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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

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ABSTRACT

Background: The association between breast cancer patients with a *TP53* pathogenic variant and risk of local recurrence and contralateral breast cancer remains largely unknown.

Methods: The study population of 11093 patients was derived from two cohorts at the Breast Center of Peking University Cancer Hospital in China from November 2003, to March 2018. *TP53* germline variants were determined for all patients.

Results: In the study, forty-one (0.37%) carried a *TP53* germline pathogenic variant, and 11052 were non-carriers (99.63%). Nineteen *TP53* carriers (46.3%) and 4173 non-carriers (37.8%) were treated with breast-conserving therapy (BCT), while the remaining were treated with mastectomy. After a median follow-up of 6.7 years, the rate of ipsilateral breast tumor recurrence (IBTR) in *TP53* carriers was significantly higher than that in non-carriers when treated with BCT (21.1% vs 3.8%, $P = 0.006$). No difference in the rate of IBTR was found between *TP53* carriers and non-carriers when treated with mastectomy (0.0% vs 2.6%, $P = 1.0$). Furthermore, the rate of IBTR in *TP53* carriers treated with BCT was significantly higher than that in those treated with mastectomy (21.1% vs 0.0%, $P = 0.038$). The 10-year cumulative risk of contralateral breast cancer in *TP53* carriers was significantly higher than that in non-carriers (17.9% vs 3.6%, hazard ratio (HR) = 7.0, 95% CI: 3.3–14.9, $P < 0.001$).

Conclusions: Patients with *TP53* variants have a high risk of IBTR when treated with BCT, and exhibit a very high risk of contralateral breast cancer. *TP53* carriers may not be suitable for BCT and prophylactic contralateral mastectomy might be considered.

1. Introduction

It is well documented that germline pathogenic variants (referred to as variants hereafter) in the *TP53* gene may lead to an autosomal dominant inherited cancer syndrome known as Li-Fraumeni syndrome (LFS) or Li-Fraumeni-like (LFL) syndrome [1–6], which is characterized by a high risk of developing a broad spectrum of tumors, including soft tissue sarcoma, osteosarcoma, breast cancer, brain tumor, and adrenocortical cancer. Currently, as next-generation sequencing, i.e., multigene panel testing, is routinely used in clinical practice, many *TP53* pathogenic variants outside of LFS or LFL syndrome are being found. We and others reported that the frequency of *TP53* pathogenic variant ranges from 0.2% to 0.5% in large cohorts of unselected breast cancer patients [7–9], and *TP53* pathogenic variant carriers had poorer survival than non-carriers in unselected breast cancer series [7]. Breast-conserving therapy (BCT) is widely applied for operable primary breast cancer. Recent retrospective studies have indicated that BCT is even superior to mastectomy in survival in large series of breast cancer [10–17]. We and others also recently suggested that *BRCA1/2* pathogenic variant carriers treated with BCT have comparable survival to

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those treated with mastectomy with or without radiotherapy [18–20], but BCT might have 2-fold risk of ipsilateral breast tumor recurrence [18]. Therefore, these findings raise a question of whether BCT is associated with an increased risk of ipsilateral breast tumor recurrence in *TP53* variant carriers.

Women with *TP53* pathogenic variants not only face a high risk of developing breast cancer [21,22], but also are at increased risk of second primary breast cancer, particularly in the contralateral breast. A recent study suggested that *TP53* variant carriers exhibits a very high risk of contralateral breast cancer [23]. On the other hand, several studies with a limited sample size reported an increased risk of ipsilateral breast tumor recurrence in *TP53* variant carriers who had a LFS or LFL syndrome [24–26]. Therefore, the risk of ipsilateral breast tumor recurrence and contralateral breast cancer should be taken into consideration when *TP53* variant carriers received a surgical therapy.

In this retrospective study, we analyzed 41 patients with *TP53* pathogenic variant from a large series of 11093 breast cancer patients who underwent either BCT or mastectomy. This cohort of patients were largely unselected for age and family history of cancer, and only few *TP53* variant carriers had a family history of a LFS or LFL syndrome. The aim of this study was to investigate the risk of ipsilateral breast tumor recurrence and the cumulative risk of contralateral breast cancer in *TP53* variant carriers and non-carriers in our cohort.

