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# The TP53 p.R337H Variant in Breast Cancer: Evidence from a Cohort Study and Literature Review

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ABSTRACT

**Background:** The *TP53* p.R337H germline variant is a Brazilian founder variant associated with Li-Fraumeni syndrome and increased cancer susceptibility. Its prevalence among patients with breast cancer (BC) remains incompletely characterized. This study aimed to evaluate the prevalence of the *TP53* p.R337H germline variant among patients with BC through a cohort study and a structured literature review.

**Methods:** One hundred patients with BC from the Antonio Pedro University Hospital were interviewed and tested for the p.R337H variant using Sanger sequencing. A structured literature review was also conducted following PRISMA 2020 recommendations, searching PubMed, LILACS, and SciELO for studies published between 1997 and 2025. Studies reporting zero detected cases were included to reduce selection bias. Because of heterogeneity among studies, no formal meta-analysis was performed, and prevalence was reported descriptively.

**Results:** Of the 100 patients tested in our study, none had the variant (0% [95% confidence interval (CI), 0.00%–3.62%]). Of 46 identified records, 17 met the inclusion criteria. A total of 173 carriers were identified among 8221 patients in the reviewed literature. Including our cohort, the combined sample totaled 8321 patients, with a crude aggregated prevalence of 2.08% (95% CI, 1.79%–2.41%). Higher prevalence was observed in patients diagnosed at ≤45 years and in those with malignant phyllodes tumors, while lower or absent prevalence was observed in unselected populations.

**Conclusion:** The prevalence of the p.R337H variant among patients with BC varied across studies according to age at diagnosis, patient selection criteria, and geographic region. Larger multicenter studies are needed to better define its role in BC risk assessment.



## INTRODUCTION

Hereditary cancer is clinically characterized by the familial clustering of tumor-specific subtypes. Individuals who meet clinical criteria can be considered for genetic screening of 1 or more susceptibility genes.[1] In breast cancer (BC), multiple predisposition genes have been described since the

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identification of *BRCA1* and *BRCA2*. In Brazil, *TP53* is one of the most frequently altered germline genes in women with BC, especially in certain regions of the country.[2–4]

Germline pathogenic and likely pathogenic variants in the tumor suppressor gene *TP53* (located at locus 17p13.1)[5] predispose carriers to multiple distinct malignancies throughout their lives. Different *TP53* variants are associated with distinct phenotypes and cancer risks, with penetrance varying according to the specific variant. Initially described by Li and Fraumeni as classic Li-Fraumeni syndrome[7], the term heritable *TP53*-related cancer syndrome has been increasingly used to indicate any phenotype associated with germline *TP53* variants.[1]

Although germline *TP53* variants predetermine general patterns of cancer risk for members of the same family, individual risks vary among carriers. In this context, carcinogenesis is a multistep process influenced by genetic background, environmental exposure, and other modifying factors.[6] This is particularly relevant for the p.R337H variant, which shows variable penetrance among carriers.[1,2,8]

*Functions of the p53 protein*

In 1992, Lane described the p53 protein as "the guardian of the genome" because of its role in maintaining genomic stability.[9] Its functions include deoxyribonucleic acid (DNA) binding as a tetramer, acting as a transcription factor, and regulating the G1 checkpoint to allow DNA repair before cell division or the induction of apoptosis.[9,10] Over the years, multiple functions of the p53 protein have been described that can influence carcinogenesis[11,12], as shown in Figure 1. Alterations in p53 protein function contribute directly to cancer development.[12]

