npj | genomic medicine

Article

Published in partnership with CEGMR, King Abdulaziz University

https://doi.org/10.1038/s41525-025-00496-2

Clinical *TP53* genetic testing is recommended for HER2-positive breast cancer patients aged 35 or younger

Jing Li[1,2,3,4,7], Lili Chen[1,2,3,7], Xuhui Chen[5,7], Meng Huang[6], Wenhui Guo[1,2,3], Minyan Chen[1,2,3], Yuxiang Lin[1,2,3], Yali Wang[1,2,3], Weifeng Cai[1,2,3], Yibin Qiu[1,2,3], Peng He[1,2,3], Qindong Cai[1,2,3], Chuan Wang[1,2,3] ✉ & Fangmeng Fu[1,2,3] ✉

Limited information is available for *TP53* pathogenic variants (PVs) in early-onset breast cancer patients in China. We investigated the prevalence and clinical relevance of *TP53* PVs among 1492 *BRCA1/2*-negative early-onset breast cancer patients. Peripheral blood samples were collected for *TP53* genetic testing through next-generation sequencing. Finally, *TP53* PVs were identified in 7 patients (0.47%). The variants p.R248P, p.I251F, and p.G266R were identified for the first time in germline mutations. *TP53* carriers exhibited significantly younger diagnosis age ($p = 0.003$) and higher prevalence of HER2-positive disease ($p = 0.020$). All carriers were diagnosed before age 35. In HER2-positive patients ≤35 years, the prevalence of *TP53* PVs was 2.3%, significantly higher than others after adjusting for a family history of breast cancer and/or ovarian cancer and a personal history of bilateral breast cancer (OR = 13.57, $p = 0.002$). These results support *TP53* genetic testing prioritization for HER2-positive patients under 35 years to guide clinical management, while validation in diverse populations remains essential.

The median age for breast cancer diagnosis in China is 47 years, which is at least 10 years younger than that in Western countries[1,2]. Early-onset breast cancer, defined as breast cancer diagnosed at age of 40 years or younger, accounts for >16% of cases, with an increasing trend in China[1,2]. In contrast, the prevalence of early-onset breast cancer in Western countries is significantly lower, ranging only from 4–6%. In other words, the population of early-onset breast cancer patients in China is substantial, roughly equivalent to the total number of early-onset breast cancer patients in Europe. Notably, young age at breast cancer diagnosis is usually considered associated with a higher frequency of carrying pathogenic variants (PVs) of breast cancer susceptibility genes[3–5]. The *BRCA1* and *BRCA2* (*BRCA1/2*) genes are the dominant genes mutated in early-onset breast cancer and genetic testing for *BRCA1/2* is recommended for all breast cancer patients with young onset. However, *BRCA1/2* mutations are only responsible for 40–60% of hereditary breast cancer cases[5–7], suggesting that other predisposing genes also play an important role in hereditary cases.

Though much rarer than *BRCA1/2* mutations, pathogenic *TP53* variants are associated with a high risk of breast cancer[8,9]. Previous studies has found that patients harbored *TP53* PVs has higher risks of developing bilateral breast cancer, higher rates of ipsilateral breast tumor recurrence after breast-conserving therapy, and even worse overall survival[10–12]. More importantly, *TP53* PVs are strongly associated with Li-Fraumeni syndrome (LFS) or Li-Fraumeni-like (LFL) syndrome[13,14], a rare autosomal dominant cancer predisposition syndrome characterized by an early age of onset and a high lifetime risk of multiple primary cancers, including early-onset breast cancer, osteosarcoma, soft tissue sarcoma, adrenocortical carcinoma, brain tumors, and leukemias. Once the first cancer develops, nearly half of patients develop another cancer after a median of 10 years[15,16]; thus, more attention is needed to monitor the occurrence of other primary cancers after breast cancer onset.

Studies on *TP53* mutations in young breast cancer patients have been conducted in Western countries with a mutation rate rang from 0% to 12.1% depending on different ethnicities, age groups and sample sizes[17,18]. The POSH study identified 0.31% of *TP53* carriers in a large early-onset breast cancer cohort of 2882 participants in the UK[19], Couch et al. identified 0.40% *TP53*-carriers in 8009 early-onset patients in America[20] and Giacomazzi

[1]Department of Breast Surgery, Fujian Medical University Union Hospital, Fuzhou, Fujian Province, China. [2]Department of General Surgery, Fujian Medical University Union Hospital, Fuzhou, Fujian Province, China. [3]Breast Cancer Institute, Fujian Medical University Union Hospital, Fuzhou, Fujian Province, China. [4]Department of Breast Surgery, Zhongshan Hospital Xiamen University, School of Medicine, Xiamen University, Xiamen, Fujian Province, China. [5]Department of Radiology, Fujian Medical University Union Hospital, Fuzhou, Fujian Province, China. [6]Fujian Center for Disease Control and Prevention, Fuzhou, Fujian province, China. [7]These authors contributed equally: Jing Li, Lili Chen, Xuhui Chen. ✉e-mail: dr_chuanwang@fjmu.edu.cn; ffm@fjmu.edu.cn

et al. reported 12.1% *TP53*-carriers in 403 patients younger than 45 years in Brazil[17]. In contrast, research on the spectrum of *TP53* mutations among young breast cancer patients in Asian populations is limited.

