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A matched case-control study of the prognosis of early breast cancer in patients with Li-Fraumeni syndrome (BREAST TP53)

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ABSTRACT

Introduction: Breast cancer (BC) is the most common type of cancer in premenopausal women with germline TP53 pathogenic variants (mTP53) (Li Fraumeni syndrome - LFS). However, little is known about the BC prognosis in these patients. This study analyzed the BC-related oncologic outcomes of patients with LFS.

Methods: We evaluated a cohort of LFS patients with BC in comparison with a control cohort of BC patients with no pathogenic variant in a hereditary cancer panel. The primary endpoint was recurrence-free survival (RFS). Due to the risk of second malignancies in LFS, only locoregional and distant recurrences were considered events for RFS. Secondary endpoints included rates of contralateral BC, overall survival (OS), and breast cancer-specific survival (BCSS).

Results: Forty-one patients were evaluated in the mTP53 group and 82 in the control group. Median age at BC diagnosis was 40 and 41 years, respectively. The mTP53 group received less adjuvant radiotherapy than the control group (63.4% vs 93.9%, $P < 0.001$). Other relevant baseline characteristics and treatment received were similar between groups. 5y-RFS rates were 79.4% in the mTP53 versus 93.6% in the control group (HR 2.43, 95% CI 0.74–8.01, $P = 0.143$); and were not impacted by the use of adjuvant radiotherapy. 5y-BCSS rates were 92.2% and 98.6%, respectively (HR 1.87, IC95% 0.25–13.48, $P = 0.534$).

Conclusions: Our results showed no statistically significant difference in BC-related RFS and BCSS between patients with mTP53 and a control group with no pathogenic variant. Larger multicentric studies are warranted to confirm these results.

1. Introduction

Li-Fraumeni syndrome (LFS) occurs due to pathogenic germline variants in the *TP53* gene, located on chromosome 17p13.1 [1,2]. The syndrome is associated with a high risk of sarcoma, breast cancer, adrenocortical cancer, brain tumor, leukemia, and lung cancer [3,4]. Carriers of germline *TP53* pathogenic or likely pathogenic variants (PV) typically develop cancer during childhood or young adulthood and have an extremely high lifetime risk of malignancies [4,5]. Different clinical criteria have been proposed for LFS diagnosis based on the pattern of cancer in a family, such as the Li-Fraumeni syndrome (LFS) (Online Mendelian Inheritance in Man - OMIM #151623) and the Li-Fraumeni-Like syndrome (LFL) criteria [6–8]. More recently, a broader indication for *TP53* testing was also proposed by the Chompret criteria (2009) and revised Chompret criteria (2015) [9,10] (Table 1).

The *TP53* gene is a crucial tumor suppressor gene that has been called 'the guardian of the genome'. *In vitro* transfection of tumor cell lines with plasmids carrying *TP53* PV indicated that the mutation compromises the ability of p53 to inhibit the growth of malignant cells *in vitro* [23,24,26]. The presence of a somatic mutation in *TP53* in the breast cancer tumor tissue represents an independent prognostic factor for poor outcomes in node-positive or negative disease, but the prognostic impact of a germline *TP53* PV for the tumor behavior is uncertain [27]. Since *TP53* mutation leads to carcinogenesis due to dysfunctional

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Table 1
Testing criteria for Li-Fraumeni Syndrome.

- Classic Li-Fraumeni syndrome (LFS) criteria [6]:
  - Combination of individual diagnosis at age <45 years with a sarcoma AND
  - First-degree relative diagnosed at age <45 years with cancer AND
  - An additional first- or second-degree relative in the same lineage with cancer diagnosed at age <45 years, or sarcoma at any age
- Chompret Criteria [9,10]
  - Individual with multiple tumors (except multiple breast cancer tumors), two of which belong to LFS tumor spectrum with the initial cancer occurring before the age of 46 years OR
  - Individual with adrenocortical carcinoma, or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype, at any age, regardless of family history OR
  - Breast cancer before 31 years of age

tumor suppression, its use as a target for novel treatments is challenging [28].