2. Materials and methods

2.1. Patients

A total of 11873 patients who were treated at the Breast Center, Peking University Cancer Hospital were determined for *TP53* germline variants by next-generation sequencing and/or Sanger sequencing. These patients were derived from two cohorts. The first cohort consisted of 10053 consecutive and unselected breast cancer patients from November 17, 2003, to May 29, 2015, as described in our previous study [7]. The mean age (SD) in the first cohort was 51.1 (11.6) years. *TP53* germline variants in the first cohort of 10053 patients were detected with a 62-gene panel [27] and/or Sanger sequencing. All *TP53* variants detected by 62-gene panel were further validated by a Sanger sequencing, and a substantial number of *TP53* variants were independently validated by an additional 560 cancer-related gene panel or whole exome sequencing in blood and/or tumor samples from these *TP53* carriers (Supplementary Table S1). The pathogenicity of *TP53* variants in the first cohort was revaluated based on the updated criteria. The second cohort was composed of 1820 breast cancer patients from June 1, 2015, to March 19, 2018, and the mean age (SD) in the second cohort was 47.4 (12.3) years. These patients were selected by age at diagnosis or family history of any cancer. Of these 1820 patients, 662 were diagnosed with breast cancer at 30 years or under; 366 were aged over 30 years but less than or equal to 40 years; 792 were patients with a family history of any cancer regardless of the age at diagnosis. *TP53* germline variants of these patients were detected by Sanger sequencing by using primers that cover exon 2 to exon 11 (1454 patients) or exon 5 to exon 7 (366 patients) of the *TP53* gene. Among the 11873 patients, 780 patients were excluded from this study due to the following reasons: patients with stage IV breast cancer at diagnosis; patients without surgery; patients were treated for local recurrence at the first admission; patients with occult breast cancer but no surgery was performed in breast; patients with synchronous bilateral breast cancer but treated with different type of surgery; patients with benign tumor; and patients with a follow-up less than 3 months. Therefore, 11093 breast cancer patients were included in this study (Supplementary Fig. S1). The criteria of LFS or LFL syndrome is described in our previous study [7].

In this retrospective study, the patients and physicians were unaware of the *TP53* gene status when they selected the surgical procedures. When patients underwent BCT, tumor-free margins were required; the margins were detected via quick frozen section diagnosis during the operation. Data on patients' clinicopathological characteristics and treatment were obtained from medical records, and the family history of cancer was obtained from medical records and telephone interviews.

Patients provided blood samples when they were diagnosed with breast cancer at our institute prior to any treatment, and written informed consent was obtained from the patients whose blood samples could be used for research purposes, including genetic testing.

Ipsilateral breast tumor recurrence (IBTR) was defined as the reappearance of breast tumor in the ipsilateral breast or chest wall regardless of whether it was true tumor recurrence or a second primary tumor; contralateral breast cancer was defined as a primary breast cancer that occurred in the contralateral breast at least 3 months after the first breast cancer. The endpoint of this study was the date of ipsilateral breast tumor recurrence, contralateral breast cancer diagnosis, death due to any cause, or date at last follow-up.

2.2. TP53 germline mutation classification

Frameshift or nonsense variants that lead to a truncated protein or splice variants affecting the splicing function were considered pathogenic. Missense variants were classified as pathogenic or likely pathogenic based on the current evidence and criteria from the International Agency for Research in Cancer germline and somatic database (IARC, R20, last updated July 2019) [28], the ClinVar database (http://www.ncbi.nlm.nih.gov/clinvar), the UMD *TP53* database (http://p53.free.fr/Database/p53_database.html), American College of Medical Genetics and Genomics guidelines [29], the ClinGen *TP53* VCEP specifications [30], and literatures. Only variants classified as pathogenic or likely pathogenic were considered pathogenic.

2.3. Statistical analysis

Pearson χ^2 test or Fisher's exact test for qualitative variables and the *t*-test (mean comparisons) for quantitative variables were used to compare the patients' clinicopathological characteristics. The Kaplan–Meier method was used to calculate the cumulative risk of contralateral breast cancer. The log-rank test was used to compare the differences between curves of the groups. The Cox proportional hazards regression model was used for univariable and multivariable analysis, and calculating hazard ratio (HR). $P < 0.05$ (two-tailed) was considered statistically significant. All analyses were performed with SPSS software (version 21, IBM Corp, USA).

