REVIEW ARTICLE
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Prevalence and clinical implications of the TP53 p.R337H mutation in Brazilian breast cancer patients: a systematic literature review

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ABSTRACT

This study assessed the prevalence and clinical implications of the TP53 p.R337H mutation in Brazilian breast cancer patients through a systematic literature review. The literature review was performed in the PubMed, Scientific Electronic Library Online (SciELO), and Medical Literature Analysis and Retrieval System Online (MEDLINE) databases from 1997 to 2018. We used the keyword "R337H" in the search since it resulted in the largest number of published articles on the subject. Initially, we found 75 articles, and, after reviewing the titles and abstracts, we selected 18 studies investigating the prevalence of the TP53 p.R337H mutation in breast cancer patients and its clinical implications. The reading of the full texts led to the inclusion of seven studies. The studies were carried out in the states of São Paulo, Rio Grande do Sul, Rio de Janeiro, and Bahia. The TP53 p.R337H mutation was detected in 87 (4.8%) of the 1.789 women with breast cancer investigated. The prevalence of the TP53 p.R337H mutation in the selected studies ranged from 0.5 to 8.6%. These findings highlight the recommendation for screening the R337H variant in breast cancer patients in Brazil and suggest the need for new research addressing the clinical and prognostic aspects of breast cancer patients with TP53 p.R337H mutation-positive.

KEYWORDS: genes, P53; cancer; mutation.

INTRODUCTION

Breast cancer is an important public health problem, with high incidence in Brazil and worldwide. The study of breast carcinogenesis and risk factors for breast cancer is relevant to disease management, and numerous genes involved in the process of breast carcinogenesis have been identified.

Changes in the *TP53* pathway are significant in the pathogenesis of several human cancers[1]. In breast cancer, *TP53* mutations are found in 30–35% of primary invasive tumors. However, the prevalence of mutations varies depending on the histological type of the disease, being found in up to 80% of triple-negative (TN) breast cancer, 10% of luminal A, 30% of luminal B, and in up to 70% of tumors rich in human epidermal growth factor receptor 2 (HER2)[2-4]. In Brazil, a *TP53* mutation called p.R337H draws the attention of professionals who deal with breast cancer, as it has been identified in a significant portion of patients with this type of cancer[5].

The tumor suppressor gene *TP53*, located on the short arm of chromosome 17 (17p13.1), encodes a nuclear phosphoprotein of 53 kilodaltons (kDa), which is responsible for regulating the expression of several genes that control the progression of the cell cycle, angiogenesis, and apoptosis, working as a transcription factor[6]. In normal cells, p53 is expressed at baseline levels. Nevertheless, when cells are exposed to agents that cause damage to the deoxyribonucleic acid (DNA), p53 expression increases and initiates transcriptional control of several target genes that prevent the cell cycle progression. Cell cycle

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blockage allows repair of cell damage, preventing replication of DNA lesions potentially involved in tumor induction, as well as the division of abnormal cells. In the case of extensive genomic involvement, p53 induces cell death due to apoptosis, preventing the spread of genetic changes[7].

Several functions are attributed to the p53 protein in the regulation of cellular response to genotoxic stress, such as that caused by ionizing radiation, free radicals, hypoxia, among others, as well as oncogene inactivation. The p53 protein also acts in the process of angiogenesis, cellular senescence, and inflammatory response[8]. The ability to recognize DNA damage and regulate the cell cycle closely connects the p53 protein to tumor suppression and cancer biology[9]. The p53 pathway can be influenced in several ways, either by the presence of somatic and germline mutations or by the presence of genetic polymorphisms. Several genes are involved in this cell regulation pathway, so a large spectrum of polymorphisms and mutations leads to individual variations in tumor phenotypes[9].