Patients' carriers of germline *TP53* PV have a very high lifetime risk of malignancies. The overall cumulative cancer incidence has been estimated to be 73–100% by age 70. In women, the most common malignancies are breast cancer and soft tissue sarcomas. Among female LFS patients, the lifetime risk of malignancies is close to 100% due to the high incidence of breast cancer, with up to 85% of the patients presenting breast cancer by age 60 [11–14].

A recent review suggested that 3.8–7.7% of the women with breast cancer younger than 31 years have a *TP53* PV [15]. In a Dutch study with 370 women diagnosed with breast cancer younger than 30 years, 2.2% harbored a germline *TP53* PV [16]. The studies suggested that women with invasive breast cancer or DCIS (ductal carcinoma in situ) with less than 30 years or with breast cancer with less than 46 years fulfilling Chompret criteria should be recommended for TP53 testing, and testing could also be considered in women with breast cancer younger than 46 years not fulfilling Chompret criteria or LFS criteria [17].

In Brazil, a specific germline *TP53* PV at codon R337H (c.1010 G > A, genomic nucleotide number 17588) in exon 10, is highly prevalent in the South and Southern regions, with a probable founder mutation effect [18,19]. This mutation was detected in 0.3% of the healthy women in the Southern region of the country [20]. The variant is associated with a high risk of breast cancer [21,22]. Individuals' carriers of *TP53* p. R337H have a similar lifetime cancer incidence to other LFS carriers (about 90%) but a lower penetrance at young ages. Less than 20% of the patients with *TP53* p. R337H have a malignancy at age 30, compared to 50% in carriers of other *TP53* PV [22,25].

Considering their particular carcinogenesis, breast cancer in hereditary cancer syndromes may present different behaviors compared to sporadic breast cancer. For instance, patients with germline *BRCA1* PV have a high proportion of the triple-negative breast cancer, while LFS patients are enriched by HER2-positive tumors. Nevertheless, while several studies have evaluated the breast cancer phenotype in germline *BRCA1/2* mutation carriers [29,30], data on the phenotype and prognosis of breast cancer among patients with germline *TP53* PV are lacking. Overall, treatment of LFS patients with breast cancer follows the same strategies of non-hereditary breast cancer, except for the caution for using radiotherapy. Since many studies correlate radiotherapy with a high risk of secondary malignancies in patients with *mTP53*, guidelines suggest avoiding this treatment if possible [31].

2. Material and methods

2.1. Study sample

In this matched case-control study, patients with a documented PV of *TP53* (*mTP53* group) were identified using blood DNA collection. Patients were followed by the Hereditary Group of the *Instituto do Cancer do Estado de Sao Paulo* between 1999 and 2022. The control group was constituted of patients with breast cancer who had an indication for hereditary cancer testing and had no PV in breast cancer-related genes. Patients were included if they had a histopathological diagnosis of localized invasive carcinoma of the breast. Almost all patients in the *mTP53* group met Revised Chompret criteria or Li Fraumeni-like syndrome or had a family member carrier of *mTP53*. Patients who had only non-epithelial breast cancer, such as sarcoma and phyllodes tumor, were excluded from the analysis. All patients with *mTP53* and breast cancer who were available were invited to participate in the study. For each *mTP53* case, we included 1–3 matched patients in the control group. Patients were matched according to age; tumor, node, metastasis (TNM) stage at diagnosis; estrogen receptor status; and HER2 status.

The *TP53* molecular analyses were initially based on the investigation of the p. R337H mutation by polymerase chain reaction/restriction fragment length polymorphism (PCR-RFLP). In this method, PCR amplicons of exon 10 of the *TP53* gene were digested by the *Hha*I restriction enzyme (GIBCO BRL, Life Technology, Rockville, MD, USA) and then separated by agarose gel electrophoresis. This analysis can distinguish between different genotypes at the p. R337H mutation site, identifying homozygous, heterozygous, and wild-type individuals for this specific mutation. Sanger sequencing of coding and splicing regions was performed in all negative cases to investigate other variants. Amplification products of exons 2–11 of *TP53* were sequenced using the BigDye terminator v3.1 cycle sequencing kit (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's instructions. Sequencing analyses were carried out on the 3130xl Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). Some patients performed hereditary germline panels with NGS (new generation sequencing) in other locations. The control group carried out germline hereditary cancer panels of different companies, including Fleury, GenomiKa, Invitae, Genoas, and others. The classification of the variant pathogenicity was done according to the American College of Medical Genetics and Genomics guidelines, using VarSome [32,33]. In this article, the abbreviation 'PV' stands for pathogenic or likely pathogenic variant.

