Breast Cancer (2024) 31:988–996
https://doi.org/10.1007/s12282-024-01612-3

ORIGINAL ARTICLE

Case series of Li-Fraumeni syndrome: carcinogenic mechanisms in breast cancer with *TP53* pathogenic variant carriers

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Received: 27 September 2023 / Accepted: 30 June 2024 / Published online: 17 July 2024

Abstract

Background Li-Fraumeni syndrome (LFS), a hereditary condition attributed to *TP53* pathogenic variants,(PV), is associated with high risks for various malignant tumors, including breast cancer. Notably, individuals harboring TP53 PVs are more likely (67–83%) to develop HER2 + breast cancer than noncarriers (16–25%). In this retrospective study, we evaluated the associations between *TP53* variants and breast cancer phenotype.

Methods We conducted a retrospective review of the medical records of patients with LFS treated at a single institution and reviewed the literature on *TP53* functions and the mechanisms underlying HER2 + breast cancer development in LFS.

Results We analyzed data for 10 patients with LFS from 8 families. The median age at the onset of the first tumor was 35.5 years. Only case 2 met the classic criteria; this patient harbored a nonsense variant, whereas the other patients carried missense variants. We observed that 9 of 10 patients developed breast cancer. Immunohistochemical analyses revealed that 40% of breast cancers in patients with LFS were HR − /HER2 + . The median age at the onset of breast cancer was slightly younger in HR − /HER2 + tumors than in HR + /HER2 − tumors (31 years and 35.5 years, respectively).

Conclusions The occurrence of HER2 + breast cancer subtype was 40% in our LFS case series, which is greater than that in the general population (16–25%). Some *TP53* PVs may facilitate HER2-derived oncogenesis in breast cancer. However, further studies with larger sample sizes are warranted to clarify the oncogenic mechanisms underlying each subtype of breast cancer in *TP53* PV carriers.

Keywords Li-Fraumeni syndrome · *TP53* · Breast cancer · Hormone receptor · Human epidermal growth factor receptor 2

Introduction

TP53 and Li-Fraumeni syndrome

Tumor protein P53 (*TP53)* expression is induced by various physiological stresses, such as DNA damage, radiation, hypoxia, and oncogene signaling. *TP53* functions as a guardian of the genome by inducing apoptosis and preventing the accumulation of genomic mutations in cells [1, 2]. Somatic pathogenic variants in *TP53* are found in 18–50% of all malignant tumors in humans [3, 4], suggesting that *TP53* is an early oncogenic driver in various types of cancers.

The p53 protein functions as a tumor suppressor primarily by binding to p53 DNA-binding sites in its target genes to regulate their expression [5]. *TP53* pathogenic variants (PVs), both germline and somatic, are primarily distributed

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in the DNA-binding domain and impair *TP53* transcription [6].

Li-Fraumeni syndrome (LFS) is a hereditary genetic condition attributed to *TP53* PVs. It is associated with high risks for a diverse spectrum of malignant tumors, including breast cancer. The frequency of *TP53* germline pathogenic variants in the general population is 0.03–0.27% [7–9].

Role of TP53 in breast cancer development

Breast cancer is the most frequent type of cancer observed in patients with LFS, accounting for 79% of cancers among female *TP53* PV carriers [10].

In a study of human high-grade ductal carcinoma in situ (DCIS), a precursor lesion of invasive ductal carcinoma (IDC), the p53 pathway was inactivated in all DCIS specimens [11]. Breast cancer is assumed to originate from mammary epithelial cells [12]. Upon the depletion of mutant *TP53* in breast cancer cells, the irregular morphology, which is a hallmark of cancer, returns to a normal mammary epithelium-like structure. This implies that mutant *TP53* contributes to the disruption of the mammary tissue architecture during breast tumorigenesis [13].

