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EPIDEMIOLOGY

Risk of ipsilateral breast tumor recurrence in primary invasive breast cancer following breast-conserving surgery with *BRCA1* and *BRCA2* mutation in China

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Abstract

Purpose *BRCA1/2* germline mutations are associated with a high risk of breast cancer, which may preclude mutation carriers from breast-conserving surgery (BCS). This study retrospectively examined whether mutation status influenced the rate of ipsilateral breast tumor recurrence (IBTR) after BCS in Chinese women.

Methods Patients who underwent BCS were enrolled in carriers group and non-carriers group according to their *BRCA1/2* mutation status in the study. The correlations were analyzed between IBTR incidence and *BRCA1/2* mutation. The IBTR cases were further separated into new primary tumor (NP) and true local recurrences (TR). The risk factors of NP were studied in multivariate analysis.

Results 1947 consecutive Chinese women with primary invasive breast cancer were selected. 103 patients were identified as *BRCA1/2* mutation carriers and 1844 were non-carriers. *BRCA1/2* mutation carriers were younger ($P < 0.001$) with more often negative HER-2 expression ($P = 0.01$) and tumor size over 2 cm ($P = 0.04$) than non-carriers. The median follow-up for all patients was 80 months. The rate of IBTR was 3.9% in mutated carriers and 2.0% in non-carriers, respectively ($P = 0.16$). In IBTR cases, NP incidence was 3.9% in carrier group and 0.6% in non-carrier group, respectively ($P < 0.01$). After adjustment of all clinical-pathological factors, *BRCA1/2* mutation was the only statistical risk factor of NP incidence (HR = 6.29, $P = 0.002$), while positive lymph node was nearly statistically significant (HR = 2.70, $P = 0.06$).

Conclusions BCS may be a rational option for Chinese *BRCA1/2* mutation carriers. High NP incidence in mutation carriers should be paid close attention in the future.

Keywords Breast cancer · Breast-conserving surgery · *BRCA1/2* mutation · Ipsilateral breast tumor recurrence

Introduction

Breast cancer has been the commonest malignant tumor in Chinese women during the last two decades. Cases in China account for 12.2% of all newly diagnosed breast cancers and 9.6% of all deaths from breast cancer worldwide [1].

BRCA1 and *BRCA2* are two of the major breast cancer susceptibility genes, which play important roles in DNA repair, cell cycle checkpoint control, transcriptional regulation, and ubiquitination [2–4]. It is well established that Caucasian women who carry a pathogenic *BRCA1* or *BRCA2* mutation may have a 57–65% or 45–49% risk for the development of breast cancer by age of 70 years [5, 6]. In previous study, we have reported 3.9% incidence in *BRCA1/2* mutation in a cohort of 5931 unselected Chinese women with breast cancer and 16.9% incidence in familial breast cancers in the same cohort [7].

Breast-conserving surgery (BCS) plus radiation therapy has been a routine treatment for early-stage breast cancer with equal survival to that of mastectomy in early-stage breast cancer [8–12]. But BCS on breast cancer with *BRCA* mutation is still controversial due to the anxiety on local recurrence as higher risk detected on contralateral breast cancer (CBC) [14]. A series of clinical studies and meta-analysis had focused on this topic in the White races [13–18]. But there is no similar report on this issue in China.

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In this study, we enrolled appropriate patients from *BRCA1/2* germline screening database of our center. Then we investigated the relationship between the risk of ipsilateral breast tumor recurrence (IBTR) and the clinicopathological characteristics of the patients including *BRCA1/2* mutation status.

Materials and methods

Patients and treatment

Eight thousand and eighty-five consecutive Chinese women with primary invasive breast cancer who were treated in the breast cancer center, Peking university cancer hospital from November 2001 to April 2017 were screened for *BRCA1/2* germline mutation. From the cohort, 1947 patients who underwent BCS were selected for this study. Axillary lymph node dissection was avoided in the population with negative sentinel lymph node (SLN) and part of positive SLN patients if they matched the character of ACOSOG Z0011 trial [19]. All patients received radiotherapy but 14 elders (including one at 63, three at 69, and ten over 70). Simultaneous bilateral breast cancers were excluded from this cohort.

BRCA1/2 mutation testing

Screening of *BRCA1/2* mutation was performed through analysis of genomic DNA extracted from patients' peripheral blood. The coding regions and exon/intron boundaries of *BRCA1/2* genes were amplified by PCR. Then the fragments were purified and sequenced on an ABI 3730 automated sequencer (Applied Biosystems, USA). The method of *BRCA1/2* mutations screening was described in our previous study [20]. All deleterious mutations were confirmed by Sanger sequencing in duplicate. Pathogenic mutation was defined as those mutations which lead to a truncated protein or which have been reported previously as disease-associated.

