prevalence of *BRCA1* and *BRCA2* genes' mutations in Brazilian patients with/or candidates to develop hereditary MC and address probands' clinical profile.

2. MATERIAL AND METHODS

This is a systematic literature review, whose information was obtained from materials already published and available in the literature, with no interventions or direct approach to human beings. To perform the articles research and selection, four databases were used: Pubmed, Science Direct, Medical Literature Analysis and Retrievel System Online (MedLine) and Latin American and Caribbean Literature in Health Sciences (LILACS). The terms used to search were “Prevalence”, “*BRCA* or *BRCA1* or *BRCA2*” and “Brazil or Brazilians”. The selected articles were published between 2011 and 2019, since there were no studies developed in 2020 or 2021. The studies investigated the prevalence of *BRCA1* and *BRCA2* genes in Brazil associated with Hereditary Breast and Ovary Cancer Syndrome (HBOC).

The inclusion criteria for articles selection beyond the period studied were: carrying out a genetic test for the *BRCA1* and/or *BRCA2* genes and studies carried out with Brazilian patients. Exclusion criteria were: articles with incomplete and/or not very consistent data, referring to the inclusion criteria, in addition to studies published outside the given period and which were not carried out in Brazil. Monographs, theses and dissertations were also excluded.

For the article filtering and selection, this study used the PRISMA flowchart (LIBERATI *et al.,* 2009), and the obtained data was transcribed in a Microsoft Office Excel Professional 2016’s table, containing: article title, name of the main author, year of publication and place of study. From these data, the articles were separated by individual tables containing the prevalence of mutations in the *BRCA1* and/or *BRCA2* genes, main founding mutations found, region where the studies were conducted, average age at the time of genetic testing, the type of test used and selection criteria for genetic testing.

Selection Results

The research resulted in a total of 101 publications, with 23 articles in PubMed database, 67 in Science Direct database, 8 in MedLine database and 3 in LILACS database. After removing duplicated articles and submitting to the eligibility criteria, 12 articles were selected (figure 1).