Based on immunohistochemical (IHC) analyses of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), breast cancer can be classified into four basic subtypes: hormone receptor (HR: ER or/and PR) + /HER2 − , HR − /HER2 + , HR + / HER2 + , and triple-negative (negative for ER, PR, and HER2), with frequencies of 68.9%, 7.5%, 10.2%, and 13.4%, respectively [14].

TP53 PV carriers have a considerably higher rate of HER2 + tumors (67–83%) than that of noncarriers (16–25%) [15, 16]. However, the mechanism underlying HER2 overexpression in LFS-associated breast cancer remains unknown. Herein, we describe a case series of LFS in our institution and review the existing literature on *TP53* functions and the mechanism underlying HER2 + breast cancer development in LFS.

Materials and methods

Case series of LFS

We conducted a retrospective review of the medical records of patients with LFS diagnosed at our institution between July 2006 and August 2021. Among 11 *TP53* PV carriers, we analyzed 10 patients, excluding one unaffected carrier. We assessed the pathogenicity of *TP53* germline variants reported from commercial laboratories and verified with ACMG/AMP guidelines (Table 1) [17].

Clinical criteria

The classic LFS criteria were used for the diagnosis of LFS [18]. Despite carrying a germline *TP53* PV, several patients did not meet these criteria. Hence, the 2015 version of Chompret criteria [10] is widely used for identifying candidates for *TP53* germline genetic testing.

Results

Case series

We identified 10 *TP53* PV carriers with a history of cancer from eight families at our institution (Table 2). Cases 8–10 were from the same family, whereas the others were from different families. All patients were women, and the median age at the onset of the first tumor was 35.5 years (range: 8–45 years). Only case 2 met the classic criteria, whereas 50% of patients and 63% of families met the 2015 Chompret criteria. We found 25 tumors among the 10 patients with LFS, and the median number of tumors was two. The distribution of tumors was as follows: breast (15), bones (2), stomach (1), lung (2), colorectum (2), endometrial (1), ovary (1), and pancreas (1) (Table 2).

Case 7 was diagnosed with LFS after tumor genomic profiling. She had ovarian cancer at the age of 53 years and

Table 1 Classification of *TP53* variants according to ACMG/AMP guidelines

	TP53 variants (NM_000546.6)	ClinVar ID	ClinVar classifications	Germline variant classification by VarSome	Criteria applied (ACMG/AMP guidelines) [17]
1	c.638G > A (p.R213Q)	135,359	P	Pathogenic	PP5, PM1, PM5, PP3, PS3, PM2
2	c.1024C > T (p.R342*)	182,970	P	Pathogenic	PVS1, PP5, PM2
3	c.817C > T (p.R273C)	43,594	P/LP	Pathogenic	PP5, PM1, PM5, PP3, PS3, PM2
4	c.797G > A (p.G266E)	161,516	P/LP	Pathogenic	PP5, PM1, PM5, PP3
5	c.1009C > T (p.R337C)	142,536	P/LP	Pathogenic	PP5, PM5, PP3, PM1, PS3, PM2
6	c.743G > A (p.R248Q)	12,356	P	Pathogenic	PP5, PM1, PM5, PP3, PS3, PM2
7	c.473G > A (p.R158H)	141,963	P/LP	Pathogenic	PP5, PM1, PM5, PP3, PS3,PM2