Electronic records were reviewed, and data were collected on clinical and pathological features, treatment received, and outcomes. The occurrence of second malignancies was also registered. The trial was approved by the Local Ethics Committee on November 30, 2018, number 3.0840,453, CAEE 01819618.7.0000.0065, and registered in Clinical Trials (NCT04966923).

2.2. Endpoints and statistical analysis

The primary endpoint was recurrence-free survival (RFS), which was considered from the date of breast cancer diagnosis until the date of locoregional or distant recurrence. Death and second malignancies were not considered as an event for RFS, since patients with *mTP53* are at increased risk of other neoplasms and death due to these second malignancies.

Secondary endpoints were clinical and pathological features, rates of contralateral breast cancer, overall survival (OS), and breast cancer-specific survival (BCSS). The BCSS was estimated from the date of breast cancer diagnosis until the date of death due to breast cancer. Patients without the events of interest were censored on the date of last follow-up or the date of death from other causes. Survival analyses were estimated by the Kaplan-Meier method and compared using the log-rank test. The Cox regression model was used to calculate the hazard ratio and 95% confidence interval.

Continuous variables were compared between groups using Student T test or Mann-Whitney test, in the case of normal and non-normal data distribution, respectively. Categorical variables were compared using the Fisher exact test. P values less than 0.05 were considered statistically significant. Statistical analyses were performed using Stata software, version 15.1 (StataCorp, Texas, USA).

3. Results

Among 138 women who met the criteria for *TP53* testing, 93 were diagnosed with *TP53* PVs, and 81 were carriers of *TP53* p. R337H. Among the *mTP53* group, 46 patients developed invasive carcinoma of the breast; 41 patients had localized breast cancer and 5 had metastatic *de novo* disease. Patients with metastatic *de novo* breast cancer were excluded from this analysis. Only 4 patients knew the *mTP53* status before the diagnosis of breast cancer.

Median age at breast cancer diagnosis was 40.2 years (range 21.5–62.8 years) in mTP53 versus 41.2 (range 3–74.9 years) in the control group. The majority of the patients in the *mTP53* group (N = 28, 68.3%) harbored a germline heterozygous *TP53* p. R337H PV (Fig. 1). The most common histologic type was invasive carcinoma of no special type in both groups (93% and 87%). In the *mTP53* group, 78% of the patients were estrogen receptor-positive, 65.8% progesterone receptor-positive, and 39% HER2-positive; in the control group, these numbers were 76.%, 65.8% and 26.8%, respectively (Table 2).

The proportion of patients who received neoadjuvant chemotherapy was similar in both groups (36.6%). After neoadjuvant chemotherapy,