Mutations that change the function of the protein encoded by the *TP53* gene, preventing its tumor suppressor activity, are widely described[9]. One of them, called p.R337H, was first identified in Brazil among children with adrenocortical tumors in families without a family history of cancer[10]. The mutation located in exon 10 of the *TP53* gene, codon 337, consists of exchanging guanine (CGC) for adenine (CAC), which results in the replacement of the amino acid arginine (R) for histidine (H) at position 337 of the protein[11]. The mutated allele encodes a protein with changes in the C-terminal domain, producing unstable p53 tetramers, which compromise its tumor suppressor function[12]. The biochemical repercussion of this mutation affects the ability of p53 to form oligomers. The formation of oligomers depends on an optimal pH, and acid-base changes in the amino acid sequence of p53 affect its biochemical properties[12]. At pH 7, the ability to form oligomers does not change, but in a slightly basic medium, oligomer formation is impaired[13]. Given this theory, several phenotypic variations present in families carrying the *TP53* p.R337H mutation are described[14].

In Brazil, the *TP53* p.R337H mutation was initially detected in the Southern Region in individuals considered unrelated, but who later had their common ancestry elucidated[15]. The historical hypothesis explains the spread of the *TP53* p.R337H mutation by proposing that the opening of Estrada dos Tropeiros, a highway between São Paulo and the south of the country, led to the migration and distribution of *TP53* p.R337H carriers to the South and Southeast regions of Brazil, which characterized the so-called founder effect[16].

Some studies[17] have investigated the prevalence of the *TP53* p.R337H mutation in Brazilian women with breast cancer. However, when comparing the different regions of the country, there are variations in prevalence and a higher concentration of studies in the South and Southeast regions. The penetrance of the *TP53* p.R337H mutation is still poorly understood in Brazil, as well as its clinical implications in breast cancer. The *TP53* p.R337H mutation has proven to be relevant in the epidemiological context of cancer in Brazil, but few updated studies assess the prevalence and clinical implications of the mutation in the Brazilian population, especially for breast cancer[17]. Also, studies are concentrated in the South and Southeast of the country, while frequencies in other regions remain unknown.

This study comprises a systematic literature review that investigated the prevalence of the *TP53* p.R337H mutation in women with breast cancer in Brazil, as well as the association of the mutation with clinical implications of tumors. Given the relevance of the *TP53* p.R337H mutation in the current Brazilian scenario, this study can help oncology professionals in the clinical management of patients with the mutation and their families, as well as guide the development of new studies that address this issue.

METHODS

Search strategy

The bibliographic review was carried out in the PubMed, Scientific Electronic Library Online (SciELO), and Medical Literature Analysis and Retrieval System Online (MEDLINE) databases, from 1997 to 2018. We used the keyword "R337H" in the search, as it resulted in the largest number of published studies on the subject. The search was limited to articles published in Portuguese, English, and Spanish. Two researchers reviewed the titles and abstracts of the articles retrieved in the initial search to determine their relevance. Disagreements in the selection and inclusion of studies were solved by a meeting, re-reading, and discussion with a third researcher.

Eligibility criteria

The articles chosen were considered eligible when they met the following inclusion criteria:

- articles investigating the prevalence of the *TP53* p.R337H mutation in Brazilian women with breast cancer;
- articles studying the influence of the *TP53* p.R337H mutation as a marker in the prognosis of breast cancer patients with this alteration;
- studies associating the *TP53* p.R337H mutation with the risk of developing breast cancer;
- primary and descriptive studies;
- articles presenting a clearly described methodology;
- studies with consistent objectives regarding the methodology;
- articles in Portuguese, English, and Spanish fully available online.

According to the exclusion criteria, the following studies were not eligible:

- publications in languages other than Portuguese, English, and Spanish;
- studies with repeated cases;
- articles investigating other *TP53* mutations in Brazilian breast cancer patients;
- case reports and systematic literature reviews.

Data extraction and analysis

We extracted the following study data: title, first author, year of publication, study objective, population studied, number of participants, type of sample investigated, case origin, molecular methods of mutation assessment, and main results. The data obtained were reviewed and synthesized in tables.

