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\%, \( P = 0.0038 \)). 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...
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 reevaluated based on the updated criteria. The second cohort was composed of 1820 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 47.4 (12.3) years. These patients were selected by age at diagnosis or 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 χ² 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
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 | cDNA change | Variant allele frequency (%)b | Age at diagnosis (years) | Tumor histology | Surgery | LFS or LFL syndrome | Chompret criteria |
|---------|--------------|-------------|-----------------------------|------------------------|----------------|---------|---------------------|------------------|
| 12015   | c.916_917insAAGC | p.R306fsx  | pathogenic                  | 21.0                   | 24              | IDC-2   | M                   | No               |
| 10782   | c.993+1G > A    | p.?         | pathogenic                  | 47.0                   | 26              | IDC-2   | BCT                 | Yes              |
| 21554   | c.673-2A > G    | p.?         | pathogenic                  | 50.0c                  | 31              | IDC     | M                   | No               |
| 2023    | c.80C > T       | p.P27L      | likely                      | 34.8                   | 63              | IDC     | M                   | No               |
| 2198    | c.107C > T      | p.P36L      | pathogenic                  | 34.3                   | 49              | IDC     | BCT                 | No               |
| 10922   | c.234_263del    | p.78_84del  | pathogenic                  | 26.0                   | 39              | IDC     | M                   | No               |
| 24210   | c.234_263del    | p.78_84del  | likely                      | 24.7                   | 47              | IDC-2   | M                   | No               |
| 6047    | c.472C > T      | p.R158C     | pathogenic                  | 24.0                   | 45              | IDC     | BCT                 | No               |
| 9986    | c.473G > A      | p.R158H     | pathogenic                  | 52.0                   | 20              | IDC     | M                   | No               |
| 3101    | c.473G > A      | p.R158H     | pathogenic                  | 50.0                   | 40              | IDC-2   | BCT                 | No               |
| 5025    | c.473G > A      | p.R158H     | pathogenic                  | 50.0                   | 46              | IDC     | M                   | No               |
| 5398    | c.473G > A      | p.R158H     | pathogenic                  | 44.4                   | 47              | IDC-2   | M                   | No               |
| 23456   | c.473G > A      | p.R158H     | pathogenic                  | 48.0                   | 48              | IDC-2   | M                   | No               |
| 14439   | c.523C > T      | p.R175C     | likely                      | 41.3                   | 30              | IDC     | M                   | No               |
| 11767   | c.524G > A      | p.R175H     | pathogenic                  | 50.0                   | 36              | IDC-2   | BCT                 | No               |
| 1809    | c.524G > A      | p.R175H     | pathogenic                  | 52.0                   | 37              | IDC-2   | BCT                 | No               |
| 11055   | c.524G > A      | p.R175H     | pathogenic                  | 32.8                   | 44              | IDC-2   | BCT                 | No               |
| 7514    | c.537T > G      | p.H179Q     | pathogenic                  | 46.8                   | 27              | IDC     | BCT                 | Yes              |
| 21262   | c.536A > G      | p.H179R     | pathogenic                  | 50.0                   | 27              | L:IDC-2 | M                   | No               |
| 15099   | c.541T > A      | p.R181C     | pathogenic                  | 50.0                   | 55              | IDC     | BCT                 | No               |
| 19460   | c.541T > A      | p.R181C     | pathogenic                  | 50.0                   | 38              | DCIS    | BCT                 | No               |
| 22334   | c.542G > A      | p.R181H     | pathogenic                  | 50.0                   | 43              | IDC-3   | M                   | No               |
| 7078    | c.542G > A      | p.R181H     | pathogenic                  | 32.0                   | 56              | IDC     | BCT                 | No               |
| 977     | c.578A > G      | p.H199R     | likely                      | 32.1                   | 24              | IDC     | BCT                 | No               |
| 12886   | c.619A > G      | p.E207G     | pathogenic                  | 33.6                   | 55              | IDC-2   | M                   | No               |
| 7136    | c.638G > A      | p.R213Q     | pathogenic                  | 46.8                   | 44              | DCIS    | M                   | No               |
| 15748   | c.701A > G      | p.T234C     | pathogenic                  | 49.5                   | 50              | IDC-2   | M                   | Yes              |
| 21250   | c.713G > A      | p.R244D     | pathogenic                  | 40.0                   | 28              | DCIS    | M                   | No               |
| 19700   | c.733G > A      | p.G245S     | pathogenic                  | 50.0                   | 26              | NA      | BCT                 | No               |
| 12210   | c.733G > A      | p.G245S     | pathogenic                  | 37.2                   | 47              | DCIS    | M                   | No               |
| 6697    | c.742C > T      | p.R248W     | pathogenic                  | 39.6                   | 33              | L:IDC-2 | M                   | No               |
| 6209    | c.742C > T      | p.R248W     | likely                      | 34.3                   | 71              | IDC     | M                   | No               |
| 11578   | c.752T > C      | p.T251T     | likely                      | 44.4                   | 49              | IDC-1   | M                   | No               |
| 7004    | c.818G > A      | p.R273H     | pathogenic                  | 50.0                   | 22              | DCIS    | M                   | Yes              |
| 10342   | c.823T > C      | p.G275R     | likely                      | 50.0                   | 32              | DCIS    | M                   | No               |
| 15596   | c.997dupC       | p.R336fs    | pathogenic                  | 31.5                   | 30              | NA      | BCT                 | No               |
| 1727    | c.1010G > A     | p.R337H     | pathogenic                  | 50.0                   | 37              | IDC     | M                   | No               |
| 15975   | c.1010G > A     | p.R337H     | pathogenic                  | 41.1                   | 53              | IDC     | M                   | 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; L:IDC, invasive lobular carcinoma; BCT, breast-conserving therapy; M, mastectomy; NA, not available.