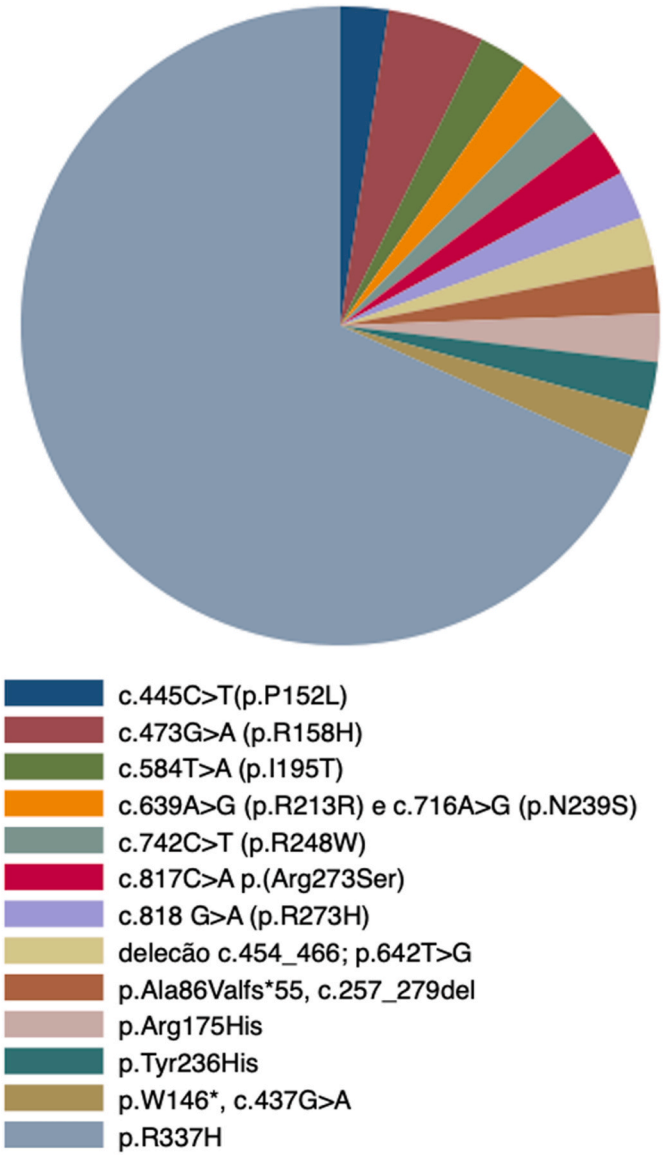

Fig. 1. Types of TP53 pathogenic/likely pathogenic variants in the mutated TP53 group.

Table 2
Patients' Characteristics. Abbreviations: *mTP53, mutated TP53;* NA, not available.

Characteristic	No of Patients (%)		P
	mTP53 group (N = 41)	Control group (N = 82)	
Age, years			0.086[a]
Median	40.3	41	
Range	21.5–62.8	23–74.9	
Estrogen-receptor			0.441[b]
Positive	32 (78.1%)	63 (76.8%)	
Negative	8 (19.5%)	19 (23.2%)	
NA	1 (2.4%)	0 (0%)	
Progesterone-receptor			0.548[b]
Positive	27 (65.9%)	54 (65.8%)	
Negative	13 (31.7%)	27 (32.9%)	
NA	1 (2.4%)	1 (1.2%)	
HER2-amplification			0.151[b]
Positive	16 (39%)	22 (26.8%)	
Negative	24 (58.6%)	60 (73.2%)	
NA	1 (2.4%)	0 (0%)	
Immunohistochemistry group			0.247[b]
ER+/HER2-	21 (51.2%)	47 (57.3%)	
ER-any/HER2+	16 (39%)	22 (26.8%)	
ER-/HER2-	3 (7.3%)	13 (15.9%)	
NA	1 (2.5%)	0 (0%)	
Stage			0.560[b]
I	15 (36.6%)	24 (29.3%)	
II	14 (34.2%)	37 (45.1%)	
III	9 (21.9%)	21 (25.6%)	
NA	3 (7.3%)	0	
T stage			0.807[b]
T1	15 (36.6%)	32 (39%)	
T2	16 (39%)	35 (42.7%)	
T3	7 (17.1%)	12 (14.6%)	
T4	0 (0%)	3 (3.7%)	
NA	3 (7.3%)	0 (0%)	
N stage			0.708[b]
N0	22 (53.7%)	43 (52.4%)	
N1 (mic)	0 (0%)	4 (4.5%)	
N1	10 (24.4%)	24 (29.3%)	
N2	5 (12.2%)	10 (12.2%)	
N3	1 (2.4%)	1 (1.2%)	
NA	3 (7.5%)	0 (0%)	

[a] Mann-Whitney.
[b] Fisher exact test.