RESULTS

Study selection

Initially, we found 75 studies by electronic data search. After reviewing the titles and abstracts of these articles, we selected 18 studies that investigated the prevalence of the *TP53* p.R337H mutation in breast cancer patients and its clinical implications. Reading the full texts of these articles resulted in the exclusion of 11 studies. In total, seven articles were eligible for the systematic review. Figure 1 shows the flowchart of the study selection process.

Characteristics of included studies

The seven studies included in this systematic review evaluated a total of 2,456 patients with and without breast cancer, with and without the *TP53* p.R337H mutation. The number of patients analyzed in the different studies ranged from 28 to 874, and the included studies were carried out in the states of São Paulo, Rio de Janeiro, Rio Grande do Sul, and Bahia. São Paulo and Rio Grande do Sul were the states that most researched the subject. The oldest article was published in 2008, and the newest is from 2014. All seven studies were published in English. Table 1 presents the characteristics of the studies included in the systematic review.

The mutation assessment methods in the selected studies included: polymerase chain reaction (PCR) associated with the analysis of restriction fragment length polymorphism (RFLP), comparative genomic hybridization based on microarrays (CGH-array), gene sequencing, high-resolution melting (HRM), immunohistochemistry (IHC), and real-time PCR (qPCR), using TaqMan probes. The study that used immunohistochemistry assessed p53 protein expression for the presence of the R337H mutation in tumor specimens. In general, the most adopted mutation analysis method was PCR-RFLP, in three studies, while the qPCR method was used in two studies, and gene sequencing was used to confirm the detected mutations.

All studies included in the analysis investigated the *TP53* p.R337H mutation in blood samples (Table 1), except one[18], which investigated the mutation only in specimens of phyllodes tumors. Two studies[19,20] that examined *TP53* p.R337H in blood samples also investigated the mutation in tumor samples.

Prevalence of *TP53* p.R337H mutation in Brazilian women with breast cancer

Seven studies investigated the prevalence of the *TP53* p.R337H mutation in a total of 1,789 women with breast cancer, of whom 87 (4.8%) had the *TP53* p.R337H mutation (Table 2). The frequencies of the *TP53* p.R337H mutation in the selected studies ranged from 0.5[21] to 8.6%[20].

Among the selected studies, three were control cases[19,21,22], and they assessed the prevalence of the *TP53* p.R337H mutation in 1,208 women — 541 with breast cancer and 667 without breast cancer. The *TP53* p.R337H mutation was detected in seven of 541 patients in the case group (1.3%) and no woman in the control