b 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 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
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Carriers who developed IBTR were more likely to be very young at onset sur-
prising, as many [10] reference; BCT, breast-conserving therapy; M, mastectomy.

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

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

| Patients treated with BCT | No. | IBTR N(%) | OR(95%CI) | P value |
|---------------------------|-----|-----------|------------|---------|
| 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)|            |         |

Fig. 1. Cumulative risk of contralateral breast cancer (%)

Number at risk

TP53 carriers 38 37 25 14 9 6 2
Non-carriers 10901 9987 8212 4479 2531 879 188

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 in TP53 carriers 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.

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.

References

[1] Li FP, Fraumeni Jr JE. Soft tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? Ann Intern Med 1969;71:747–52. https://doi.org/10.7326/ 0003-4819-71-4-747.

[2] Li FP, Fraumeni Jr JE, Mulvihill JJ, Blatter MA, Dreyfus MG, Tucker MA, et al. A cancer family syndrome in twenty-four kindreds. Cancer Res 1988;48:5358–62.

[3] Malkin D, Li FP, Strong LC, Fraumeni Jr JE, Nelson CE, Kim DH, et al. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 1990;250:1233–8. https://doi.org/10.1126/science.197857.

[4] Srivastava S, Zou ZQ, Pirillo W, Blatter M, Chang EH. Germ-line transmission of a mutated p53 gene in a cancer-prone family with Li-Fraumeni syndrome. Nature 1990;348:747–9. https://doi.org/10.1038/348747a0.

[5] Birch JM, Hartley AL, Tricker KJ, Prosser J, Condie A, Kelsey AM, et al. Prevalence and diversity of constitutional mutations in the p53 gene among 21 Li-Fraumeni families. Cancer Res 1994;54:1298-304.

[6] Eeles RA. Germline mutations in the TP53 gene. Cancer Surv 1995;25:101–24.

[7] Sheng S, Xu Y, Guo Y, Yao L, Hu L, Ouyang T, et al. Prevalence and clinical impact of TP53 germline mutations in Chinese women with breast cancer. Int J Cancer 2020;146:487–95. https://doi.org/10.1002/ijc.32424.

[8] Momozawa Y, Iwasaki Y, Parsons MT, Kamatani Y, Takahashi A, Tamura C, et al. Germline pathogenic variants of 11 breast cancer genes in 7,051 Japanese patients and 11,241 controls. Nat Commun 2018;9:4083. https://doi.org/10.1038/s41467-018-06581-8.

[9] Wrubel E, Natwick R, Wright GP. Breast-conserving therapy is associated with improved survival compared with mastectomy for early-stage breast cancer: a propensity score matched comparison using the national cancer database. Ann Surg Oncol 2021;28:914–9. https://doi.org/10.1245/s10434-020-08829-4.