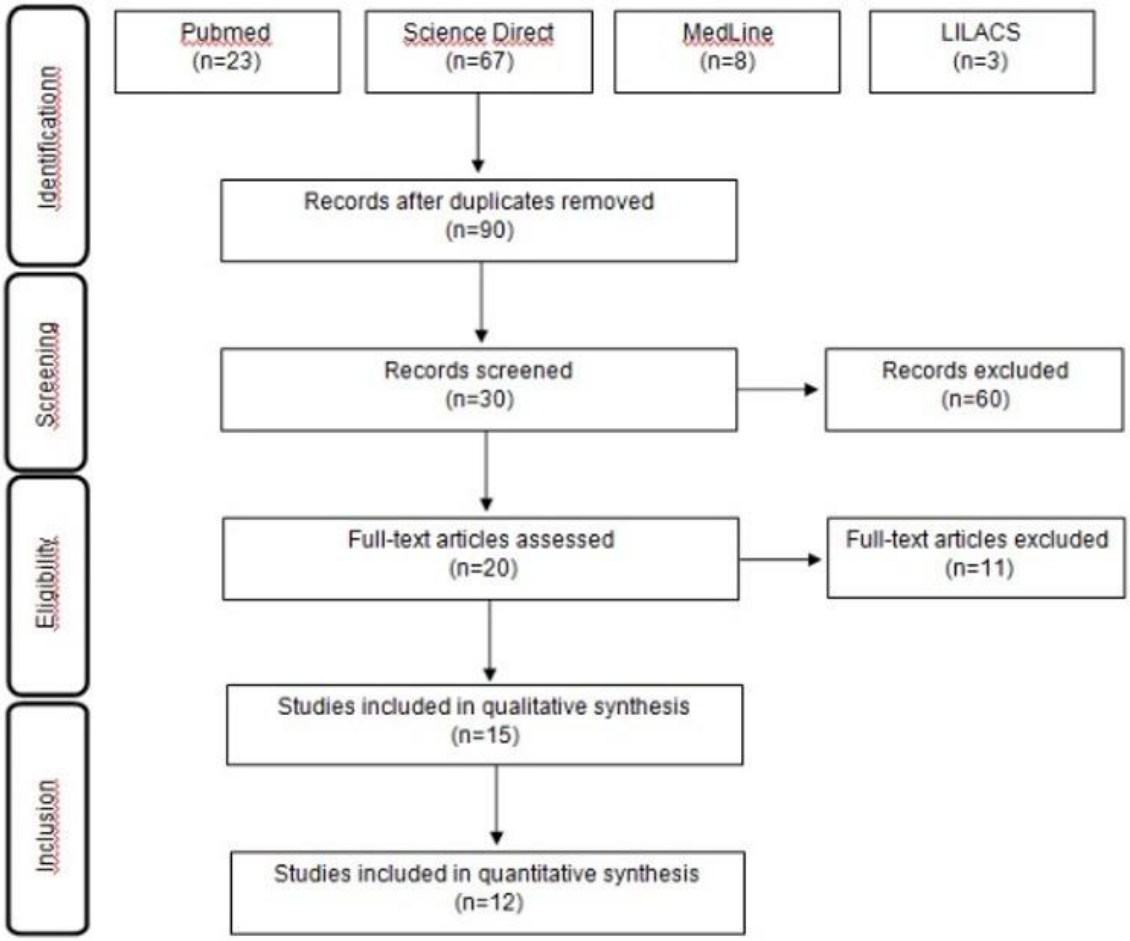

Figure 1. PRISMA Flowchart for article selection.

3. RESULTS AND DISCUSSION

The studies included in the study, as well as the number of participants and the mutations' prevalence, are shown in Table 1. All articles investigated the *BRCA1* and/or *BRCA2* genes, as well as described mutations' prevalence. The sample size within all selected studies ranged from 27 to 1380 participants, and *BRCA* mutation rate ranged from 0.65 to 27.3%.

In most studies, it's been verified that mutation prevalence in *BRCA1* was higher compared to the *BRCA2* gene. It's been also observed a frequency ranging from 2.6 to 17.1% of individuals with mutations in *BRCA1* gene and from 0.65 to 15.9% in *BRCA2* gene, with Alemar *et al*. (2017) reporting that 2 patients were mutants for both *BRCA1* and *BRCA2* genes.

The mutation frequency is higher for *BRCA1* gene because this gene contains a higher number of Alu elements (42% vs 20% of the *BRCA2* gene), part of which corresponds to a portion of the DNA capable of generating copies of itself and then inserting it in the genome at random positions (BATZER; DEININGER, 2002); THOMPSON; EASTON, 2004). Other

similar studies have also demonstrated this same proportion of mutations between the two genes (ESTEVES *et al*., 2009; GOMES *et al*., 2011; PALMERO *et al*., 2018).

Table 1. Scientific articles published between December 2011 and September 2019 regarding the prevalence of mutations in *BRCA1* and *BRCA2* genes in Brazil (in descending chronological order).

	References	Nº sample	Nº of individuals with *BRCA* mutation	% mutation
1	CIPRIANO *et al*., 2019	44	12 (27,3%)	*BRCA1* - 5 (11,4%) *BRCA2* - 7 (15,9%)
2	COTRIM *et al*., 2019	158	33 (20,9%)	*BRCA1* - 27 (17,1%) *BRCA2* - 6 (3,8%)
3	FELICIO *et al*., 2018	1380	9 (0,65%)	*BRCA2* - 9 (0,65%)*
4	GUARNERI *et al*., 2018	27	7 (25,9%)	*BRCA1* - 6 (22,2%) *BRCA2* - 1 (3,7%)
5	GUARNERI *et al*., 2018	418	80 (19,1%)	*BRCA1* - 49 (11,7%) *BRCA2* - 29 (6,9%) *BRCA1/BRCA2* - 2 (0,5%)
6	ALEMAR *et al*., 2016	232	8 (3,4%)	*BRCA1* - 6 (2,6%) *BRCA2* - 2 (0,8%)*
7	EWALD *et al*., 2016	145	7 (4,8%)	*BRCA1* - 4 (2,8%) *BRCA2* - 3 (2%)
8	FERNANDES *et al*., 2016	349	75 (21,5%)	*BRCA1* - 49 (14%) *BRCA2* - 26 (7,4%)
9	MAISTRO *et al*., 2016	100	19 (19%)	*BRCA1* - 17 (17%) *BRCA2* - 2 (2%)
10	SILVA *et al*., 2014	120	27 (22,5%)	*BRCA1* - 20 (16,7%) *BRCA2* - 7 (5,8%)
11	CARRARO *et al*., 2013	54	11 (20,4%)	*BRCA1* - 7 (13%) *BRCA2* - 4 (7,4%)
12	EWALD *et al*., 2011	137	7 (5%)	*BRCA1* – 7 (5%)*

*Studies that only assessed the prevalence of founder mutations.
Source: Research data.