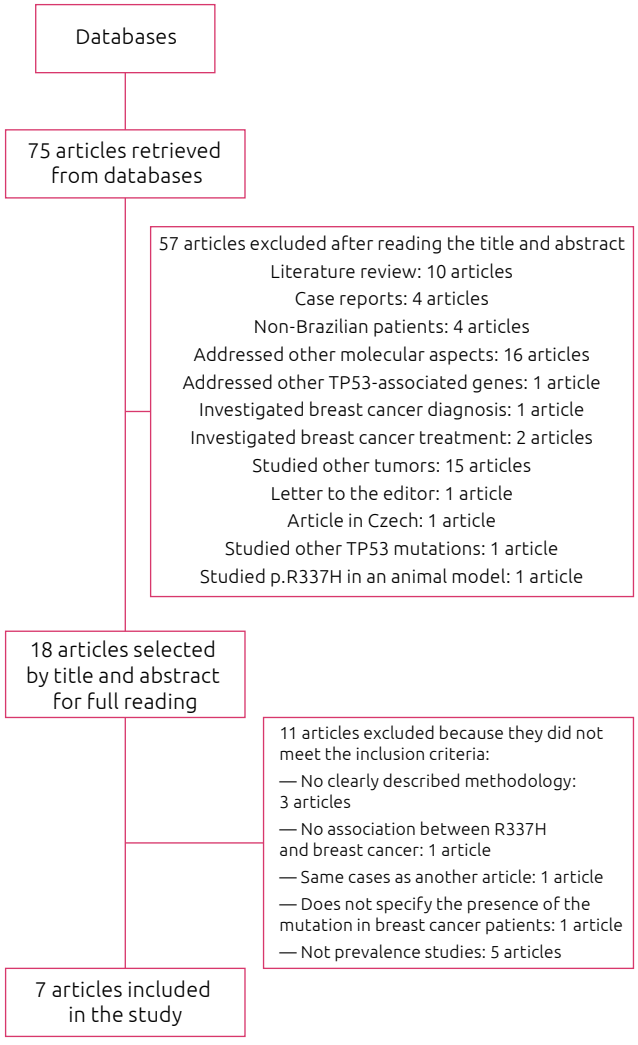

Figure 1. Flowchart of the study selection process.

Table 1. Characteristics of the studies included in the systematic review.

Reference	Case Origin	Objective/Sampling	Analyzed Biological Material/ Method	Results
Silva et al., 2014[14]	São Paulo, SP, Brazil	To investigate genetic changes in a group of 120 women with hereditary breast and ovarian cancer (HBOC) syndrome.	Blood. CGH-array and real-time PCR for mutation detection.	Three out of 120 women with breast cancer had the *TP53* p.R337H mutation.
Giacomazzi et al., 2013[18]	Porto Alegre, RS, Brazil; Barretos, SP, Brazil	To assess the presence of the *TP53* p.R337H mutation in 148 women with phyllodes tumor.	Tumor sample. Real-time PCR/ TaqMan and DNA sequencing.	Eight out of 148 women had the *TP53* p.R337H mutation, three with a malignant tumor and five with a benign tumor.
Assumpção et al., 2008[19]	Campinas, SP, Brazil	To determine the prevalence of the *TP53* p.R337H mutation in 123 women with breast cancer and 223 control women without breast cancer.	Blood and tumor sample. PCR-RFLP and IHC to detect the mutated protein.	Three out of 123 women with breast cancer had the *TP53* p.R337H mutation, and no women in the control group had the mutation.
Giacomazzi et al., 2014[20]	Porto Alegre, RS, Brazil	To assess the prevalence of the *TP53* p.R337H mutation in a group of 874 women with breast cancer.	Blood and tumor sample. Real-time PCR/TaqMan for mutation detection, DNA sequencing, and PCR-RFLP for tumor tissue analysis.	Out of the 874 breast cancer patients, 72 had the *TP53* p.R337H mutation.
Gomes et al., 2012[21]	Rio de Janeiro, RJ, Brazil	To assess the prevalence of the *TP53* p.R337H mutation in 390 women with breast cancer and 324 controls without breast cancer.	Blood. Allele-specific PCR (amplification refractory mutation system — ARMS) and DNA sequencing.	Two out of the 390 women in the case group had the *TP53* p.R337H mutation. No woman in the control group had the mutation.
Cury et al., 2014[22]	Ribeirão Preto, SP, Brazil	To investigate the prevalence of the *TP53* p.R337H mutation in 28 women with HBOC and 120 controls without cancer.	Blood. High resolution melting (HRM) for mutation detection.	Two out of 28 women with breast cancer had the *TP53* p.R337H mutation. No woman in the control group had the mutation.
Felix et al., 2014[24]	Salvador, BA, Brazil	To investigate mutations in 106 women with HBOC.	Blood. Allele-specific PCR, PCR-RFLP, and DNA sequencing.	One out of 106 women with HBOC had the *TP53* p.R337H mutation.

PCR: polymerase chain reaction; DNA: deoxyribonucleic acid; RFLP: restriction fragment length polymorphism; CGH-array: comparative genomic hybridization based on microarrays; IHC: immunohistochemistry.

Table 2. Studies that investigated the prevalence of the *TP53* p.R337H mutation in Brazilian patients with breast cancer (BC).