3. Results

3.1. Clinicopathological characteristics between TP53 carriers and non-carriers in the entire cohort

In this cohort of 11093 breast cancer patients, 41 patients (0.37%) carried a *TP53* pathogenic variant, while 11052 patients (99.63%) were non-carriers. The rates of *TP53* variant were 0.34% in the first cohort and 0.38% in the second cohort, respectively. The age at diagnosis of breast cancer in *TP53* carriers were significantly younger than that in non-carriers (mean age at diagnosis, 39.9 vs 50.4, $P < 0.001$), and *TP53* carriers were more likely to be estrogen receptor (ER)-negative and HER2-positive tumors than non-carriers (Table 1). There were no differences in other characteristics between *TP53* carriers and non-carriers. This cohort of patients were mainly derived from a series of unselected breast cancer patients (see above methods section). Of these 41 *TP53* carriers, only 4 patients met the criteria for LFS or LFL syndrome, and 12 patients met the Chompret revised criteria [31] (Table 2). In addition, three out of 41 *TP53* carriers had a personal history of other malignancies, including one developed gastric cancer 3 years after breast cancer diagnosis; one developed thyroid cancer and lung cancer (3 years before breast cancer diagnosis and 1 year after breast cancer diagnosis, respectively); and another one developed sarcoma in the chest wall 12

Table 1
Clinicopathologic characteristics of *TP53* carriers and non-carriers in the entire cohort.

Characteristics	No.	*TP53* carriers	Non-carriers	*P* value
		N(%)	N(%)	
Total	11093	41(0.37)	11052 (99.63)	
Follow-up(years)				
Median (range)	6.7 (0.3–18.0)	6.8 (1.7–16.4)	6.7 (0.3–18.0)	
Age at diagnosis(years)				
Mean ± SD	50.4 ± 11.6	39.9 ± 11.9	50.4 ± 11.6	<0.001
Median (range)	49(16–98)	40(20–71)	50(16–98)	
≤30	336	12(29.3)	324(2.9)	<0.001
31–40	1970	9(22.0)	1961(17.7)	
41–50	3589	14(34.1)	3575(32.3)	
>50	5198	6(14.6)	5192(47.0)	
Tumor size				
≤2 cm	4700	17(44.7)	4683(43.5)	0.88
>2 cm	6102	21(55.3)	6081(56.5)	
Unknown	291	3	288	
Tumor histology				
DCIS	890	7(17.1)	883(8.0)	0.09
IDC	8958	29(70.7)	8929(80.8)	
Other	1245	5(12.2)	1240(11.2)	
Tumor grade[a]				
I	946	1(4.0)	945(10.6)	0.41
II	6482	21(84.0)	6461(72.8)	
III	1473	3(12.0)	1470(16.6)	
Unknown	1302	9	1293	
Lymph node status				
Negative	6858	23(59.0)	6835(63.4)	0.57
Positive	3969	16(41.0)	3953(36.6)	
Unknown	266	2	264	
ER status				
Negative	2961	16(41.0)	2945(27.1)	0.050
Positive	7957	23(59.0)	7934(72.9)	
Unknown	175	2	173	
PR status				
Negative	3552	14(35.9)	3538(32.6)	0.66
Positive	7354	25(64.1)	7329(67.4)	
Unknown	187	2	185	
HER2 status				
Negative	7922	22(57.9)	7900(74.8)	0.017
Positive	2681	16(42.1)	2665(25.2)	
Unknown	490	3	487	
Surgery				
BCT	4192	19(46.3)	4173(37.8)	0.26
M	6901	22(53.7)	6879(62.2)	
Adjuvant therapy				
Chemotherapy	2488	12(29.3)	2476(22.4)	0.30
Endocrine therapy	2909	6(14.6)	2903(26.3)	
Chemotherapy and endocrine therapy	4763	18(43.9)	4745(42.9)	
None	933	5(12.2)	928(8.4)	
Radiation therapy				
Yes	5717	26(63.4)	5691(52.2)	0.15
No	5236	15(36.6)	5221(47.8)	
Unknown	140		140	
Family history of breast cancer				
Yes	1294	7(17.1)	1287(11.6)	0.28
No	9799	34(82.9)	9765(88.4)	
Family history of any cancer				
Yes	4256	19(46.3)	4237(38.3)	0.29
No	6837	22(53.7)	6815(61.7)	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; BCT, breast-conserving therapy; M, mastectomy.