Given the epidemiological patterns of breast cancer susceptibility gene variants vary by race and space, the research on the spectrum of *TP53* gene mutation among young breast cancer patients in China holds significant implications for this demographic. The identification of carriers of *TP53* PVs among early-onset breast cancer patients is critical not only for the secondary prevention of breast cancer in patients but also for hereditary risk management in their relatives. In the face of a large number of early-onset breast cancer patients in China, which is a developing country, genetic testing for all young patients would impose a substantial healthcare burden. Information about the spectrum and characteristics of mutation carriers may guide the selection of appropriate individuals for genetic testing.

The objective of this study was to determine the prevalence of germline PVs in *TP53* among Chinese women with early-onset breast cancer who tested negative for *BRCA1/2* PVs and to further explore the clinicopathological characteristics of mutation carriers to guide genetic testing strategies for young patients.

Results

Characteristics of the patients screened for this study

A total of 1492 patients diagnosed with early-onset breast cancer between 2005 and 2023 and unselected for family history were screened for this study. The median age at diagnosis of first primary breast cancer was 36 years, ranging from 33–38 years, in the overall cohort. Additionally, 214 (14.3%) of the patients were diagnosed at age 30 years or younger, and 1278 (85.7%) were aged between 31 and 40 years. A family history of breast cancer and/or ovarian cancer was recorded in 98 (6.6%) patients. The majority of all young patients (70.6%, 1054/1492) were diagnosed with HR+ breast cancer; among them, 1031 patients had ER+ disease and 877 patients had PR+ disease. HER2+ breast cancer comprised 27.6% (412/1492) of the overall patient cohort. Invasive ductal carcinoma is the most common pathological type (83.9%). More details of the baseline characteristics of the overall patient cohort are displayed in Table 1.

PVs identified in patients with early-onset breast cancer

Seven patients (0.47%) carried *TP53* PVs, including four pathogenic variants (p.R175H, p.R248P, p.G266R and p.E286K), two pathogenic or likely pathogenic variants (p.R273C and p.R337C), and one likely pathogenic variant (p.I251F) (Table 2). All variants were missense mutations and identified only once for each. No other types of mutations, including nonsense, indels, and splice variants, were detected. Notably, 43% (3/7) of the mutations were identified for the first time in germline mutations, including p.R248P, p.I251F, and p.G266R.

Associations of demographic characteristics with PVs

The median age at diagnosis was 30 years among patients harboring *TP53* PVs, which was significantly younger than the 36 years among non-carriers ($p = 0.003$). The prevalence of *TP53* PVs was 1.9% (4/214) among patients at or below age 30, which was significantly higher than 0.23% (3/1278) at age 31–40 ($p = 0.010$) (Table 1). *TP53*-carriers had a higher likelihood of a positive family history of breast cancer and/or ovarian cancer than non-carriers (28.6% vs. 6.5%), while the difference was close to statistical significance for *TP53* PVs ($p = 0.072$). Only one *TP53*-carrier was diagnosed with bilateral breast cancer (14.3%, $p = 0.197$) (Tables 1 and 3).

None of the seven *TP53*-carriers met classic LFS criteria, while four met the Chompret 2015 of breast cancer diagnosis age younger than 31 years without other LFS-related tumors or a family history suggestive of LFS, and only one met the criteria of Chompret 2009 (c.796 G > A, p.G266R), who had tibial sarcoma at age 17 years and was diagnosed with unilateral breast cancer at age 33 years, and the proband's father was diagnosed with myelodysplastic syndrome at age 55 years (Fig. 1).

Associations of clinical characteristics with PVs

TP53 PVs were enriched among HER2-positive breast cancer (71.4%), significantly higher than HER2-negative breast cancer (28.6%, $p = 0.020$). Likewise, patients diagnosed with HER2-positive breast cancer also had a higher frequency of *TP53* PVs (5/412, 1.2%) than HER2-negative breast cancer patients (2/1080, 0.19%). Furthermore, the most common molecular subtype among *TP53* carriers was HER2 + /HR- (3/7, 42.9%), followed by HER2 + /HR+ (2/7, 28.6%) and HER2-/HR+ (2/7, 28.6%), and none of the *TP53* carriers was TNBC ($p = 0.044$) (Table 1 and Table 3).