Table 2 Patient characteristics in the LFS case series

No	Sex	last follow-up age	Age (genetic testing)	1st tumor	2nd tumor	3rd tumor	4th and later	Classic criteria	Chompret criteria	TP53 variant (NM_000546.6)	Molecular consequence from IARC TP53 database	Age at brest cancer	Bilateral breast cancer	Breast cancer phenotype and treatment			Family history with breast cancer	
														Right	Left			
1	F	73	55	Chondrosarcoma (29 years)	Right breast cancer (39 years)	Left breast cancer (44 years)	*Endometrial cancer (48 years) etc	No	Yes	c.638G > A (p.R213Q)	Misssense	39	Yes	IDC, unknown for ER/PR/HER2	DCIS		No	N/A
														Bilateral Bt + Ax, RT (−)				
2	F	38	29	Osteosarcoma (8 years)	Left breast cancer (28 years)	Lung cancer (34 years)	Left breast cancer (37 years)	Yes	Yes	c.1024C > T (p.R342*)	Nonssense	28	No	N/A	IDC, ER − / PR − / HER2:3 +	IDC, ER + / PR + / HER2:0	Yes	Mother at 60's, and paternal grandmother at 30's
															Bp + SNB, RT (−)	Bt + SNB, RT (−)		
3	F	50	40	Bilateral breast cancer (34 years)	Lung cancer (37 years)	N/A	N/A	No	No	c.817C > T (p.R273C)	Misssense	34	Yes	DCIS	IDC, ER − / PR − / HER2:3 +		No	N/A
														Bilateral Bt + SNB, RT (−)				
4	F	36	26	Left breast cancer (26 years)	Right breast cancer (34 years)	N/A	N/A	No	Yes	c.797G > A (p.G266E)	Misssense	26	No	IDC, ER + / PR + / HER2: 1 +	IDC, ER + / PR + / HER2: 0		NO	N/A
														Bt + SNB, RT (−)	Bt + Ax, RT (+)			
5	F	47	41	Left breast cancer (41 years)	Colon cancer (47 years)	N/A	N/A	No	Yes	c.1009C > T (p.R337C)	Misssense	41	No	N/A	IDC, ER − / PR − / HER2: 3 +		Yes	Bilateral breast cancer at 50's in mother
															Bt + SNB, RT (−)			
6	F	37	35	Left breast cancer (28 years)	Right breast cancer (34 years)	N/A	N/A	No	Yes	c.743G > A (p.R248Q)	Misssense	28	Yes	DCIS	IDC, ER − / PR − / HER2: 3 +		No	N/A
														Bt + SNB, RT (−)	Bt + Ax, RT (+)			
7	F	58	56	Ovarian cancer (53 years)	Pancreatic cancer (54 years)	N/A	N/A	No	No	c.743G > A (p.R248Q)	Misssense	N/A	N/A	N/A	N/A		Yes	Mother at 60's

Table 2 (continued)

No	Sex	last follow-up age	Age (genetic testing)	1st tumor	2nd tumor	3rd tumor	4th and later	Classic criteria	Chompret criteria	TP53 variant (NM_000546.6)	Molecular consequence from IARC TP53 database	Age at breast cancer	Bilateral breast cancer	Breast cancer phenotype and treatment		Family history with breast cancer	
														Right	Left		
8	F	38	34	Left breast cancer (33 years)	N/A	N/A	N/A	No	No	c.473G > A (p.R158H)	Misssense	33	No	N/A	IDC, ER + / PR + / HER2: 0 Bt + SNB, RT (−)	Yes	Mother at 30's, and maternal grandmother at 40's
9	F	47	43	Bilateral breast cancer (43 years)	N/A	N/A	N/A	No	No			43	Yes	DCIS Bilateral Bt + SNB, RT (−)	ILC, ER + / PR + / HER2: 1 +		
10	F	40	37	Left breast cancer (35 years)	N/A	N/A	N/A	No	No			35	No	N/A	IDC, ER + / PR +, HER2: 2 +, FISH − Bp + Ax, RT (−)		

*Case 1 also had endometrial cancer at the age of 48 years, gastric cancer at the age of 55 years, and colorectal cancer at the age of 71 years.

pancreatic cancer at the age of 54 years. The patient received somatic tumor panel testing at the age of 54 years, which indicated potential germline *TP53* PVs. Thereafter, genetic testing confirmed that she carried a c.743G > A (p.R248Q) variant, the same variant detected in case 6.