33.3% of the patients in the *mTP53* group had a pathologic complete response compared to 36.7% in the control group (P = 1.000). Complementary treatment received and response to neoadjuvant chemotherapy are detailed in Table 3. All HER2-positive patients received neoadjuvant and/or adjuvant trastuzumab. The proportion of mastectomy was also similar in both groups (48.8% and 41.5%; P = 0.436). Fewer patients received adjuvant radiotherapy in the *mTP53* group than in the control group (63.4% vs 93.9%; P < 0.001).

After a median follow-up of 51 months in the *mTP53* group and 41 months in the control group, 14.6% of the *mTP53* patients had a disease recurrence compared to 6.1% in the control group (P = 0.177). Regarding the site of recurrence, 9.7% of the patients with LFS had a distant recurrence compared to 4.9% in the control group. Sites of recurrence are detailed in Table 4. The RFS at 5 years was 79.4% (95% CI 59.2–90.3%) versus 93.6% (95% CI 79.1–98.1%) (HR 2.43, 95%CI 0.74–8.01, P = 0.143), respectively (Fig. 2). Seventeen LFS patients (41.4%) developed a second malignancy; the most common was contralateral breast cancer (n = 6; 14.6%), followed by soft tissue sarcomas (n = 4; 9.5%) and lung cancer (n = 3; 7.3%). Two patients (7.7%) in the *mTP53* group and none in the control group developed a radiotherapy-induced malignancy in the irradiated field. In the control group, 9 patients (10.9%) developed second malignancies.

To evaluate if the difference in the use of adjuvant radiotherapy between groups could have influenced the outcomes observed, we performed two exploratory analyses. In a univariate Cox regression,

Table 3
Treatment received and response to neoadjuvant therapy. Abbreviations: *mTP53,* mutated *TP53;* NA, not available; NAC, neoadjuvant chemotherapy.

Characteristic	No of Patients (%)		P
	mTP53 group (N = 41)	Control group (N = 82)	
Chemotherapy			0.366[a]
Neoadjuvant	15 (36.6%)	30 (36.6%)	
Adjuvant	16 (39%)	41 (50%)	
No chemotherapy	9 (21.9%)	11 (13.4%)	
NA	1 (2.4%)	0 (0%)	
Chemotherapy regimen			0.556[a]
Anthracycline and taxane-based	19 (65.5%)	53 (74.6%)	
Taxane-based	9 (31%)	15 (21.1%)	
Anthracycline-based	1 (3.4%)	3 (4.2%)	
Response to NAC	n = 15	n = 30	0.700[a]
Complete response	5 (33.3%)	11 (36.7%)	
Partial response	10 (66.7%)	15 (50%)	
Stable disease	0 (0%)	3 (10%)	
Progressive disease	0 (0%)	1 (3.3%)	
Type of breast surgery			0.436[a]
Breast-conserving surgery	19 (46.3%)	45 (54.9%)	
Mastectomy	20 (48.8%)	34 (41.5%)	
NA	2 (4.9%)	3 (3.7%)	
Adjuvant radiotherapy	26 (63.4%)	77 (93.9%)	<0.001[a]

[a] Fisher exact test.

Table 4
Absolute and relative numbers of recurrence and deaths. Abbreviations: *mTP53,* mutated *TP53.*

Characteristic	No of Patients (%)		P
	mTP53 group (N = 41)	Control group (N = 82)	
Recurrence	6 (14.6%)	5 (6.1%)	0.177[a]
Local only	1 (2.4%)	1 (1.2%)	
Distant only	4 (9.7%)	4 (4.9%)	
Both (local and distant)	1 (2.4%)	0 (0%)	
New primary breast cancer	6 (14.6%)	1 (1.2%)	0.006[a]
Death	5 (12.2%)	3 (3.7%)	0.115[a]
Death due to breast cancer	2 (4.8%)	2 (2.4%)	0.600[a]

[a] Fisher exact test.