[10] Wang Q, Su L, Ouyang T, Li J, Wang T, Fan Z, et al. Comparison of survival after breast-conserving therapy vs mastectomy among patients with or without the BRCA1/2 variant in a large series of unselected Chinese patients with breast cancer. JAMA Netw Open 2021;4:e216259. https://doi.org/10.1001/jama networkopen.2021.6299.

[11] Hong L, Tang J, Wang Y, Song H, Li Y, Lin X, et al. BRCA1 and BRCA2 mutation carriers with operable breast cancer: comparison of breast conservation and mastectomy. Breast Cancer Res Treat 2010;121:389–98. https://doi.org/10.1007/s10549-010-0894-z.

[12] van den Broek AJ, Schmidt MK, van ’t Veer LJ, Oldenburg HSA, Rutgers EJ, Russell NS, et al. Prognostic impact of breast-conserving therapy versus mastectomy of BRCA1/2 mutation carriers compared with noncarriers in a consecutive series of young breast cancer patients. Ann Surg 2019;270:364-72. https://doi.org/10.1097/SLA.0000000000002804.

[13] May PL, Best AF, Peters JA, DeCastro RM, Khincha PP, Loud JT, et al. Effects of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. Cancer Am Cancer Soc 2016;122:3673–81. https://doi.org/10.1002/cncr.30248.

[14] Fu F, Zhang D, Hu L, Sundaram S, Ying D, Zhang Y, et al. Association between 15 known or potential breast cancer susceptibility genes and breast cancer risks in Chinese women. Cancer Biol Med 2021. https://doi.org/10.20982/jissn.2095-3941.2021.0338.

[15] Hyder Z, Harkness EF, Woodward ER, Bowers NL, Pereira M, Wallace AJ, 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 2020;12. https://doi.org/10.3390/cancers12020378.

[16] Heymann S, Delaloge S, Rahal A, Caron O, Frebourg T, Barreau L, et al. Radio-induced malignancies after breast cancer postoperative radiotherapy in patients with Li-Fraumeni syndrome. Radiat Oncol 2010;5:104. https://doi.org/10.1186/1748-717X-5-104.

[17] Alyami H, Yoo TK, Cheun JH, Lee HB, Jung SM, Ryu JM, et al. Clinical features of breast cancer in South Korean patients with germline TP53 gene mutations. J Breast Cancer 2021;24:175–82. https://doi.org/10.4048/jbc.2021.24.e16.

[18] Rippinger N, Fischer C, Sinn HP, Dikow N, Sutter C, Rhiem K, et al. Breast cancer characteristics and surgery among women with Li-Fraumeni syndrome in Germany-A retrospective cohort study. Cancer Med 2021;10:7747–58. https://doi.org/10.1002/cam4.4300.

[19] Sun J, Meng H, Yao L, Lv M, Bai J, Zhang J, et al. Germline mutations in breast cancer susceptibility genes in a large series of unselected breast cancer patients. Clin Cancer Res 2017;23:6113–9. https://doi.org/10.1158/1078-0432.CCR-16-3227.

[20] Bouaoun L, Sonkin D, Ardin M, Hollstein M, Byrnes G, Zavadil J, et al. TP53 variations in human cancers: new lessons from the IARC TP53 database and Genomics data. Hum Mutat 2016;37:865–76. https://doi.org/10.1002/humu.23055.

[21] Richards S, Aziz N, Bale S, Bick D, Sast, Gastier-Foster J, 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 2015;17:405–24. https://doi.org/10.1038/gim.2015.30.

[22] Fortuno C, Lee K, Olivier M, Pesanan T, Mai PL, de Andrade KC, et al. Specifications of the ACMG/AMP variant interpretation guidelines for germline TP53 variants. Hum Mutat 2021;42:223–36. https://doi.org/10.1002/humu.24152.

[23] Bouguerd G, Renaux-Petel M, Flaman JM, Charbonnier C, Ferrmy P, Belotti M, et al. Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. J Clin Oncol : Off J Am Soc Clin Oncol 2015;33:2345–52. https://doi.org/10.1200/JCO.2014.39.5728.

[24] Su L, Xu Y, Ouyang T, Li J, Wang T, Fan Z, et al. Contralateral breast cancer risk in BRCA1 and BRCA2 mutation carriers in a large cohort of unselected Chinese breast cancer patients. Int J Cancer 2020;146:3335–42. https://doi.org/10.1002/ijc.32918.