Breast *cancer* characteristics

We observed 15 breast cancers in 9 out of 10 *TP53* PV carriers (Table 2). The median age at the onset of breast cancer was 34 years (range: 26–45 years). The pathological features of the 15 breast cancers were as follows: IDC (10), invasive lobular carcinoma (ILC) (1), and DCIS (4). According to IHC analyses of 11 invasive breast cancer specimens, excluding 1 tumor that was not assessed by IHC (Case 1), 40% (4 out of 10) of tumors were HR − /HER2 + , whereas the remaining 60% were the HR + /HER2- subtype. Furthermore, among all patients with breast cancer, 56% (five of nine) had bilateral breast cancer and 67% (six of nine) had a family history of breast cancer in their mothers (Table 2).

Case 8, diagnosed with ER + /PR + /HER2- breast cancer at 33 years, was a proband in this family carrying a c.473G > A (p.R158H) variant. The elder sisters of the patient (cases 9 and 10), who later underwent a *TP53* analysis, also carried the same *TP53* PV. In case 9, the first surveillance breast MRI detected bilateral breast cancer at the age of 43 years; DCIS in the right breast and ER + /PR + /HER2 − ILC in the left breast. Case 10 had a history of ER + /PR + /HER2 − IDC diagnosed at the age of 35 years (Table 2, Fig. 1).

Radiotherapy for breast *cancer*

Among 15 breast cancers, only 2 tumors were treated with radiotherapy (RT). Case 4 had bilateral breast cancer. The first tumor was left breast cancer at 26 years (Stage III, IDC,