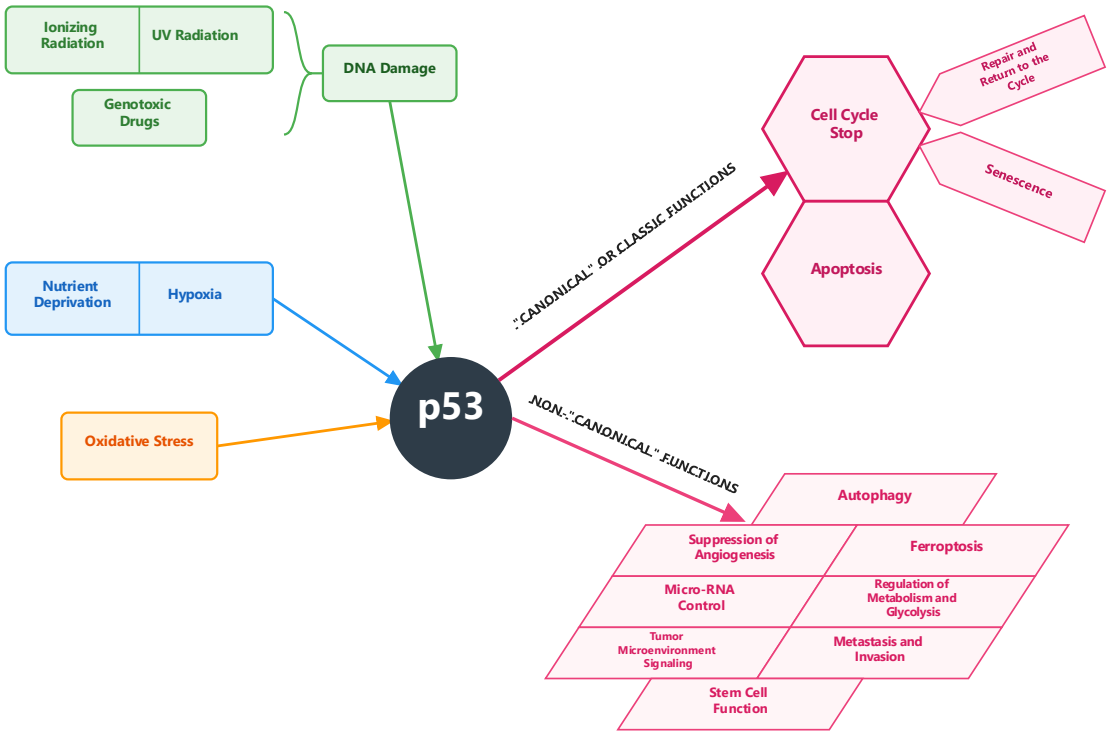


**Figure 1.** Activation of the p53 Protein by Cellular Stressors and Its Canonical and Noncanonical Functions. The p53 protein is activated by multiple cellular stressors and exerts canonical and noncanonical functions.[10,13,14]

*The TP53 p.R337H variant*

The *TP53* p.R337H variant was initially detected in a pediatric patient with an adrenocortical tumor.[15] Later studies demonstrated a founder origin of this variant.[15–17] This germline *TP53* variant (p.Arg337His) has been widely described and discussed in Brazil, but its predisposition to different types of cancer, including BC, remains controversial. The variant consists of a substitution of arginine for histidine (CGC to CAC) at codon 337 in exon 10, which is the region responsible for oligomerization.[2,18,19]

Variants affecting the tetramerization domain are less frequent among somatic alterations of p53, with p.R337H being the most common.[11,19] Most reported cases are from Brazil, although the variant has also been described in South Africa, Portugal, Japan, Germany, France, and China.[20]

Carriers of pathogenic *TP53* variants are susceptible to a wide spectrum of childhood and adult malignancies, such as BC. Phenotypic variability among carriers suggests that additional environmental and genetic factors contribute to cancer risk. Family histories of cancer associated with the *TP53* p.R337H variant range from isolated cancer cases to those meeting classic criteria for Li-Fraumeni syndrome.[2,8]

A proposed structural hypothesis is that the replacement of arginine by histidine alters the hydrogen bonds between the 2 monomers, making tetramerization of p53 pH dependent. Therefore, the p.R337H variant may have variable, pH-dependent functional effects because histidine gains a proton at lower pH and loses it at higher pH. This leads to differences in the stability of the p53 tetramer. This molecular feature may explain the lower, context-dependent penetrance observed with p.R337H under physiological conditions compared with other pathogenic *TP53* variants.[2,18,19] In addition, modifier genes such as *XAF1* may influence susceptibility by acting as a genetic modifier of p53 function.[8]

Because BC is one of the most prevalent cancers worldwide, identifying individuals at higher risk is crucial. Determining the prevalence of p.R337H among patients with BC may contribute to designing prospective studies and informing discussions about targeted surveillance strategies in high-prevalence populations, such as indications for risk-reduction mastectomies.[1,3]

## METHODS

This study included 2 complementary parts: an original cohort study evaluating the prevalence of the *TP53* p.R337H germline variant among patients with BC treated at a Brazilian university hospital, and a structured literature review of published studies reporting the prevalence of this variant in patients with BC.