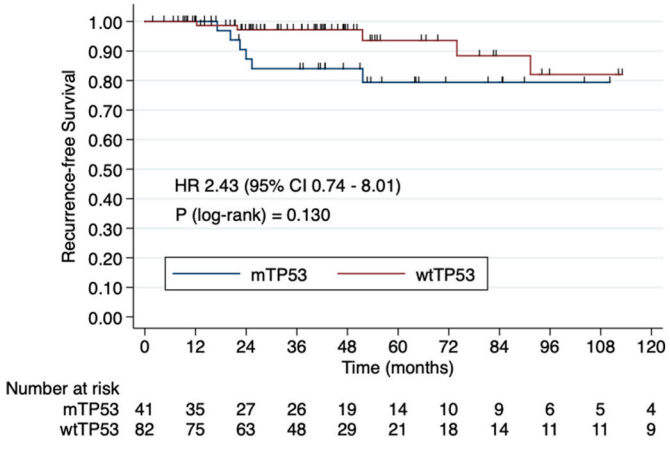

Fig. 2. Kaplan-Meier curves for breast cancer-related recurrence-free survival according to TP53 status. Abbreviations: mTP53, mutated TP53; wtTP53, wild-type TP53.

radiation therapy was not associated with RFS neither in the overall cohort (HR 0.91, 95% CI 0.11–7.31, P = 0.935) nor in the *mTP53* cohort separately (HR 1.19, 95% CI 0.13–10.7, P = 0.874). In addition, the association between the study group (*mTP53* group versus control group) and RFS remained similar when stratified by adjuvant radiotherapy (2.28, 95% CI 0.64–8.14, P = 0.203).

In the m*TP53* group, 5 patients (12.2%) died; 2 died due to breast cancer and 3 due to other malignancies (jaw osteosarcoma, lung cancer, and pleomorphic sarcoma). In the control group, 3 patients (3.7%) died, and the causes of death were breast cancer in 2 patients and COVID-19 infection in 1 patient. The 5-year BCSS rates were 92.2% (95% CI 71.5%–98%) in the *TP53* group and 98.6% (95% CI 90.7%–99.8%) in the control group (HR 1.87, IC95% 0.25–13.48, P = 0.534). BCSS and OS curves are shown in Fig. 3.

4. Discussion

In accordance with previous literature, patients with LFS in our cohort had a high frequency of second malignancies, including new primary breast cancer [34]. Regarding histologic and molecular features, breast cancer in patients with LFS is mainly invasive carcinoma of no special subtype, with frequent positivity for estrogen receptor and HER2. Indeed, in the present study, LFS patients had a high proportion of estrogen receptor-positive (78%) and HER2-positive (39%) tumors.

Due to the risk of second malignancies in LFS patients, only ipsilateral and distant recurrence were considered as events for RFS in this study. Along the same lines, the BCSS was selected as an outcome to better illustrate the breast cancer behavior and prognosis in LFS considering the competing risks of these patients. To the best of our