In addition, among patients with HER2-positive disease, *TP53* PVs were identified in 4 of 68 (4.4%) patients aged 30 years or younger, 2 of 150 (1.3%) patients aged 31–35 years, and none of 194 (0%) patients aged 36–40 years. In total, *TP53* PVs accounted for 4.4% (3/68) of patients aged 30 years or younger, 2.3% (5/218) of patients aged 35 years or younger, and 1.2% (5/412) of patients aged 40 years or younger (Table 4). Given that 40% (2/5) of HER2-positive *TP53* carriers were between the ages of 31 and 35 years, we further analyzed the subgroup mutation risk in patients at or younger than 35 years, rather than 30 years, compared with others in this early-onset cohort. After adjusting for a family history of breast cancer and/or ovarian cancer and a personal history of bilateral breast cancer, the prevalence of *TP53* PVs was significantly increased in HER2-positive patients with a diagnosis age of 35 or younger (OR 13.57, $p = 0.002$).

Invasive ductal carcinoma was observed in all 7 *TP53* PV carriers (Table 1). Patients carried *TP53* PVs were weakly associated with more aggressive pathological features than non-carriers, including higher histologic grade (57.1% vs. 35.0%), larger tumor size (71.4% vs. 55.3%), and higher Ki-67 index (85.7% vs. 75.0%), although the differences were non-significant (Table 1).

Discussion

Given that the large population of young breast cancer patients remains a substantial health burden for China and the limited data available for *TP53* PVs of that population, we investigated the germline *TP53* PVs with data derived from 1492 patients with early-onset breast cancer unselected for family history to inform efficient strategies for genetic testing. To our knowledge, this is the largest study to date that provides insight into the prevalence and clinical characteristics of *TP53* PVs in early-onset breast cancer in China.

Seven patients were found to be carriers of *TP53* PVs with mutation rates of 0.47% in this study, which was lower than 1.0% reported by Sheng et al. in the corresponding age subgroups of another large unselected breast cancer cohort in China[11], but slightly higher than the rate of 0.31% in UK[19] and 0.40% in America[20]. Additionally, given the rare mutation frequency of 0.47% among our early-onset breast cancer cohort, the onset age contributed limited to *TP53* gene testing.

One of the variants detected in this study is *TP53* 1009 C > T (p.R337C), a pathogenic or likely pathogenic variant commonly associated with LFS. It should be noted that this variant differs from p.R337H (*TP53* 1010 G > A)[17], a variant that has been identified in 12.1% of patients diagnosed with breast cancer at or before age 45, regardless of their family history of cancer. The p.R337H is identified as a founder mutation in the Brazilian population, representing 70.3% of all *TP53* PVs in Brazil[21]. However, no recurrent variants were found in our study. Although the identification of founder mutations allows targeted detection of single mutations and saves testing costs, current research has not found any founder mutations in the Chinese population.

Among the variations detected in this study, p.R175H is a hotspot of *TP53* PVs among breast cancer and LFS patients in both Western and Asian populations[11,22]. Specifically, while codons 248 and 273 are acknowledged *TP53* hotspots[11,16,22], with p.R248Q, p.R248W, and p.R273H mutations frequently reported, our cohort uniquely identified p.R248P mutations within these codons, and p.R273C has not been previously reported in breast cancer patients. Additionally, p.R248P, p.I251F had not been identified in breast tumors before and are also being reported for the first time as germline mutations. The p.G266R mutation was identified as a somatic

Table 1 | Characteristic of overall population and comparisons between *TP53* carriers vs. non-carriers