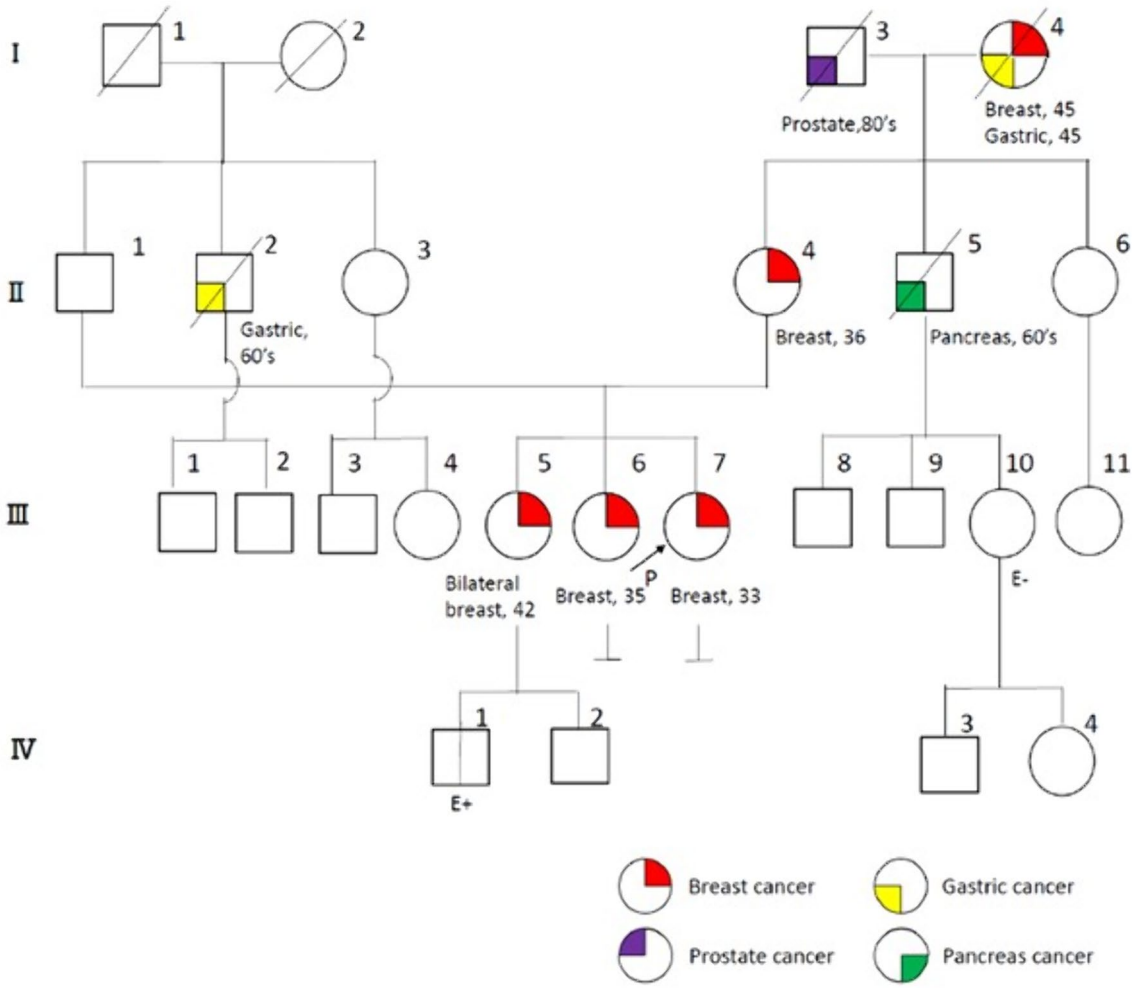

Fig. 1 Family tree of cases 8–10. According to the family history of case 8, the mother was diagnosed with breast cancer at 36 years, maternal uncle with pancreatic cancer at 60 years, and maternal grandmother with breast and gastric cancers at 45 years of age. IV-1 was an unaffected carrier with the same pathogenic *TP53* variant.

ER + /PR + /HER2 −) treated with neoadjuvant chemotherapy with anthracycline followed by taxane, then by mastectomy with axillary lymph node dissection (Ax), with residual cancer in five nodes. Adjuvant RT and endocrine therapy were administered.

Case 6 also had bilateral breast cancer, the first tumor was left breast cancer (Stage III, IDC, ER − /PR − /HER2 +) at 28 years treated with neoadjuvant chemotherapy with anthracycline followed by a taxane plus trastuzumab regimen, and then mastectomy with Ax, with no invasive residual cancer in the breast or lymph nodes. Adjuvant trastuzumab and RT were administered.

In case 2, left breast cancer was diagnosed at 27 years and treated with breast-conserving surgery and sentinel node biopsy (no metastasis), pathological findings revealed ER − / PR − /HER2 + IDC. She did not undergo RT because we identified that she had a *TP53* c.1024C > T (p.R342*) variant after surgery. A new primary breast cancer, ER + /PR + / HER2 − IDC, was detected in her remaining left breast at 38 years.

Discussion

Tumor distribution in *TP53* pathogenic variant carriers

In our study, 63% of families with LFS met the 2015 Chompret criteria (Table 2) with a lower positivity rate than that previously reported; the sensitivity of the 2009 Chompret criteria is 57–82% [10, 19]. In the largest investigation of LFS in Japan (68 individuals from 48 families), 60.4% of families met the 2015 Chompret criteria [20], comparable with our results. They reported lower frequencies of soft tissue sarcoma (7.8% vs. 19.0%) and breast cancer (19.5% vs. 31.4%) in Japanese patients than in French patients with LFS [20]. In our study, 90% of patients with LFS were affected by breast cancer, accounting for 60% of all tumors (15 out of 25). Notably, these data may be biased because our institution specifically treats patients with cancer, and the number of patients with breast cancer is particularly high. This may explain why all the patients were women in this study as well as the high probability of breast cancer.

TP53 hot spots and the distribution of TP53 variants

The distribution of *TP53* PVs is shown in Fig. 2. We found that 3 out of 10 patients carried variants in sites previously reported as mutation hotspots, such as R175, R245, R248, R249, R273, and R282, corresponding to the p53 DNA-binding domain [6]. Most (75%) *TP53* somatic variants are missense variants [5]. In our study, 9 out of 10 patients carried a missense variant, whereas one patient carried a nonsense variant (Fig. 2).