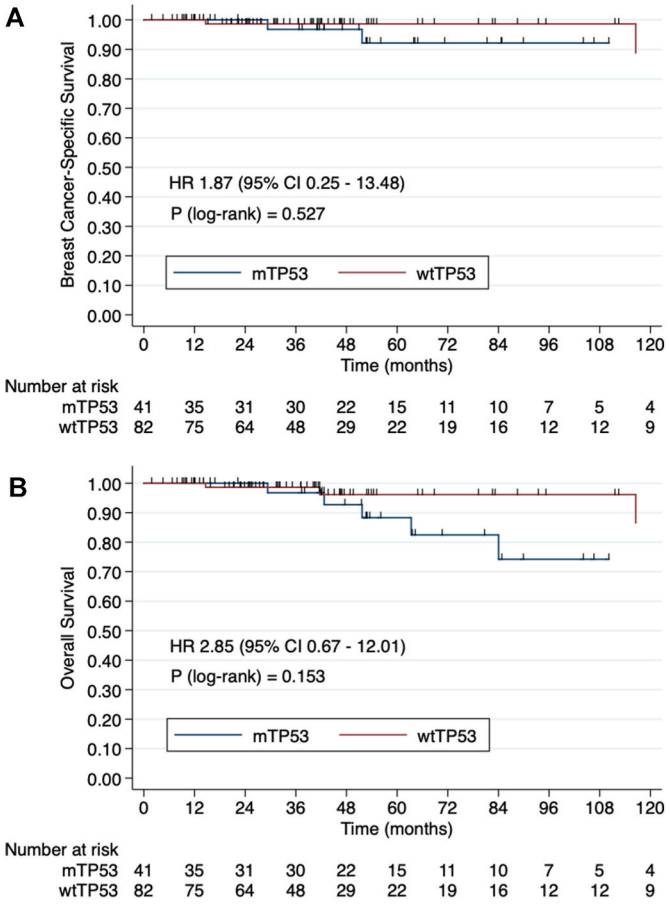

Fig. 3. Kaplan-Meier curves for breast cancer-specific survival and overall survival according to TP53 status. Abbreviations: mTP53, mutated TP53; wtTP53, wild-type TP53.

knowledge, no previous study evaluated BCSS in LFS patients.

The 5-year RFS was only 79.4% in the *mTP53* group compared to 93.6% in a matched control group, although the difference was not statistically significant. While types of surgery and systemic therapy were similar between groups, fewer patients with LFS received adjuvant radiotherapy than in the control group, probably due to the concern with the risk of secondary radio-induced malignancies [31]. However, additional analyses herein presented suggested that the use of adjuvant radiotherapy did not impact RFS in this cohort.

A Chinese cohort also suggested that breast cancer in patients with germline *TP53* PV have an unfavorable recurrence-free survival (RFS), distant recurrence-free survival (DRFS), and OS. In the study, patients with germline *mTP53* had a 2.24 times higher risk of recurrence or death than a control group of unselected breast cancer patients [34]. However, different from the present study, death from any cause was also considered an event for the RFS and DRFS outcomes. In addition, treatments received by the groups were not detailed, limiting their comparability. Another previous study suggested a high rate of ipsilateral breast cancer recurrence in LFS patients [35]. In our cohort, however, the majority of the cases recurred at distant sites (12.1%).

Due to the rarity of LFS, studies evaluating cancer outcomes in this population are mainly small and retrospective cohorts. Considering the sample size of our study, we believe that a distinct disease behavior of breast cancer in LFS patients cannot be ruled out. Moreover, since most patients in our cohort had a *TP53* p. R337H PV, the generalizability of these results is uncertain. As previously mentioned, this founder mutation has a distinct phenotype compared to other *TP53* PV in terms of the type of malignancies and age of disease onset [22,25]. Thus, breast cancer biology could also be influenced by the type of *TP53* PV. Additional larger multicentric collaborative studies are warranted and might have power to further elucidate these questions.

5. Conclusion

Patients with LFS and breast cancer had a higher rate of second malignancies, but no difference was seen in breast cancer -related RFS and BCSS in comparison with a matched control group of breast cancer patients without a hereditary cancer-related germline PV.

Declaration of competing interest

VP: Speaker fees and/or honoraria for consultancy or advisory functions: AstraZeneca, Daiichi-Sankyo, Novartis; Financial support for educational programs and symposia: Daiichi-Sankyo. RCB: Speaker fees and/or honoraria for consultancy or advisory functions: Daiichi-Sankyo, Nestle; Financial support for educational programs and symposia: AstraZeneca, Daiichi-Sankyo; Institutional Research Funding: Novartis, AstraZeneca. LT: Consulting or Advisory Role: Lilly, Novartis, MSD, AstraZeneca, Daiichi-Sankyo; Educational Support: Pfizer, Lilly, Zodiac, AstraZeneca; Speaker: Novartis, Roche, Pfizer, Zodiac, Lilly, MSD, AstraZeneca, Daichii-Sankyo; Institutional Research Funding: Novartis. DJBHC: Speaker fees and/or honoraria for consultancy or advisory functions: Novartis, Daiichi-Sankyo, AstraZeneca; Financial support for educational programs and symposia: Gilead. AC: Speaker fees and/or honoraria for consultancy or advisory functions: AstraZeneca, Libbs. RGC: Speaker fees and/or honoraria for consultancy or advisory functions: AstraZeneca, MSD, GSK; Financial support for educational programs and symposia: AstraZeneca.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2023.02.002.

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