[a] Only for invasive breast cancer.

years after radiotherapy. Detailed information on the clinicopathological characteristics of all 41 *TP53* carriers is presented in Table 2. In this study, we found a subset of *TP53* carriers with a variant allele frequency (VAF) less than 35% (Table 2). In order to exclude the possibility of mosaicism or clonal hematopoiesis, 13 of 28 *TP53* carriers initially detected by 62-gene panel (including 8 patients with initial VAF <35%) were further validated by a 560 cancer-related gene panel or whole exome sequencing (WES) in blood and/or tumor samples from these cases, and an independent Sanger sequencing was performed for all the 28 patients who were detected by the initial 62-gene (Supplementary Table S1). We found that the *TP53* variants were presented in the tumor tissues from these *TP53* carriers, thus clonal hematopoiesis could be excluded (Supplementary Table S1). However, a few cases (3 cases) still exhibited a VAF <35% but >20% after these validations, we could not exclude the possibility of mosaic mutation for these cases (Supplementary Table S1).

3.2. The rate of ipsilateral breast tumor recurrence in TP53 carriers and non-carriers

For the 41 *TP53* carriers, 19 patients (46.3%) were treated with BCT, and 22 patients (53.7%) were treated with mastectomy (Table 1). For the 11052 non-carriers, 4173 patients (37.8%) were treated with BCT, and 6879 patients (62.2%) were treated with mastectomy (Table 1). After a median follow-up of 6.7 years, the rate of ipsilateral breast tumor recurrence (IBTR) in *TP53* carriers was significantly higher than that in non-carriers when treated with BCT (21.1% vs 3.8%, odds ratio (OR) = 6.7, 95% CI: 2.2–20.4, $P = 0.006$) (Table 3). No difference in IBTR was found between *TP53* carriers and non-carriers when treated with mastectomy (0.0% vs 2.6%, $P = 1.0$) (Table 3). Among the 41 *TP53* carriers, the rate of IBTR in patients treated with BCT was significantly higher than that in patients treated with mastectomy (21.1% vs 0.0%, $P = 0.038$) (Table 3). When patients were restricted to patients with invasive breast cancer, *TP53* carriers treated with BCT exhibited a significantly higher rate of IBTR compared with non-carriers treated with BCT (22.2% vs 3.8%, OR = 7.2, 95% CI: 2.4–22.2, $P = 0.004$) (Supplementary Table S2).

3.3. The risk of contralateral breast cancer in TP53 carriers and non-carriers

For the 41 *TP53* carriers, 10 (24.4%) developed bilateral breast cancer. Of these 10 patients, 3 (7.3%) were diagnosed with synchronous bilateral breast cancer (bilateral breast cancer was diagnosed simultaneously), and the remaining 7 (17.1%) were diagnosed with asynchronous bilateral breast cancer (contralateral primary breast cancer occurred at least 3 months after the first breast cancer diagnosis). Of these 7 asynchronous bilateral breast cancer patients, the median time from the first breast cancer diagnosis to the development of contralateral breast cancer was 8.1 years (range, 2.9–15.4 years). For the 11052 non-carriers, 151 (1.4%) were diagnosed with synchronous bilateral breast cancer, and 316 (2.9%) were diagnosed with asynchronous bilateral breast cancer. The 10-year cumulative risk of contralateral breast cancer in *TP53* carriers was significantly higher than that in non-carrier (17.9% vs 3.6%, hazard ratio (HR) = 7.0, 95% CI:3.3–14.9, $P < 0.001$) (Fig. 1). *TP53* carriers with early-onset (age ≤30 years) exhibited a higher 10-year cumulative risk of contralateral breast cancer than those with age over 30 years, although the difference did not reach a significance (31.4% vs 8.0%, adjusted HR = 2.9, 95% CI: 0.3–25.9, $P = 0.35$) (Supplementary Table S3). *TP53* carriers with family history of any cancer also had a higher 10-year cumulative risk of contralateral breast cancer than those without family history of any cancer (30.4% vs 4.8%, adjusted HR = 6.7, 95% CI: 0.7–61.3, $P = 0.09$) (Supplementary Table S3). There was no significant difference in risk of contralateral breast cancer whether *TP53* carriers treated with BCT or mastectomy (data not shown).