Variable n (%)	All cases (*n* = 1492)	Non-*TP53* (*n* = 1485)	*TP53* carriers (*n* = 7)	*p*
Age at first BC diagnosis, years				
Median age (range)	36.0 (33.0–38.0)	36.0 (33.0–38.0)	30.00 (28.5–33.5)	0.003
≤30	214 (14.3)	210 (14.1)	4 (57.1)	0.010
>30	1278 (85.7)	1275 (85.9)	3 (42.9)	
FH of BC/OC				0.072
None	1394 (93.4)	1389 (93.5)	5 (71.4)	
Yes	98 (6.6)	96 (6.5)	2 (28.6)	
bilateral BC				0.197
No	1446 (96.9)	1440 (97.0)	6 (85.7)	
Yes	46 (3.1)	45 (3.0)	1 (14.3)	
HER2 status				0.020
negative	1080 (72.4)	1078 (72.6)	2 (28.6)	
positive	412 (27.6)	407 (27.4)	5 (71.4)	
ER status				0.683
negative	461 (30.9)	458 (30.8)	3 (42.9)	
positive	1031 (69.1)	1027 (69.2)	4 (57.1)	
PR status				0.456
negative	615 (41.2)	611 (41.1)	4 (57.1)	
positive	877 (58.8)	874 (58.9)	3 (42.9)	
HR status				0.425
negative	438 (29.4)	435 (29.3)	3 (42.9)	
positive	1054 (70.6)	1050 (70.7)	4 (57.1)	
Molecular subtypes				0.044
HER2 + /HR-	193 (12.9)	190 (12.8)	3 (42.9)	
HER2 + /HR+	219 (14.7)	217 (14.6)	2 (28.6)	
HER2-/HR+	835 (56.0)	833 (56.1)	2 (28.6)	
HER2-/HR-	245 (16.4)	245 (16.5)	0 (0)	
Ki-67				1.000
<20%	362 (24.9)	361 (25.0)	1 (14.3)	
≥20%	1090 (75.1)	1084 (75.0)	6 (85.7)	
unknown	40	40	0	
Tumor size				0.471
≤2 cm	653 (44.6)	651 (44.7)	2 (28.6)	
>2 cm	811 (55.4)	806 (55.3)	5 (71.4)	
unknown	28	28	0	
Lymph node status				0.714
negative	709 (47.5)	705 (47.5)	4 (57.1)	
positive	783 (52.5)	780 (52.5)	3 (42.9)	
Histological Grade				0.249
I+II	906 (64.9)	903 (65.0)	3 (42.9)	
III	490 (35.1)	486 (35.0)	4 (57.1)	
unknown	96	96	0	
Morphology				0.606
IDS	1197 (83.9)	1190 (83.8)	7 (100.0)	
Others	230 (16.1)	230 (16.2)	0 (0)	
unknown	65	65	0	

Abbreviations: *BC* breast cancer, *FH* family history, *OC* ovarian cancer, *HER2* human epidermal growth factor receptor-2, *ER* estrogen receptor, *PR* progesterone receptor, *HR* hormone receptor, *Ki-67* cell proliferation antigen protein, *IDC* invasive ductal carcinoma.

Table 2 | Pathogenic variants of *TP53* identified in this cohort

Exon	HGVS.c	HGVS.p	Mutation type	Classification
5	c.524 G > A	p.Arg175His (p.R175H)	missense	P
7	c.743 G > C	p.Arg248Pro (p.R248P)	missense	P
7	c.751 A > T	p.Ile251Phe (p.I251F)	missense	LP
8	c.796 G > A[a]	p.Gly266Arg (p.G266R)	missense	P
8	c.817 C > T	p.Arg273Cys (p.R273C)	missense	P/LP
8	c.856 G > A	p.Glu286Lys (p.E286K)	missense	P
10	c.1009 C > T	p.Arg337Cys (p.R337C)	missense	P/LP

[a]Patient met the criteria of Chompret 2009.
Abbreviations: *P* Pathogenic; *LP* Likely Pathogenic.

Table 3 | Characteristic of *TP53* PVs identified in patients with early-onset breast cancer

Dx	FH with BC/OC	HER2 Status	ER/PR Status	Grade	Bilateral BC
30	None	+	+ / +	III	No
34	An aunt (BC)	+	− / −	III	No
30	Mother (BC)	+	+ / +	III	No
34	None	−	+ / +	II	No
26	None	−	+ / −	III	No
33[a]	None	+	− / −	II	No
27	None	+	− / −	I	Yes

[a] Patient met the criteria of Chompret 2009.
Abbreviations: *Dx* age at initial diagnosis of breast caner, *FH* family history, *BC* breast cancer, *OC* ovarian cancer, *HER2* human epidermal growth factor receptor-2, *ER* estrogen receptor, *PR* progesterone receptor, + positive, − negative.

mutation in breast tumor specimens in a Japanese study[23], and it has not been previously reported as a germline mutation. Our research findings revealed the specific *TP53* PVs in Chinese patients with early-onset breast cancer and reflected the necessity of investigating diverse populations to better understand unique genetic variations.

In previous studies, the frequencies of *TP53* PVs among patients aged 30 years or younger were ranging from <2%–8%[16,18,24–26]. In our study, the mutation rate of *TP53* PVs in the corresponding population was 1.9%, which is found to be significantly higher than the frequency in breast cancer patients aged 31–40 years ($p = 0.01$). The comparison underscored the higher propensity for *TP53* PVs in the patients with younger age.

Some previous studies have found a significant association between *TP53* PVs and bilateral breast cancer[9,11,20,27], leading to the recommendation of bilateral mastectomy for affected patients[28,29]. Furthermore, Couch et al. reported that *TP53* PVs were only associated with a family history of ovarian cancer, but not with a family history of breast cancer in a larger nationwide sample of unselected breast cancer[20]. Conversely, Siraj et al. did not observe any association between *TP53* PVs and family history of breast cancer or any cancer among early onset Middle Eastern breast cancer patients[27]. In our current study, we did not find a significant association between *TP53* PVs and personal history of bilateral breast cancer or family history of breast cancer and/or ovarian cancer. This suggests that these two factors may not be appropriate decision criteria for *TP53* genetic testing in younger patients.