The studies define some criteria in which patients must meet to undergo the genetic test of *BRCA1* and *BRCA2* genes. The best known guidelines are established by the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN). Both guidelines were used in one study (study 6). The NCCN guideline was used by 4 authors (studies 3, 4, 5 and 11), and the standards established by the ASCO were used by 3 studies (1, 7 and 12). Study 10 was based on the NCCN guidelines, modifying them to select its patients.

The remaining authors did not use any known criteria, they used random criteria such as presence of invasive epithelial ovarian cancer, prior probability of harboring a *BRCA* mutation ≥ 30% by lineage analysis using Myriad mutation prevalence tables or prediction

model of Penn II mutation or women with a diagnosis of bilateral BC under the age of 50 years, regardless of family history.

In Brazil, around 75% of the population depends on Brazil's Unified Public Health System (SUS), but genetic testing is currently not widely available at SUS (GOSS *et al*., 2013). The states have the autonomy to create laws regarding the exams covered by SUS, however, at the national level, the law has not been approved yet. The bill that obligates SUS to carry out genetic testing of *BRCA1* and *BRCA2* genes was presented in February 2020. It has been approved by woman's rights defense committee, but is still pending in the Deputies' Chamber (BRAZIL, 2020). In Brazil's private healthcare system, there is coverage for molecular tests on individuals who meet the criteria established by the National Health Agency (ANS) which are based on the NCCN criteria (ANS, 2018).

As for the type of test for germline analysis of *BRCA1* and *BRCA2* genes, 4 studies used the Multiplex Link Dependent Probe Amplification (MLPA) method (studies 6, 7, 8 and 10), an alternative method to the Sanger Sequencing and that can identify large genomic rearrangements (LGR) (WALLACE, 2016).

Studies 9 and 5 used Next Generation Sequencing (NGS) and/or Sanger Sequencing. The Sanger sequencing method is considered the gold standard for DNA sequencing, but it has a limited yield, as it can not identify LGR, in addition to being less cost-effective compared to the NGS method (WALLACE, 2016). Study 1 used High Resolution Fusion Technology (HRM), while the other articles only reported that the germline mutation test was performed by PCR amplification and DNA sequencing, without describing the test used.

Regarding geographic distribution (figure 2), most studies evaluated, 56.25% (9/16), were carried out in the southeast region, followed by the south region, with 37.5% (6/16), and the northeast region, with 6.5% (1/16). Two articles were conducted in two regions (south and southeast), and one article was carried out in three regions (south, southeast and northeast). According to Goss *et al*. (2013), oncology services are located in the largest cities, where there are most oncology specialists, in addition to the required equipment to provide cancer diagnosis and therapeutic services, which explains the greater number of studies concentrated in those regions, which are more developed.

According to the National Cancer Institute (INCA), besides non-melanoma skin tumors, female BC is the most frequent in all Brazilian regions, with an estimated risk of 81.06 per 100,000 in the southeast; 71.16 per 100,000 in the south region; 45.24 per 100,000 in the midwest region; 44.29 per 100,000 in the northeast region; and 21.34 per

100,000 in the northern region (INCA, 2019). However, hereditary BC corresponds to 5% to 10% of all BC cases (INSTITUTO NACIONAL DE CANCER JOSÉ ALENCAR GOMES DA SILVA, 2019).

Figure 2: Geographical distribution of selected articles about the prevalence of *BRCA1* and *BRCA2* genes in Brazil.

In terms of age, unlike sporadic BC, women with *BRCA1* and *BRCA2* mutations have a tendency to develop the disease at a younger age compared to women who don't have genetic mutations (MALONE *et al*., 2010). About four out of five cases of sporadic BC happen after the age of 50 (INSTITUTO NACIONAL DE CANCER JOSÉ ALENCAR GOMES DA SILVA, 2019).

Among the 12 articles that reported the age of the participants, 11 had the mean age at the time of cancer diagnosis (Table 2), which ranged from 37.9 to 55 years, demonstrating that hereditary BC occurred at a younger age when compared to Sporadic BC. Carraro *et al*. (2013), evaluated 54 young patients, up to 35 years old, but did not establish the mean age at diagnosis.

Table 2. Age of participants at diagnosis.