4. Discussion

In this study, we investigated the rate of ipsilateral breast tumor recurrence (IBTR) and contralateral breast cancer risk in patients with or

Table 2
The detailed information of the 41 breast cancer patients with a *TP53* germline pathogenic variant.

Case ID	*TP53* variant		Variant classification	Variant allele frequency (%)[a]	Age at diagnosis (years)	Tumor histology	Surgery	LFS or LFL syndrome	Chompret criteria (revised version)
	cDNA change	Amino acid change							
12015	c.916_917insAAGC	p.R306fs	pathogenic	21.0	24	IDC	M	No	Yes
10782	c.993+1G > A	p.?	pathogenic	47.0	26	IDC-2	BCT	Yes	Yes
21554	c.673-2A > G	p.?	pathogenic	50.0[b]	31	IDC	M	No	No
2023	c.80C > T	p.P27L	likely pathogenic	34.8	63	IDC	M	No	No
2198	c.107C > T	p.P36L	likely pathogenic	34.3	49	IDC	BCT	No	No
10922	c.234_263del	p.78_88del	likely pathogenic	28.8	47	DCIS	M	No	No
7947	c.234_263del	p.78_88del	likely pathogenic	24.7	47	IDC-2	M	No	No
920	c.375del	p.T125fs	pathogenic	25.8	30	ILC	BCT	No	Yes
8868	c.395A > G	p.K132R	likely pathogenic	24.5	43	IDC-2	M	No	No
6047	c.472C > T	p.R158C	likely pathogenic	39.7	45	IDC	BCT	No	No
9986	c.473G > A	p.R158H	pathogenic	27.2	20	ILC	BCT	No	Yes
3101	c.473G > A	p.R158H	pathogenic	50.0[b]	40	IDC-2	BCT	No	No
5025	c.473G > A	p.R158H	pathogenic	50.0[b]	46	IDC-2	BCT	No	No
5398	c.473G > A	p.R158H	pathogenic	44.4	47	L: IDC-2 R: IDC-2	M	No	No
23456	c.473G > A	p.R158H	pathogenic	50.0[b]	48	IDC-2	M	No	No
14349	c.523C > T	p.R175C	likely pathogenic	41.3	30	IDC-2	M	No	Yes
11767	c.524G > A	p.R175H	pathogenic	50.0[b]	36	IDC-2	BCT	No	No
1809	c.524G > A	p.R175H	pathogenic	20.9	37	IDC-3	BCT	No	No
11055	c.524G > A	p.R175H	pathogenic	32.8	44	IDC-2	BCT	No	No
7514	c.537T > G	p.H179Q	pathogenic	46.8	27	IDC-2	BCT	Yes	Yes
21262	c.536A > G	p.H179R	pathogenic	50.0[b]	27	L:IDC-2 R:DCIS	M	No	Yes
15099	c.541C > T	p.R181C	pathogenic	50.0[b]	55	IDC-2	BCT	No	No
19460	c.541C > T	p.R181C	pathogenic	50.0[b]	38	DCIS	BCT	No	No
22334	c.542G > A	p.R181H	pathogenic	50.0[b]	43	IDC-3	M	No	No
7078	c.542G > A	p.R181H	pathogenic	24.3	56	IDC-2	BCT	No	No
977	c.578A > G	p.H193R	likely pathogenic	32.1	24	IDC	BCT	No	Yes
12886	c.620A > G	p.D207G	likely pathogenic	33.6	55	IDC-2	M	No	No
7136	c.638G > A	p.R213Q	pathogenic	46.8	44	DCIS	M	No	No
5873	c.638G > A	p.R213Q	pathogenic	42.4	50	IDC-2	M	Yes	No
15748	c.701A > G	p.Y234C	pathogenic	49.5	35	L:IDC-2 R:IDC-1	BCT	No	No
21250	c.731G > A	p.G244D	pathogenic	40.0[b]	28	DCIS	M	No	Yes
19700	c.733G > A	p.G245S	pathogenic	50.0[b]	26	NA	BCT	No	Yes
13210	c.733G > A	p.G245S	pathogenic	37.2	47	DCIS	M	No	No
6692	c.742C > T	p.R248W	pathogenic	39.6	33	IDC2-3	BCT	No	No
9771	c.743G > A	p.R248Q	pathogenic	34.3	71	IDC-2	M	No	No
11578	c.752T > C	p.I251T	likely pathogenic	44.4	49	IDC-1	M	No	No
7004	c.818G > A	p.R273H	pathogenic	50.0[b]	22	DCIS	M	Yes	Yes
10342	c.823T > C	p.C275R	likely pathogenic	50.0	32	DCIS	M	No	No
15596	c.997dupC	p.R333fs	pathogenic	31.5	30	NA	BCT	No	Yes
1727	c.1010G > A	p.R337H	pathogenic	50.0[b]	37	IDC	M	No	No
15975	c.1010G > A	p.R337H	pathogenic	41.1	53	Invasive papilla carcinoma	M	No	No