Reference	N	Inclusion criteria	Investigated gene region	Mutation screening method	N (%) p.R337H
Giacomazzi et al., 2014[20]	59	High-risk BC	*TP53* p.R337H	qPCR TaqMan, sequencing, and PCR-RFLP	2 (3.4%)
Giacomazzi et al., 2014[20]	815	Unselected BC	*TP53* p.R337H	qPCR TaqMan, sequencing, and PCR-RFLP	70 (8.6%)
Silva et al., 2014[14]	120	High risk BC	*TP53* p.R337H	CGH-array and qPCR	3 (2.5%)
Giacomazzi et al., 2013[18]	148	Phyllodes tumor	*TP53* p.R337H	qPCR TaqMan, sequencing	3 (2.0%)
Assumpção et al., 2008[19]	123	Unselected BC	*TP53* p.R337H, *TP53* geneexon 10	PCR-RFLP and IHC	3 (2.4%)
Gomes et al., 2012[21]	390	Unselected BC	*TP53* p.R337H	ARMS-PCR, sequencing	2 (0.5%)
Cury et al., 2014[22]	28	High risk BC	Full gene by HRM	HRM	2 (7.1%)
Felix et al., 2014[24]	106	High risk BC	*TP53* p.R337H	AS-PCR, PCR-RFLP, sequencing	1 (0.9%)

HRM: high-resolution melting; qPCR: real-time polymerase chain reaction; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; CGH-array: comparative genomic hybridization based on microarrays; AS-PCR: allele-specific PCR; ARMS: amplification refractory mutation system; IHC: immunohistochemistry.

group (Table 3). Two of these studies[19,21] reported that the women with breast cancer who had the *TP53* p.R337H mutation were under 45 years old. The third study[22] described two patients with *TP53* p.R337H, one diagnosed at the age of 30 and another with bilateral breast cancer, whose first cancer was detected at the age of 61, in the right breast, and the second at the age of 62, in the left breast. The data available in the selected studies did not allow a more detailed analysis of the age or clinical characteristics of patients with breast cancer and *TP53* p.R337H mutation.

Clinical implications in patients with the *TP53* p.R337H mutation and breast cancer

Information regarding clinical tumor characteristics, such as age at diagnosis, histological type, clinical staging, and status of immunohistochemical markers, is scarce in studies assessing the *TP53* p.R337H mutation in breast cancer patients. None of them followed the patients' response after the cancer diagnosis, nor did they assess the recurrence and/or survival of those carrying the *TP53* p.R337H mutation.

Regarding the age of the patients, a study carried out in Rio de Janeiro[21] evaluated a series of 390 breast cancer patients, with ages ranging from 25–60 years and a mean age of 46 years at diagnosis. Two patients (0.5%) under the age of 40 presented the *TP53* p.R337H mutation, one aged 35 years and the other aged 39 years. The two patients with the *TP53* p.R337H mutation reported a family history of other cancers.

The largest series of breast cancer cases selected in this review[20] investigated the prevalence of the mutation in women with breast cancer in different age groups. The study included 403 patients diagnosed with breast cancer before the age of 42 and 412 aged 55 years or older. The mean age of the patients at diagnosis was 38 (standard deviation — SD=5) and 66 (SD=9) years, respectively, in both groups. Invasive carcinomas were the most prevalent (90.5%), and the genotyping performed on tumor specimens showed a prevalence of the *TP53* p.R337H mutation of 8.6% in genotyped samples. The study also revealed an inverse relationship between age and mutation prevalence: in the group of women diagnosed at the age of 45 or younger, the prevalence was 12.1%, while in women diagnosed at the age of 55 or older, the prevalence was 5.1% (p<0.001). When women with breast cancer diagnosed at the age of 30 or younger were assessed, the prevalence of the mutation was 20% (8/40, 95% confidence interval — 95%CI 9.0–35.6%). The analysis of *TP53* p.R337H in the tumors indicated that, out of the 70 mutation-positive cases, 68 (97.1%) were heterozygous (c.1010 AG). Only two cases had mutant alleles detected in the tumors, suggesting that the patients were constitutive mutant homozygotes or hemizygotes.