### *Cohort study*

We included 100 patients between March 2021 and January 2022 who were referred to the mastology service of the Antonio Pedro University Hospital (HUAP) in Niterói, Rio de Janeiro, Brazil.

All patients had a confirmed diagnosis of BC and were invited to participate; those who provided written informed consent prior to enrollment were included. Peripheral blood samples were collected, and genomic DNA was extracted using the Gentra Puregene Blood Kit (QIAGEN). The p.R337H variant was analyzed using polymerase chain reaction amplification of exon 10 of *TP53*, followed by bidirectional Sanger sequencing with previously validated primers. Sequences were analyzed using SeqMan software (DNASTAR). The study was approved by the Research Ethics Committee of HUAP (Certificate of Presentation for Ethical Appreciation: 21312619.8.0000.5243).

### *Structured literature review*

A structured literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 recommendations.[21] Because of methodological heterogeneity among studies, no formal meta-analysis was performed.

Electronic searches were performed in PubMed (MEDLINE), Latin American and Caribbean Health Sciences Literature (LILACS) via the Virtual Health Library, and Scientific Electronic Library Online (SciELO) for studies published from January 1997 to December 2025. The search strategy was: ("R337H" OR "p.R337H" OR "p.Arg337His") AND ("breast cancer").

Studies that performed genetic testing for the germline p.R337H variant in patients with BC and had clear, extractable data were included; studies reporting zero detected cases were also included to reduce selection bias. Articles in languages other than Portuguese and English, duplicate records, studies without extractable prevalence data, and studies focused exclusively on other cancers were excluded.

Two independent reviewers screened the articles by title and abstract, followed by full-text assessment. Discrepancies were resolved by consensus. The search identified 46 records (40 in PubMed, 6 in LILACS, and 0 in SciELO). After duplicates were removed, records were screened by title and abstract, followed by full-text assessment. A total of 17 studies met the inclusion criteria, as shown in Figure 2.

The following data were extracted from each study: first author, publication year, geographic location, sample size (number of patients with BC tested), number of p.R337H carriers, selection criteria, and testing methodology.

### *Statistical analysis*

Prevalence estimates were calculated as proportions with 95% confidence intervals (CIs) using the binomial Clopper-Pearson method. Because of differences in study design, referral criteria, and population characteristics, no formal meta-analysis was performed, which would limit the interpretability of a pooled estimate. Therefore, the combined prevalence reported in this study should be interpreted as a crude aggregated estimate, rather than a pooled summary effect.