Sheng et al. indicated that breast cancer patients with germline *TP53* mutations have a poorer prognosis compared to non-carriers[11]. Additionally, *TP53* carriers are at an increased risk of developing radiation-induced secondary malignancies after adjuvant radiotherapy[25,28]. Consequently, mastectomy may be more appropriable for *TP53* carriers to avoid the need for radiotherapy following breast-conserving surgery. The decision to use radiotherapy post-mastectomy also warrants careful consideration. The European Reference Network for Genetic Tumour Risk Prediction (GENTURIS) guidelines emphasize the importance of identifying *TP53* carriers before the initiation of treatment to potentially avoid radiotherapy in carriers[30]. Moreover, asymptomatic carriers in the families of *TP53* mutation patients face a significantly increased risk of cancer, necessitating regular surveillance, particularly in pediatric carriers[25,29]. Therefore, the identification of *TP53* carriers among breast cancer patients not only aids in optimizing treatment strategies for patients but also enhances cancer surveillance in at-risk family members.

In clinical practice, *BRCA1/2* gene testing is recommended for young breast cancer patients, with emphasis on testing for HER2-negative patients because it accounts for the majority of *BRCA1/2* PVs. However, the majority of *TP53* carriers were HER2-positive patients (71.4%) in our study, consistent with 67%–83% from previous studies[31,32]. Consistent with the majority of previous studies, our research found a significant association between *TP53* mutations and HER2-positive status[31–33]. Compared to HER2-negative disease, patients with HER2-positive status have a significantly higher frequency of *TP53* PVs (1.2%) in the whole cohort, similar to the 1.4%-1.5% found in previous studies of early-onset patients[6,33]. In addition, we observed that the prevalence of *TP53* PVs in HER2-positive patients aged 35 years or younger was 2.3%, which is approximately 13 times higher than that of the remaining cohort after adjustment for family history and personal history of bilateral breast cancer. Although the prevalence of *TP53* PVs can be as high as 4.4% in HER2-positive patients aged 30 years or younger, it should be highlighted that 40% of *TP53* PVs occurred in patients between age 31 and 35 years old, which should not be omitted. Consequently, our findings recommend that *TP53* genetic testing could serve as a crucial supplement for HER2-positive patients with early-onset, particularly in patients younger than 35 years old.

There are some limitations to our study. First, although this study has the largest sample size of patients with early-onset breast cancer to date, the rare mutation rate of breast cancer susceptibility genes led to a limited number of identified carriers, potentially reducing the statistical power of our analyses. Therefore, the results should be interpreted with caution. Additionally, this study focused on Chinese patients with early-onset breast cancer. Due to the regional and ethnic specificity of genetic mutations, the *TP53* mutation spectrum observed in this cohort may not be generalizable to other populations, and further validation is needed. Second, although we collected LFS-related family history for individuals carrying *TP53* mutations, we did not collect such information for all study participants, which may have limited our ability to comprehensively evaluate the association between *TP53* mutations and LFS-associated malignancies. Third, long-term follow-up was not available for all individuals, and the survival data were immature. Previous studies have reported that *TP53* carriers have a high rate of ipsilateral breast tumor recurrence after breast-conserving surgery[18]. Therefore, further prognostic analysis is necessary to estimate the impact of different treatment options on survival in PV carriers and non-carriers, so as to offer optimal management for carriers. Finnally, this study did not include a control group of young individuals who are not affected by