Regarding the histological type of the tumors, most studies mentioned that the *TP53* p.R337H mutation-positive tumors were invasive carcinomas, without other specifications. One study[18] assessed the prevalence of the *TP53* p.R337H mutation in 148 women with phyllodes tumors, reporting the presence of the mutation in eight women and classifying the mutant cases as malignant (n=3), benign (n=5), and borderline (n=0). A malignant phyllodes tumor with the *TP53* p.R337H mutation has also been described in a study developed in the Southern region of the country[19].

DISCUSSION

In Southern Brazil, the germline *TP53* p.R337H mutation is highly associated with pediatric adrenocortical tumors and has low penetrance and limited tumor specificity in most families presenting this mutation. Among mutation-associated tumors, breast cancer is the most frequently found in *TP53* p.R337H-positive women, suggesting that this variant is relevant for breast carcinogenesis. Based on the studies included in this systematic review, the prevalence of the *TP53* p.R337H mutation in Brazilian breast cancer patients is high, ranging from 0.5 to 8.6%. These findings reinforce the recommendation for screening the R337H variant in breast cancer patients in Brazil.

The role of the R337H mutation in breast cancer is not yet clear. Most (90%) of the germline mutations in the *TP53* gene are in its DNA-binding domain. These mutations interrupt the protein structure and impair the function of the encoded protein. In contrast, the germline *TP53* p.R337H mutation occurs in the p53 tetramerization domain and seems to cause a more subtle

Table 3. Case-control studies that investigated the prevalence of the TP53 p.R337H mutation in breast cancer patients.

Reference	Type of study	Number of cases/ controls	TP53 p.R337H	Age of patients at diagnosis
Assumpção et al., 2008[19]	Control case	123 cases 223 controls	3/123 0/223	19 years, 29 years, and 44 years Mean age: 30.6 years
Gomes et al., 2012[21]	Control case	390 cases 324 controls	2/390 0/324	35 years and 39 years Mean age: 37 years
Cury et al., 2014[22]	Control case	28 cases 120 controls	2/28 0/120	30 years, 61 years (left breast), and 62 years (right breast) Mean age: 45.5 years

defect in the protein, which becomes functionally deficient only under certain conditions.

Germline *TP53* mutations are related to the Li-Fraumeni syndrome (LFS) with cancer predisposition. Individuals with germline *TP53* mutations have two characteristic disease phases, one in childhood with a tendency to develop rare cancers and one in adulthood with a tendency to develop more common cancers, but with early onset. The risk of childhood cancer versus adult cancer depends on the type of *TP53* mutation, as well as on genetic modifiers, including polymorphisms in *TP53* and genes encoding p53 regulators, such as murine double minute 2 (Mdm2), among others[9].

A recent study used a full genome sequencing to analyze a 2 Mb region at the *TP53* locus in samples of adrenocortical carcinomas. Selected common and rare variants were genotyped in 204 *TP53* p.R337H-positive cancer patients and a control group of 67,359 newborns. A commonly shared haplotype containing the E134* variant of the *XAF1* gene was detected in a subgroup (42%) of patients with adrenocortical carcinomas. This rare variant was identified in 70% of patients with *TP53* p.R337H. The cosegregation of both variants was found in 79% of cancer patients and was significantly higher in individuals with sarcoma and multiple malignancies, including breast cancer[23]. The results of this study should be expanded and may contribute to elucidate the role of the *TP53* R337H mutation and its modifiers.