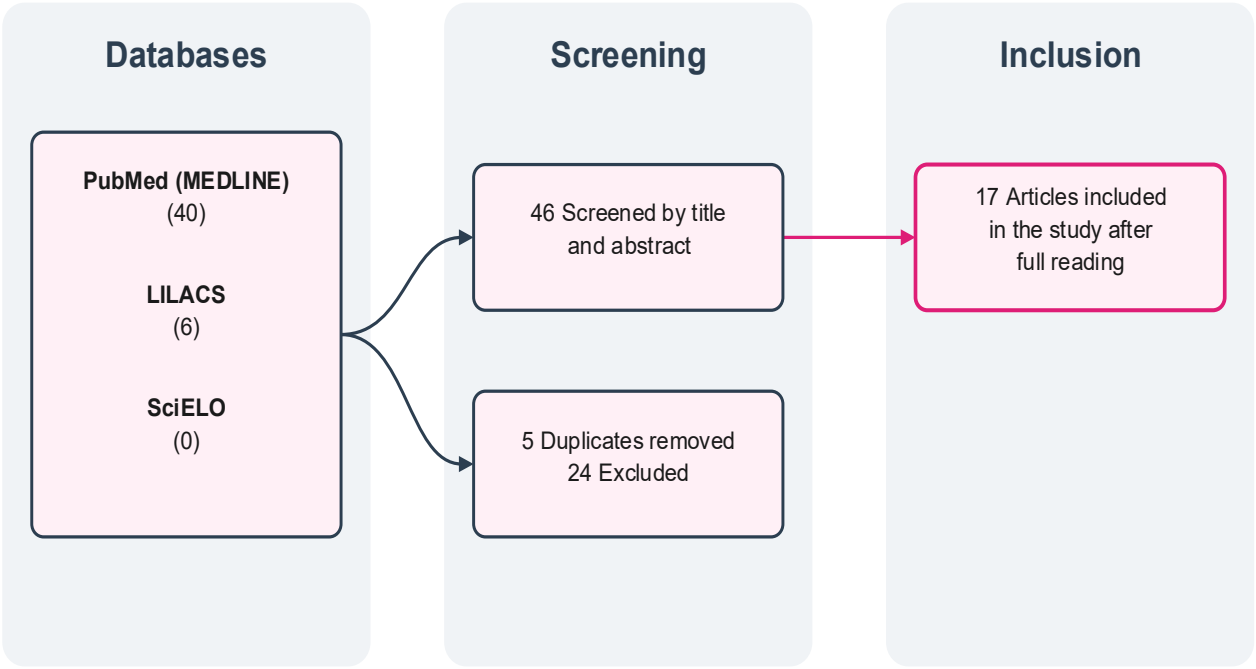


**Figure 2.** Flowchart of Study Identification, Screening, and Inclusion for the Structured Literature Review.

## RESULTS

*Cohort study*

Among the 100 patients with BC evaluated, no p.R337H carriers were identified. The estimated prevalence was 0% (95% CI, 0.00%–3.62%). This CI indicates that a low prevalence cannot be excluded.

All participants were women aged 30 to 87 years (mean age, 57.4 years). Regarding histological subtype, most patients had invasive ductal carcinoma.

*Literature review*

Across the 17 included studies, a total of 173 patients with BC were identified as p.R337H carriers among 8221 patients. Including our cohort (0 of 100), the combined total was 173 carriers among 8321 patients with BC, which corresponds to a crude aggregated prevalence of 2.08% (95% CI, 1.79%–2.41%). Reported prevalence across studies ranged from 0% to 23.1% (Table 1).

Studies evaluating unselected BC populations generally showed lower prevalence, ranging from 0% to approximately 2.4%. Studies including patients selected according to hereditary breast and ovarian cancer (HBOC) criteria showed wider variation, with prevalence ranging from 1.0% to 7.1%.

Higher prevalence was reported in studies focused on younger patients, particularly those aged ≤45 years. In the largest age-stratified cohort, Giacomazzi *et al.*[22] reported a prevalence of 12.2% among women diagnosed at ≤45 years, compared with 5.1% among women aged ≥55 years. Most patients had invasive carcinomas. No data on family history were available in that study.[22] Similarly, Hahn *et al.*[23] investigated 2 independent groups and observed higher prevalence among younger patients (6 of 239 patients with BC aged ≤45 years) than in unselected adult populations. Together, these age-based cohorts showed a prevalence of 8.6% (55 of 642) among women diagnosed at ≤45 years.

The highest prevalence estimate was observed in malignant phyllodes tumors, for which Giacomazzi *et al.*[24] reported a prevalence of 23.1% (3 of 13). This high frequency suggests a possible association between the p.R337H variant and phyllodes tumors.[24]

Assumpção *et al.*[25] reported similar frequencies among patients with sporadic and familial BC, suggesting that family history alone may not reliably distinguish carriers.