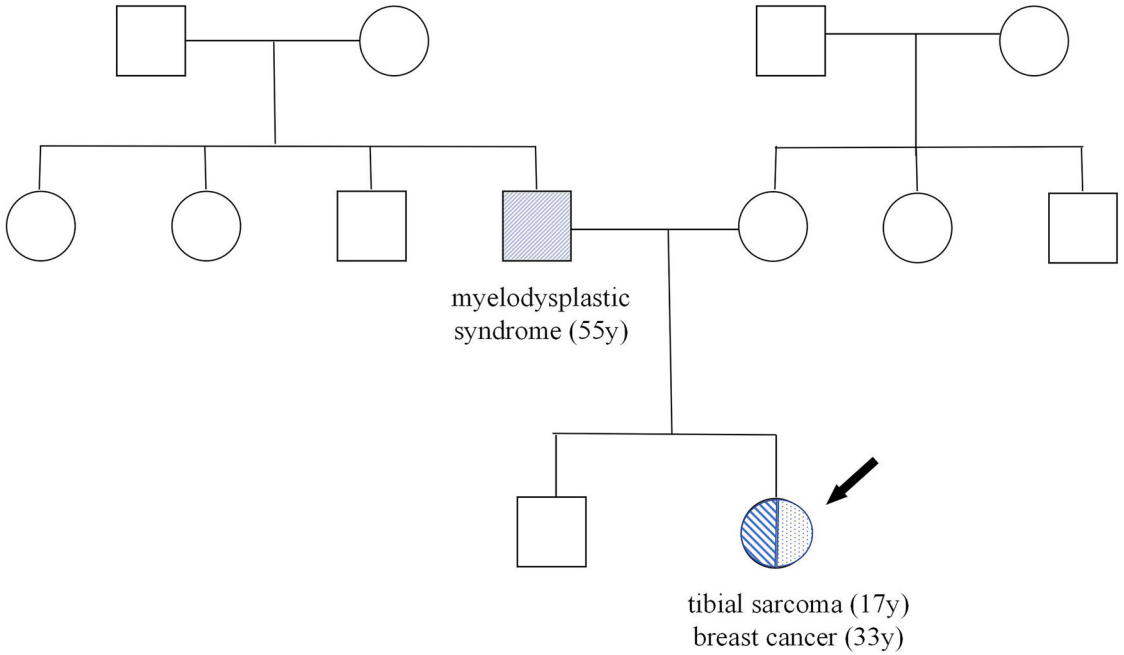

Fig. 1 | Pedigrees of the family with *TP53* c.796 G > A (p.G266R). The proband is marked with an arrow. Individuals with cancer are indicated with filled symbol quadrants. Abbreviations: y, years, age of onset. Written consent was obtained for publication of this pedigrees. (This figure was created using WPS Office software).

Table 4 | Prevalence of *TP53* PVs based on diagnosis age and HER2 status

	HER2-positive			HER2-negative			All		
	total (*n*)	*TP53* carriers (*n*; frequency)		total (*n*)	*TP53* carriers (*n*; frequency)		total (*n*)	*TP53* carriers (*n*; frequency)	
Dx group 1									
≤30	68	3	4.4%	146	1	0.68%	214	4	1.9%
31–35	150	2	1.3%	336	1	0.30%	486	3	0.62%
36–40	194	0	0	598	0	0	692	0	0
Dx group 2									
≤30	68	3	4.4%	146	1	0.68%	214	4	1.9%
≤35	218	5	2.3%	482	2	0.41%	700	7	1.0%
Total	412	5	1.2%	1080	2	0.19%	1492	7	0.47%

Abbreviations: *Dx* age at initial diagnosis of breast caner, *HER2* human epidermal growth factor receptor-2.

breast cancer, limiting our ability to evaluate the risk for the development of early breast cancer in young carriers of *TP53* PVs.

In conclusion, we demonstrated that the prevalence of *TP53* PVs were 0.47% in the largest early-onset breast cancer cohort in China. *TP53* PVs are significantly associated with younger age at diagnosis and HER2-positive status. Multivariate logistic regression results indicated that the prevalence of *TP53* PVs was significantly increased in HER2-positive patients with a diagnosis age of 35 or younger; thus, we emphasized that target *TP53* genetic testing needs to be considered in that population.

Methods

Study population and data collected

In a cohort of women with early-stage breast cancer diagnosed at Fujian Medical University Union Hospital (Fuzhou, China) between 2005 and 2023, patients who met all the following eligibility requirements were screened for the study: (1) diagnosis of breast cancer at age 40 or younger; (2) confirmation of invasive breast cancer by histopathology; and (3) negativity for *BRCA*1 and *BRCA*2 PVs. All the procedures performed in studies involving human participants adhered to the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki and its later amendments or comparable ethical standards.

Demographic data, including age at first diagnosis of breast cancer, sex, personal history of breast cancer and family history of breast cancer and/or ovarian cancer, were obtained by face-to-face questionnaires during their clinic visits. A positive family history of breast and/or ovarian cancer is defined as having one or more first- or second-degree relatives with a history of breast or ovarian cancer. The criteria for LFS and LFL syndrome were determined with reference to the classical LFS criteria and the 2009 and 2015 versions of the Chompret criteria[14,16,34].

Clinical data, including tumor size, lymph node status, histologic type, histologic grade, and immunohistochemical characteristics, were extracted from medical records. Immunohistochemistry (IHC) was used to detect the presence of the estrogen receptor (ER) and progesterone receptor (PR). Nuclear staining in >10% of cells was used as the criterion to define ER-positive (ER +) and PR-positive (PR +) cases. Hormone receptor (HR)-positive cases were defined as ER+ and/or PR+ cases. Immunohistochemical staining with a score of 3+ and/or fluorescence in situ hybridization (FISH) amplification of the human epidermal growth factor receptor-2 (HER2) gene was used to identify HER2-positive (HER2 +) cases.