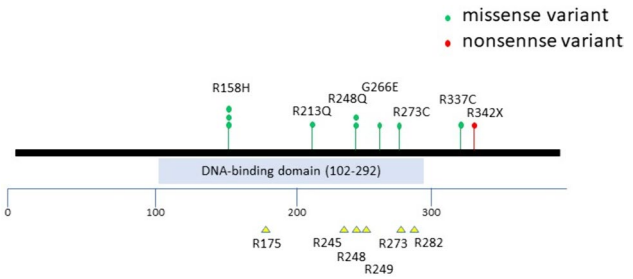

Fig. 2 *TP53* hotspots. Six previously reported *TP53* hotspots in human cancers from the IARC database are described in the lower part [6]. The spectrum of *TP53* variants in our case series is shown in the upper part: green circles indicate missense variants, whereas red circles indicate nonsense variants

In our study, only case 2 had a nonsense variant; this was the only case involving a history of sarcoma and meeting the classic LFS criteria in our case series (Table 2; Fig. 2). These findings were consistent with the results obtained by Rana et al., who reported that loss-of-function variants were associated with an earlier tumor onset, increased frequency of sarcoma, and higher rate of meeting classic LFS criteria than missense variants [21].

TP53 hot spot variants facilitate HER2-derived oncogenesis

In vivo, *Trp53 PV* knock-in mice (R175H, R273H, and R248Q) exhibit a higher tumor bulk with an increased grade and invasion, metastatic ability, and shorter life span than those of *Trp53*-null mice [22, 23]. These *Trp53* PVs have also been identified in humans [6] (Fig. 2).

HER2 overexpression in breast cancer activates pathways that promote cell proliferation, reduce apoptosis, and increase metastasis [24]. In vitro, p53 variants (R248Q and R273C) increase *HER2* expression, whereas the suppression of PV *TP53* reduces *HER2* expression and inhibits the downstream pathway [25]. In a HER2 transgenic mouse model, a PV *Trp53* allele induces the formation of multicentric mammary tumors and leads to early tumor onset and short survival [26].

Notably, somatic *TP53* PVs are most frequent in breast cancer, reaching incidence rates of 28–37% [27, 28], and are especially frequent in the HER2 + than in the HR + subtype (72%, and 12–29%, respectively) [27]. An analysis of the HER2 + breast cancer dataset revealed that the level of *HER2* mRNA expression is also considerably higher in tumors expressing *TP53* PV than in tumors expressing the wild-type *TP53* [29]. In our study, all HER2 + cases (4 out of 4 tumors) were graded as IHC 3 + , indicating high *HER2*

mRNA expression. Most HER2 IHC 3 + cases (94.7%) have been reported to show HER2 amplification by FISH [30].

These previous reports suggest that specific *TP53* PVs facilitate HER2-derived oncogenesis and cancer progression in HER2 + breast cancer, potentially resulting in a high proportion of HER2 + breast cancers in patients with LFS.

Mechanisms underlying both HER2 + and HR + tumors arising in TP53 PV carriers

Although there were no HR + /HER2 + tumors in our study, HR + /HER2 + tumors are also more frequent in patients with LFS than in the general population (53% and 10%, respectively) [31, 32]. In vitro, ER binds to wild-type TP53 directly and represses its transcriptional activation [33]. Conversely, estrogen increases p53 protein levels, whereas estrogen deprivation reduces p53 levels [34]. Thus, contradictory results have been obtained regarding the relationship between ER and wild-type *TP53*.

Regarding the relationship between ER and TP53 PV, limited data exist; estrogen increases TP53 *PV* protein expression, whereas estrogen deprivation reduces TP53 expression levels [34]. In *TP53* PV carriers, estrogen-ER signaling might affect the early onset of breast cancer; both ER and HER2 signaling are drivers of cell proliferation and disease progression in breast cancer, and their crosstalk might facilitate breast cancer development; however, further investigations are required to clarify these relationships.