The studies included in this review were conducted in the states of São Paulo, Rio de Janeiro, Rio Grande do Sul, and Bahia. São Paulo and Rio Grande do Sul had the largest number of publications on the subject, and the highest prevalence of *TP53* p.R337H mutation in women with breast cancer was found in Porto Alegre (8.6%) and Ribeirão Preto (7.1 %). A study carried out in Bahia showed that one out of 106 women with breast cancer assessed had the *TP53* p.R337H mutation, indicating that the mutation is not restricted to the South and Southeast regions[24].

One of the studies included in the systematic review[20] investigated the prevalence of the *TP53* p.R337H mutation in a large group of breast cancer patients from three important reference centers for cancer treatment in Brazil and performed the geographical distribution of the cases assessed. The study revealed a significant variation in the disposition of breast cancer cases with the *TP53* p.R337H mutation. This variation can be explained by the differential dissemination of the founder haplotype in some regions of the country due to the migratory effect and sociodemographic differences that intrinsically affect the risk of developing breast cancer in the Brazilian population. The lack of studies in different geographic regions of Brazil demands the development of new research on this subject.

The studies included in this article used several methods to detect the *TP53* p.R337H mutation, especially PCR-RFLP and qPCR with TaqMan probes. An investigation that assessed 95 genomic DNA samples compared the performance, cost, and response time of the Sanger, PCR-RFLP, TaqMan-PCR, and HRM sequencing methods employed in the *TP53* p.R337H genotyping, and the results were 100% concordant for all methods[25]. Nonetheless, DNA sequencing is considered the gold standard among the methods and recommended to confirm the mutation.

This systematic review included three case-control studies[19,21,22]. The *TP53* p.R337H mutation was detected in seven of the 541 patients in the case group (1.3%), and none of the 667 women in the control group. Despite the considerable number of cases evaluated, the heterogeneity of the studies did not allow a combined analysis of the data in the form of meta-analysis, which prevented the assessment of the risk of *TP53* p.R337H-positive patients developing breast cancer.

An important limitation of this study is the fact that prognostic aspects of *TP53* p.R337H-positive breast cancer could not be assessed since none of the included articles addressed these variables. Retrospective studies that include large series and the possibility of patient follow-up are necessary to elucidate the prognostic role of the *TP53* p.R337H mutation in breast cancer.

As described in the "Results" section, information regarding clinical tumor characteristics, such as their histological type, clinical staging, and status of immunohistochemical markers, was extremely scarce in the studies included in this work. Immunohistochemical data from 66 breast cancer patients positive for *TP53* p.R337H were reviewed and compared to data from 12 patients with other functional *TP53* mutations[26]. In the group of patients with other functional *TP53* mutations, 75% of the tumors showed overexpression of HER2 (3+), corroborating previous studies, while 22.7% of the patients with *TP53* p.R337H presented HER2 overexpression. These results reinforce the hypothesis that different germline *TP53* mutations act through different pathways of carcinogenesis, suggesting that the histopathological and immunohistochemical aspects of *TP53* p.R337H-positive breast cancer should be further investigated in future studies.

The seven studies included in this review showed that 87 (4.8%) of the 1,789 women with breast cancer investigated in Brazil had the *TP53* p.R337H mutation. These results indicate that the *TP53* p.R337H variant contributes to an important portion of breast cancers diagnosed in our population and that screening for this variant needs to be considered in the diagnosis and prevention of these tumors. The prevalence of the *TP53* p.R337H variant is high when compared to other particular mutations detected in *TP53* and should be taken into account in the genetic counseling of Brazilian breast cancer patients.

AUTHORS' CONTRIBUTIONS

V.A.S.: Conceptualization, funding acquisition, investigation, methodology, investigation, project administration, supervision, validation, visualization, writing – review & editing.
D.C.A.: investigation, validation, visualization, writing – review & editing.

E.S.V.C.: Data curation, formal analysis, Investigation, writing – original draft.
I.F.M.: Data curation, formal analysis, investigation, writing – original draft.
N.A.N.: Conceptualization, data curation, formal analysis, investigation, visualization, writing – original draft, writing – review & editing.
F.M.A.: Methodology, validation, writing – review & editing.

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