DNA extraction and NGS

Peripheral blood samples were obtained from patients at the time of breast cancer diagnosis, and whole blood genomic DNA was subsequently isolated. Sequencing of all coding regions and exon-intron boundaries of the *TP53* genes was performed through NGS (Illumina NovaSeq) by Shanghai AITA Genetics Technology Co., Ltd and AmoyDx Biomedical Technology Co., LTD. The sequencing results were then aligned to the *TP53* (NM_000546.5) sequences using the Burrows-Wheeler Aligner (BWA) tool. Base quality score recalibration, indel realignment, and variant calling were performed using the Genome Analysis Toolkit (GATK). All the variants were annotated with ANNOVAR (http://www.openbioinformatics.org/annovar/) and subsequently validated by Sanger sequencing. Novel mutations were identified by excluding variants with a population frequency >0.1% in the gnomAD and ExAC databases and confirming their absence in ClinVar (ncbi.nlm.nih.gov/clinvar/) and the IARC *TP53* database (p53.iarc.fr/). The pathogenicity of mutations was predicted using PolyPhen-2 and SIFT, and variants were classified according to the ClinVar and American College of Medical Genetics and Genomics (ACMG) criteria[35]. Both pathogenic and likely pathogenic mutations were recorded as PVs in this study.

Statistical analysis

The Fisher's exact test for categorical variables and the Mann-Whitney test for continuous variables were performed to compare characteristics between pathogenic mutation carriers and non-carriers. Multivariate logistic regression was used to determine the risk factors for mutation carriers and calculate the odds ratio (OR) and 95% confidence interval (CI). A difference was considered statistically significant if the p-value was <0.05. Statistical analysis was performed with R software (version 4.3.0). WPS Office (version 12.1.0) were used to create the pedigree charts.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Received: 10 February 2024; Accepted: 22 April 2025;
Published online: 02 July 2025