	Author	Average age at diagnosis (years)
1	CIPRIANO *et al*., 2019	44,5
2	COTRIM *et al*., 2019	54,7
3	FELICIO *et al*., 2018	37,9
4	GUARNERI *et al*., 2018	42
5	ALEMAR *et al*., 2017	41,6 (breast) 45,3 (ovary)
6	ALEMAR *et al*., 2016	43 (breast) – variation of 23-74 47 (ovary) – variation of 19-66
7	EWALD *et al*., 2016	43
8	FERNANDES *et al*., 2016	41
9	MAISTRO *et al*., 2016	55 – variation of 33–81
10	SILVA *et al*., 2014	43
12	EWALD *et al*., 2011	43,4

Source: Research data.

Regarding *BRCA* gene mutations, they are present in all ethnic groups, but the prevalence varies in different populations, characterizing the so-called founder mutations (Alemar *et al*., 2016). Identifying these mutations allows a more accurate estimate of the mutation-specific cumulative incidence of cancer in a given population, also facilitating the identification of genetic and environmental risk modifiers (PEIXOTO *et al*., 2011). However, in Brazil, data on the occurrence of major rearrangements are still insufficient.

Examples of manifestations of a founder effect are seen among Jews, with the mutations c.68_69del (185delAG) and c.5266dup (5382insC) in *BRCA1* and c.5946del (6174delT) in *BRCA2* being the best known in the Ashkenazi Jewish population, with 3% of individuals carrying one of the three founder mutations (ROA *et al*., 1996). Regarding the c.68_69del (185delAG) mutation in *BRCA1*, Alemar *et al*. (2017) were the only ones to identify it in only one proband, while the mutation c.5946del (6174delT) in *BRCA2* was found in 3 probands.

Table 3 shows the founder mutations most frequently found in the selected studies. It has been observed that the c.5266dup (5382insC) mutation in *BRCA1* was the most prevalent, present in 10 studies (1, 2, 4, 5, 6, 8, 9, 10, 11, and 12) and 56 probands. In the *BRCA1* gene, the second most prevalent mutation was c.3331_3334delCAAG, described in 6 studies (1, 2, 5, 6, 8 and 9), totalizing 17 mutated probands. This mutation has not been evaluated on an international scale, and the ancestral origin has yet to be determined. A recent study suggests that it comes from Europe and was introduced in Colombia and South

America at the beginning of the country's colonization, resulting in a high prevalence of mutation in the population (TUAZON *et al*., 2020).

In the *BRCA2* gene, the c.156_157insAlu mutation was the most prevalent, 4 studies (3 5, 8 and 12) identified 14 mutant probands (Table 3). It is a Portuguese founder mutation that originated about 500 years ago and has been described as responsible for most mutations in *BRCA2*, in addition to being present in one third of all malicious germline mutations in Portuguese families with HBOC (PEIXOTO *et al*., 2011).

Other prevalent mutations such as c.1687C>T in *BRCA1* and c.2808_2811delACAA and c.1138delA in *BRCA2* were not found in the literature as founder mutations (Table 3).

Table 3. Founding mutations found more frequently in the selected studies.

Mutation	Gene	Origin/Population	Nº of studies	Nº of probands
c.5266dup (5382insC)	*BRCA1*	Ashkenazi jewish	10	56
c.3331_3334delCAAG	*BRCA1*	Europe	6	17
c.156_157insAlu	*BRCA2*	Portugal	4	14
c.1687C>T	*BRCA1*	-	4	6
c.2808_2811delACAA	*BRCA2*	-	2	6

Source: Research data.

4. FINAL CONSIDERATIONS

Few studies on the prevalence of *BRCA*-positive patients have been published in Brazil to date, which makes it difficult to trace the mutational profile of the Brazilian population. In this study, it was possible to verify a wide variation in the prevalence of mutations in *BRCA* genes, with mutations in *BRCA1* being more frequent than *BRCA2*. It is noteworthy that the low sample size presented in most studies can influence the results, making it necessary to increase the number of probands in order to obtain a comprehensive knowledge of the types and frequencies of *BRCA* mutations in the Brazilian population.

Most studies were conducted in the south and southeast regions and, therefore, these data found may not reflect Brazil as a whole, since Brazilian population is very heterogeneous and has high levels of immigration.

In short, considering the high incidence and prevalence of BC in Brazil and the fact that 5% to 10% of these tumors are caused by germline alterations in genes of hereditary predisposition to BC and ovary, usually in young patients, it is extremely important to concentrate efforts to make *BRCA* mutation testing and genetic counseling available to all high-risk patients in Brazil, thus detecting early-stage cancers and providing appropriate treatment for these individuals.

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