Abbreviations: LFS, Li-Fraumeni syndrome; LFL, Li-Fraumeni like; L, left breast cancer; R, right breast cancer; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; BCT, breast-conserving therapy; M, mastectomy; NA, not available.

[a] Allele frequency of *TP53* variant that was detected with a 62-gene panel testing.

[b] These cases were detected by Sanger sequencing and the approximate ratio of *TP53* variants were presented.

without *TP53* germline pathogenic variants in a large cohort of 11093 breast cancer patients. We found that the rate of IBTR in *TP53* carriers treated with breast conserving therapy (BCT) was significantly higher than that in non-carriers treated with BCT (21.1% vs 3.8%), and the 10-year risk of contralateral breast cancer in *TP53* carriers was significantly higher than that in non-carriers (17.9% vs 3.6%). Furthermore, *TP53* carriers treated with BCT exhibited a higher rate of IBTR than those treated mastectomy (21.1% vs 0.0%), but no differences in the risk of contralateral breast cancer between BCT group and mastectomy group. The cohort of *TP53* variant carriers was largely derived from unselected breast cancer patients, and the patients and physicians were unaware of the *TP53* variant status when the patients were selected to undergo BCT or mastectomy. In addition, of the 41 *TP53* variant carriers, only 4 met the criteria for LFS or LFL syndrome. Therefore, our study may reflect the real-world data of *TP53* variant carriers in unselected breast cancer patients.

BCT is currently widely applied in breast cancer patients worldwide, especially in young women and those with early-stage disease. Recent

Table 3
The rate of ipsilateral breast tumor recurrence for *TP53* carriers and non-carriers according to different type of surgery.

	No.	IBTR N(%)	OR(95%CI)	*P* value
Patients treated with BCT				
TP53 carriers	19	4(21.1)	6.7(2.2–20.4)	0.006
Non-carriers	4173	160(3.8)	1.0(ref)	
Total	4192	164(3.9)		
Patients treated with M				
TP53 carriers	22	0(0.0)	–	1.0
Non-carriers	6879	177(2.6)	–	
Total	6901	177(2.6)		
TP53 carriers				
Treated with BCT	19	4(21.1)	–	0.038
Treated with M	22	0(0.0)	–	
Total	41	4(9.8)		
Non-carriers				
Treated with BCT	4173	160(3.8)	1.5(1.2–1.9)	<0.001
Treated with M	6879	177(2.6)	1.0(ref)	
Total	11052	337(3.0)		

Abbreviations: IBTR, ipsilateral breast tumor recurrence; OR, odds ratio; ref, reference; BCT, breast-conserving therapy; M, mastectomy.