The Portuguese cohort identified no carriers among 573 patients with BC, confirming that this founder variant is uncommon outside Brazil.[26]

Higher frequencies were generally reported in southern and southeastern Brazil, consistent with the known founder effect of the p.R337H variant.[3,22,23,25,27]

**Table 1**: Characteristics of Included Studies and Prevalence of the p.R337H Variant Among Patients with Breast Cancer

| Author, year | Location | Population selection | Patients, No. | p.R337H Mutations, No. | Prevalence, % |
|---|---|---|---|---|---|
| Assumpção *et al.*[25] 2008 | Campinas, Brazil | BC patients (sporadic and familial) vs controls | 123 | 3 | 2.44 |
| Gomes *et al.*[28] 2012 | Rio de Janeiro, Brazil | Unselected BC patients vs controls | 390 | 2 | 0.51 |
| Giacomazzi *et al.*[24] 2013 | Porto Alegre and Barretos, Brazil | Malignant phyllodes tumor patients | 13 | 3 | 23.08 |
| Giacomazzi *et al.*[22] 2014[a] | Porto Alegre,Sao Paulo and Barretos | HBOC criteria + age-selected (≤45 or ≥55 years) | 874 | 72 | 8.24 |
| Giacomazzi *et al.*[26] 2014[b] | Portugal | Unselected BC patients | 573 | 0 | 0.00 |
| Cury *et al.*[29] 2014 | Ribeirão Preto, Brazil | BC patients with HBOC criteria | 28 | 2 | 7.14 |
| Silva *et al.*[30] 2014 | São Paulo, Brazil | BC patients with HBOC criteria | 120 | 3 | 2.50 |
| Felix *et al.*[31] | Bahia, Brazil | BC patients at high risk for HBOC | 101 | 1 | 0.99 |
| Hahn *et al.*[23] 2018[c] | Porto Alegre, Brazil | Unselected BC ≥18 years + BC ≤45 years without Chompret criteria | 554 | 7 | 1.26 |
| Cipriano *et al.*[32] 2019 | Divinópolis, Brazil | BC patients with HBOC criteria | 39 | 1 | 2.56 |
| Mathias *et al.* [27] 2020 | Curitiba And Cascavel, Brazil | Unselected BC patients (sporadic) | 805 | 19 | 2.36 |
| Sandoval *et al.* [33] 2021 | Brasília, Brazil | BC patients referred for genetic testing | 219 | 6 | 2.74 |
| Guindalini *et al.* [3] 2022 | Multicentric, Mainly South Brazil | BC patients referred for multigene panel testing | 1663 | 26 | 1.56 |
| Matta *et al.* [34] 2022 | Rio de Janeiro, Brazil (Inca) | BC patients with HBOC criteria (public health system) | 248 | 3 | 1.21 |
| Da Silva *et al.*[35] 2022 | Goiânia, Brazil | Early-onset BC with HBOC and Li-Fraumeni-like criteria, BRCA1/BRCA2 negative | 83 | 1 | 1.20 |
| Corrêa *et al.*[36] 2024 | Brasília, Brazil | BC patients with National Comprehensive Cancer Network criteria (public health system) | 180 | 2 | 1.11 |
| Oliveira *et al.*[4] 2024 | Multicentric, Brazil | BC patients referred for multigene panel testing | 2208 | 22 | 1.00 |
| Oliveira *et al.* 2025 | Niterói, Brazil | Unselected BC patients | 100 | 0 | 0.00 |

[a] Included only patients with malignant phyllodes tumors.
[b] Included age-stratified cohorts: 12.2% (55 of 451) in women aged ≤45 years and 5.1% (17 of 333) in women aged ≥55 years.
[c] Included 6 of 239 patients aged ≤45 years without Chompret criteria.
BC, breast cancer; HBOC, hereditary breast and ovarian cancer.

## DISCUSSION

Because BC is one of the primary manifestations of Li-Fraumeni syndrome[1], and the p.R337H variant is relatively frequent in Brazil[2], characterizing the prevalence of p.R337H among patients with BC based on available evidence is important. This may help guide the development of targeted follow-up strategies and the implementation of preventive, therapeutic, educational, and counseling measures to reduce costs, morbidity, and mortality when managing this population.

In the present study, no carriers were identified among the 100 unselected patients with BC evaluated at our institution. Although our sample size was limited, this finding is consistent with studies of unselected populations in which a lower prevalence has generally been reported. However, because of the

limited sample size, this study has low statistical power to detect rare variants.