References

1. Guo, R. et al. Changing patterns and survival improvements of young breast cancer in China and SEER database, 1999−2017. *Chin. J. Cancer Res.* **31**, 653–662 (2019).
2. Li, J. et al. Trends in disparities and transitions of treatment in patients with early breast cancer in China and the US, 2011 to 2021. *JAMA Netw. Open* **6**, e2321388 (2023).
3. Franco, I. et al. Genomic characterization of aggressive breast cancer in younger women. *Ann. Surg. Oncol.* https://doi.org/10.1245/s10434-023-14080-4 (2023).
4. Buys, S. S. et al. A study of over 35,000 women with breast cancer tested with a 25-gene panel of hereditary cancer genes. *Cancer* **123**, 1721–1730 (2017).
5. Momozawa, Y. et al. Germline pathogenic variants of 11 breast cancer genes in 7,051 Japanese patients and 11,241 controls. *Nat. Commun.* **9**, 4083 (2018).
6. Breast Cancer Association Consortium et al. Pathology of tumors associated with pathogenic germline variants in 9 breast cancer susceptibility genes. *JAMA Oncol.* **8**, e216744 (2022).
7. Susswein, L. R. et al. Pathogenic and likely pathogenic variant prevalence among the first 10,000 patients referred for next-generation cancer panel testing. *Genet. Med. J. Am. Coll. Med. Genet.* **18**, 823–832 (2016).
8. Easton, D. F. et al. Gene-panel sequencing and the prediction of breast-cancer risk. *N. Engl. J. Med.* **372**, 2243–2257 (2015).
9. Fu, F. et al. Association between 15 known or potential breast cancer susceptibility genes and breast cancer risks in Chinese women. *Cancer Biol. Med.* **19**, 253–262 (2021).
10. Hyder, Z. et al. Risk of contralateral breast cancer in women with and without pathogenic variants in BRCA1, BRCA2, and *TP53* genes in women with very early-onset (<36 Years) Breast Cancer. *Cancers* **12**, 378 (2020).
11. Sheng, S. et al. Prevalence and clinical impact of *TP53* germline mutations in Chinese women with breast cancer. *Int. J. Cancer* **146**, 487–495 (2020).
12. Guo, Y. et al. Risk of ipsilateral breast tumor recurrence and contralateral breast cancer in patients with and without *TP53* variant in a large series of breast cancer patients. *Breast Edinb. Scotl.* **65**, 55–60 (2022).
13. Li, F. P. & Fraumeni, J. F. Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome?. *Ann. Intern. Med.* **71**, 747–752 (1969).
14. Li, F. P. et al. A cancer family syndrome in twenty-four kindreds. *Cancer Res.* **48**, 5358–5362 (1988).
15. Mai, P. L. et al. Risks of first and subsequent cancers among *TP53* mutation carriers in the national cancer institute Li-fraumeni syndrome cohort. *Cancer* **122**, 3673–3681 (2016).
16. Bougeard, G. et al. Revisiting Li-fraumeni syndrome from *TP53* mutation carriers. *J. Clin. Oncol.* **33**, 2345–2352 (2015).
17. Giacomazzi, J. et al. Prevalence of the *TP53* p.R337H mutation in breast cancer patients in Brazil. *PLoS ONE* **9**, e99893 (2014).
18. Rogoża-Janiszewska, E. et al. Prevalence of germline *TP53* variants among early-onset breast cancer patients from Polish population. *Breast Cancer Tokyo Jpn.* **28**, 226–235 (2021).
19. Copson, E. R. et al. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. *Lancet Oncol.* **19**, 169–180 (2018).
20. Couch, F. J. et al. Associations between cancer predisposition testing panel genes and breast cancer. *JAMA Oncol.* **3**, 1190–1196 (2017).
21. Guindalini, R. S. C. et al. Detection of germline variants in Brazilian breast cancer patients using multigene panel testing. *Sci. Rep.* **12**, 4190 (2022).
22. Wasserman, J. D. et al. Prevalence and functional consequence of TP53 mutations in pediatric adrenocortical carcinoma: a children's oncology group study. *J. Clin. Oncol.* **33**, 602–609 (2015).
23. Takahashi, M. et al. Distinct prognostic values of p53 mutations and loss of estrogen receptor and their cumulative effect in primary breast cancers. *Int. J. Cancer* **89**, 92–99 (2000).
24. Lalloo, F. et al. BRCA1, BRCA2 and *TP53* mutations in very early-onset breast cancer with associated risks to relatives. *Eur. J. Cancer* **42**, 1143–1150 (2006).
25. Blondeaux, E. et al. Germline *TP53* pathogenic variants and breast cancer: a narrative review. *Cancer Treat. Rev.* **114**, 102522 (2023).
26. Mouchawar, J. et al. Population-based estimate of the contribution of *TP53* mutations to subgroups of early-onset breast cancer: Australian breast cancer family study. *Cancer Res.* **70**, 4795–4800 (2010).
27. Siraj, A. K. et al. Prevalence of germline *TP53* mutation among early onset middle eastern breast cancer patients. *Hered. Cancer Clin. Pract.* **19**, 49 (2021).
28. Alyami, H. et al. Clinical features of breast cancer in South Korean patients with germline TP53 gene mutations. *J. Breast Cancer* **24**, 175–182 (2021).
29. Schon, K. & Tischkowitz, M. Clinical implications of germline mutations in breast cancer: *TP53*. *Breast Cancer Res. Treat.* **167**, 417–423 (2018).
30. Frebourg, T., Bajalica Lagercrantz, S., Oliveira, C., Magenheim, R. & Evans, D. G. Guidelines for the Li–fraumeni and heritable *TP53*-related cancer syndromes. *Eur. J. Hum. Genet.* **28**, 1379–1386 (2020).
31. Melhem-Bertrandt, A. et al. Early onset HER2 positive breast cancer is associated with germline *TP53* mutations. *Cancer* **118**, 908 (2012).
32. Wilson, J. R. F. et al. A novel HER2-positive breast cancer phenotype arising from germline *TP53* mutations. *J. Med. Genet.* **47**, 771–774 (2010).

33. Rath, M. G. et al. Prevalence of germline *TP53* mutations in HER2+ breast cancer patients. *Breast Cancer Res. Treat.* **139**, 193–198 (2013).
34. Gonzalez, K. D. et al. Beyond Li fraumeni syndrome: clinical characteristics of families with p53 germline mutations. *J. Clin. Oncol. J. Am. Soc. Clin. Oncol.* **27**, 1250–1256 (2009).
35. Richards, S. et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American college of medical genetics and genomics and the association for molecular pathology. *Genet. Med. J. Am. Coll. Med. Genet.* **17**, 405–424 (2015).

Acknowledgements

I would like to express my gratitude to all participants. We thank Prof. Chunfu Zheng for editing our manuscript. This study was supported by the Natural Science Foundation of Fujian Province (2020J01995), and the joint funds for the Innovation of Science and Technology, Fujian Province (2018Y9205, 2019Y9103).

Author contributions

J.L.: data curation, writing of the main manuscript text, collection of the blood samples and clinical information; L.L.C.: planning and design of the study, resources, recruitment of the patients, collection of the blood samples. X.H.C. and M.H.: Data curation. M.Y.C., W.H.G. and Y.X.L.: Recruiting the patients, collection the blood samples. Y.L.W., W.F.C., Y.B.Q., P.H. and Q.D.C.: collection clinical information. F.M.F. and C.W.: planning and design of the study, resources, project administration, recruitment of the patients. All the authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of Fujian Medical University Union Hospital (2020KJT031). Informed consent was obtained from all individual participants.

Patient consent for publication

Consent to publish has been obtained from all participants.

Additional information

Correspondence and requests for materials should be addressed to Chuan Wang or Fangmeng Fu.