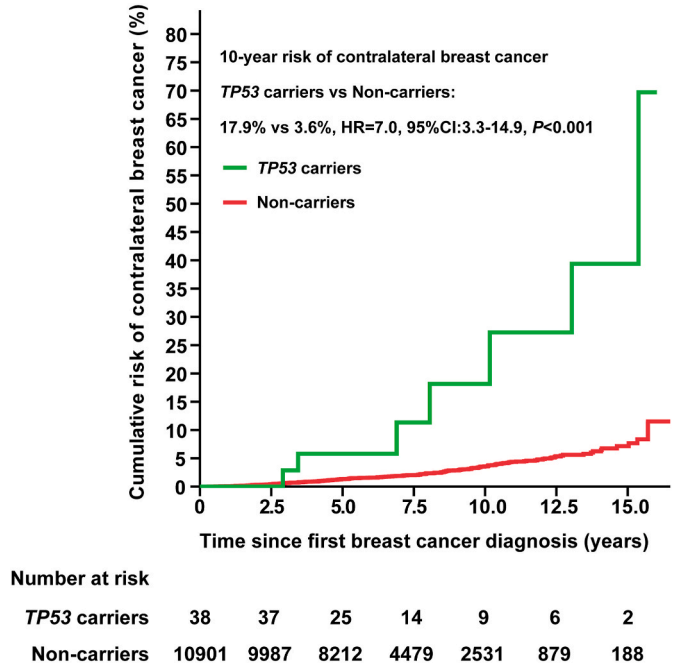

Fig. 1. Cumulative risk of contralateral breast cancer in *TP53* carriers and non-carriers (patients with synchronous bilateral breast cancer were not included).

studies suggested that BCT showed at least equal to or even better survival than mastectomy in large cohorts of breast cancer patients [10–17]. Of the 41 *TP53* carriers, 46.3% received BCT. This is not surprising, as many *TP53* carriers develop breast cancer at a very young age. For *TP53* carriers, the rate of IBTR in BCT group was 21.1% compared to none in the mastectomy group, and all the 4 patients who developed IBTR were occurred in the BCT group. We observed that *TP53* carriers who developed IBTR were more likely to be very young at onset (all ≤30 years) and harbored ER- and PR-negative tumors. Only one of the 4 carriers had LFS or LFL syndrome, and the remaining 3 carriers did not have LFS or LFL syndrome; thus, IBTR might not be mainly due to LFS or LFL syndrome. Overall, we noted that the rate of IBTR in *TP53* carriers treated with BCT was approximately 6.7-fold higher than that in non-carriers treated with BCT. Therefore, a certain of *TP53* carriers with high risk of IBTR may not be suitable for undergoing BCT.

The 10-year cumulative risk of contralateral breast cancer in *TP53* carriers was 17.9% in this study, and the risk of contralateral breast cancer was comparable to that in *BRCA1* (15.5%) and *BRCA2* (17.5%) carriers, as reported in our previous study [32]. We also noted that the 10-year cumulative risk of contralateral breast cancer in *TP53* carriers with very early-onset age (age ≤30 years) was 31.4% in this study. A recent study suggested that 10-year cumulative risk of contralateral breast cancer was 53.1% in *TP53* carriers under the age of 36 years [23]. Therefore, *TP53* carriers with early-onset breast cancer might have a high risk of developing contralateral breast cancer. The risk of contralateral breast cancer was not different regardless of whether BCT or mastectomy was performed. Therefore, when we treated primary breast cancer in *TP53* carriers, prophylactic contralateral breast mastectomy may be taken into consideration.

There are several limitations to this study. First, although we included 41 *TP53* pathogenic variant carriers from a large series of breast cancer patients and the sample size was larger than that of many previous studies when considering the low frequency of the *TP53* germline variant in unselected breast cancer patients, the sample size was not large enough when stratified by different groups. Second, *TP53* germline variants were determined by multi-gene panel and/or Sanger sequencing in this study, and the rearrangements of *TP53* gene cannot be detected. Thus, we may underestimate the rate of *TP53* mutation. Third, we still found a few cases with a VAF <35% but >20%, therefore, we cannot exclude the possibility of mosaic mutation for these cases. As these cases were younger than 45 years at diagnosis, therefore, clonal hematopoiesis is unlikely.

5. Conclusions

We reported that *TP53* carriers treated with BCT have a higher risk of IBTR compared with non-carriers treated with BCT, and *TP53* carriers treated with BCT have a higher risk of IBTR than those treated with mastectomy. Additionally, *TP53* carriers are at a high risk of contralateral breast cancer. Therefore, our study indicates that mastectomy rather than BCT may be more suitable for *TP53* variant carriers, and prophylactic contralateral mastectomy may also be taken into consideration when managing the primary breast cancer in *TP53* variant carriers.

Ethical approval

This study was conducted in accordance with the ethics principles of the Declaration of Helsinki and was approved by the Ethics Committee of Peking University Cancer Hospital (Approval number: 2011KT12).

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Declaration of competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2022.07.002.

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