In the literature, 17 eligible studies were identified. Across these studies and the present cohort, 173 carriers were found among 8321 patients with BC, corresponding to a crude aggregated prevalence of 2.08%. However, this estimate should be interpreted with caution because the included studies differed substantially in patient selection criteria, methodology, and geographic origin.

In studies that specifically evaluated patients meeting hereditary or familial criteria,[31,34] prevalence estimates were variable. In addition, discrepancies in how family history was defined among studies make it difficult to determine who should be considered at increased risk based on family history alone.[1,2,25]

Regarding malignant phyllodes tumors, one study reported a prevalence as high as 23.1% when only this subtype was considered. Because *TP53* variants are associated with sarcomas, and malignant phyllodes tumors share similarities with sarcomas, this association is biologically plausible and deserves further investigation.[24]

In studies that stratified patients by age, women diagnosed at ≤45 years had a prevalence of 8.6% (55 of 642). This high prevalence at younger ages supports the known association between *TP53* variants and early-onset cancer.[22,23]

Geographic variation was also observed, with higher frequencies generally reported in southern and southeastern Brazil, consistent with the known founder effect of the *TP53* p.R337H variant.[3,22,23,25,27]

The lower and variable penetrance of p.R337H, which is related to its pH-dependent effect on tetramer stability, may also help explain the heterogeneity observed across studies.[2,8,19]

*Limitations*

This study has several limitations. First, our cohort included only 100 patients, which limited the statistical power to detect rare variants; no formal power calculation was performed prior to the study. However, reporting zero-event data remains relevant for improving the accuracy of prevalence estimates. These negative findings should be interpreted in context: our study population was in Rio de Janeiro, where the prevalence of the variant is lower than in southern Brazil. Additionally, no control group was included, which limits direct comparisons with the general population. Regarding laboratory methodology, Sanger sequencing—which is appropriate for this context—was used for targeted single-variant screening, employing previously validated primers and bidirectional sequencing.

The literature review also has limitations: the search was conducted in only 3 databases, the review protocol was not registered in advance, and no formal risk-of-bias tool was applied. Because of substantial heterogeneity among studies in selection criteria, sample size, and geographic origin, no formal meta-analysis was performed; therefore, the combined prevalence should be interpreted as a crude aggregated estimate. Publication bias also cannot be excluded, particularly for smaller studies.

## CONCLUSION

*TP53* variants are among the most relevant hereditary alterations linked to BC. Understanding the specific contribution of each variant is important for improving prevention, diagnosis, and clinical management.

The Brazilian founder *TP53* p.R337H variant has shown heterogeneous prevalence among patients with BC. In our cohort, no carriers were identified, which may reflect either the lower prevalence observed in unselected populations or our limited sample size. Across the reviewed studies and the present cohort, 173 of 8321 patients with BC carried the p.R337H variant, corresponding to a crude aggregated prevalence of 2.08%. Higher frequencies were consistently observed in younger patients, hereditary-risk cohorts, patients in southern and southeastern Brazil, and those with malignant phyllodes tumors.

These findings suggest that age at diagnosis and patient selection criteria are key variables when evaluating the prevalence of p.R337H in BC, particularly in the Brazilian context. Whether these findings support changes to current genetic testing guidelines requires confirmation by larger, multicenter studies using standardized methodologies.

## ETHICAL CONSIDERATIONS

Ethical approval was obtained after consultation with the hospital research committee. Written informed consent was obtained from each participant.

## DATA AVAILABILITY

The data that support the findings of this study are not publicly available due to privacy and ethical restrictions. Data may be available from the corresponding author upon reasonable request and subject to ethical approval.

## CONFLICT OF INTERESTS

The authors declare no conflict of interest.

## FUNDING

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**AI DISCLOSURE**

Artificial intelligence was used to assist in the editing of this manuscript.

**AUTHOR CONTRIBUTION**

PSDO: Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing; LSPA: Investigation, Writing – review & editing; AVS: Investigation, Writing – review & editing; FAA: Investigation, Writing – review & editing.

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