Age at breast *cancer* onset in TP53 PV carriers

The median age of *TP53* PV carriers at the time of diagnosis of breast cancer appears to be similar in Japan and France: the median ages were 34 years in our study, 32 years in the study by Funato et al. [20], and 33 years in a study of the French LFS working group [10]. The median age in all three independent studies was over 31 years, which is the age criterion considered for the *TP53* genetic test according to the Chompret criteria.

The reported prevalence of *TP53* PVs is 2.2–4.0% in women with breast cancer before the age of 31 years [35, 36]. In a study focused on HER2 + breast cancer, the prevalence of *TP53* PV is 3% in patients diagnosed before 41 years; however, the prevalence increases to 8.5% in patients diagnosed before the age of 31 years [37]. In our study, the median age at the onset of breast cancer was slightly younger for HR − /HER2 + tumors than for HR + / HER2 − tumors (31 years and 35.5 years, respectively), although our study was limited by a small sample size. This suggests that *TP53* genetic testing should be considered for patients with breast cancer at a slightly older age than 31 years, especially in HER2 + breast cancer. Similarly, Evans et al. suggested new criteria for *TP53* germline testing to include women diagnosed with HER2 + breast cancer before the age of 36 years [38]. At our institution, *TP53* germline testing is recommended for women diagnosed with breast cancer who are negative for BRCA1 and BRCA2, regardless of subtype, before 31 years of age.

Radiotherapy

TP53 PV carriers are susceptible to a high risk of radiation-induced secondary malignancy after RT. The LFS guideline recommends avoiding radiotherapy when possible [39]. In our study, two cases (cases 4 and 6) underwent adjuvant RT due to axillary lymph node metastasis and the high risk of recurrence. The patients did not have any tumors within the radiation field at follow-up times of 10 years and 9 years after RT. However, longer follow-up periods are needed because the period of radiation-induced secondary malignancy is 3–22 years (median 7 years) [40].

Mastectomy, rather than lumpectomy, is preferable to avoid a second malignancy; however, for a *TP53* PV carrier with advanced breast cancer, adjuvant RT should be considered carefully depending on the risk of recurrence.

Conclusions

In summary, our study included a relatively large LFS case series from a single institution. The HER2 + breast cancer subtype was more frequent in patients with LFS (40%) than in patients with sporadic breast cancer (16–25%), consistent with previous studies. HER2 signaling is a well-known driver of cell proliferation and progression in breast cancer. Previous reports suggest that *TP53* PVs facilitate HER2-derived oncogenesis, which might account for the high proportion of HER2 + breast cancer in *TP53* PV carriers. It also might explain the slight difference in the onset of breast cancer between HR − /HER2 + and HR + /HER2 − tumors in our study. A limitation of our study was the small sample size at a single institution, and future investigations are warranted to clarify the oncogenic mechanisms in each subtype of breast cancer. Considering the rarity of germline *TP53* PVs, clinical data collection at multiple institutions in several countries as an international collaborative study is desirable.

Acknowledgements We thank the patients who participated in this study and their families.

Author contributions Conceptualization: M.H. and A.U.; data curation: K.K., H.S., and A. H.; tumor board: I.F., N.H., and S.T.; writing—original draft preparation: M.H.; writing—review and editing: T.K., H.I, T.M., Y.H., A.N., E.N., T.N., T. T., and T.U.; and supervision: S. O. and A.U. All authors have read and agreed to the published version of the manuscript.

Funding This study received no external funding.

Data availability Data available on request due to privacy restrictions. The variant information that support the findings of this study are openly available in Table1 and 2. Some data that support the findings of this study are available on request from the corresponding author, MH. The data are not publicly available due to restrictions their containing information that could compromise the privacy of research participants.

Declarations

Conflict of interest Dr. Takayuki Ueno and Dr. Toshimi Takano are editorial board members; all other authors have no conflicts of interest.

Ethical approval This retrospective study was approved by the Institutional Review Board of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (2022-GB-024), approved on August 4, 2022.

Informed consent Informed consent was obtained from all individual participants included in the study.

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