Follow-up

In this study, IBTR of the 1947 patients was defined as the period from BCS to the reemergence of tumor in the previously treated breast or last follow-up. It was classified as either new primary tumors (NP) or true local recurrences (TR). Patients were defined as NP if the recurrence was distinctly different from the primary tumor with respect to the immunohistochemical subtype or the recurrence location was in a different quadrant. TR was considered to be the relapses with the same location and immunohistochemical subtype simultaneously [21]. The cut-off date of follow-up was September 30, 2018. Breast cancer-related events in this study were defined as IBTR or death. Other events were recorded but not further analyzed including regional recurrence, CBC, and metastasis. Loss to follow-up was defined as event-free patients out of touch for more than 1.5 years whose follow-up period was over 5 years, or out of touch for more than 1 year whose follow-up period was within 5 years.

Statistical analysis

All statistical analysis was conducted by using SPSS 22.0. A two-tailed $P < 0.05$ indicated statistical significance. Continuous variable was described as mean ± standard deviation, and categorical variable was described in terms of percentages. The frequency tables were analyzed using the chi-squared test. Bonferroni correction was used for multiple comparison if necessary.

The endpoint was the incidence of IBTR (including NP and TR). Patient without recurrence was censored at the last follow-up. The univariate Kaplan–Meier method with log-rank estimates was conducted to produce survival curves and compare survival outcomes among different conditions of patient. Cox proportional hazards model was used to obtain the hazard ratio (HR) for each clinicopathological variables. Independent prognostic factors were selected with a backward stepwise selection procedure.

Result

BRCA1/2 mutation prevalence and clinical-pathological characteristics

One hundred and three pathogenic *BRCA1/2* germline mutation carriers were identified, including 31 in *BRCA1* and 72 in *BRCA2*. Other 1844 patients were defined as non-carriers. The prevalence of *BRCA1* or *BRCA2* mutation in this cohort was 1.6% and 3.7%, respectively.

Table 1 shows the clinicopathological characteristics according to the *BRCA1/2* status in the two groups: carrier group was significantly younger than non-carrier group in mean age. (44.8 vs 49.6, $P < 0.001$) 15 carriers (14.6%) and 165 non-carriers (8.9%) were diagnosed as breast cancer before 35-year old. Tumor size over 2 cm was more frequent in carrier group than non-carrier group (56.3% versus 43.7%, $P = 0.036$). Human epidermal growth factor receptor-2 (HER2) positive was more often in non-carrier group than that in carrier group (15.6% versus 4.9%, $P = 0.012$). There was no statistical significance in pathological type, estrogen receptor (ER) status, and axillary lymph node status between the two groups.

Table 1 Clinicopathological characteristics according to *BRCA1/2* status

Clinicopathological characteristics	Carriers		Non-carriers		*P* value
	n = 103	%	*n* = 1844	%	
Age at diagnosis (year)	21–71		21–87		0.00
Mean	44.8		49.6		
Median	45		48		
Age distribution					
≤ 35	15	14.6	165	8.9	
36–45	41	39.8	561	30.4	
46–55	36	35.0	619	33.6	
> 55	11	10.7	499	27.1	
Tumor size (cm)					0.04
≤ 2	41	39.8	972	52.7	
> 2	58	56.3	805	43.7	
Unknown	4	3.9	67	3.6	
Pathological type					0.44
IDC	88	85.4	1644	89.2	
ILC	5	4.9	56	3.0	
Other	10	9.7	144	7.8	
HR status					0.71
Positive	77	74.8	1442	78.2	
Negative	25	24.3	387	21.0	
Unknown	1	1.0	15	0.8	
HER2 status					0.01
Positive	5	4.9	288	15.6	
Negative	89	86.4	1402	76.0	
Unknown	9	8.7	154	8.4	
Lymph node status					0.83
Positive	39	37.9	674	36.6	
Negative	64	62.1	1170	63.4	

ER estrogen receptor, *HER2* human epidermal growth factor receptor-2, *IDC* invasive ductal cancer, *ILC* invasive lobular cancer

Survival estimates

The median follow-up for all patients was 80 months (range 1–192) with 5.0% lost to follow-up. There was no significant difference in IBTR (containing NP and TR) between the two groups (Fig. 1). But remarkably we found the NP incidence in carriers and non-carriers was 3.9% and 0.6%, respectively ($P = 0.001$). All events detected in follow-up are shown in Table 2.

The risk factor of NP

The risk of NP incidence was estimated for patient subgroups defined by clinical-pathological characteristics. The univariate and multivariate HRs associated with each of the factors are presented in Table 3. The risk was much higher for *BRCA1/2* mutation carriers than non-carriers

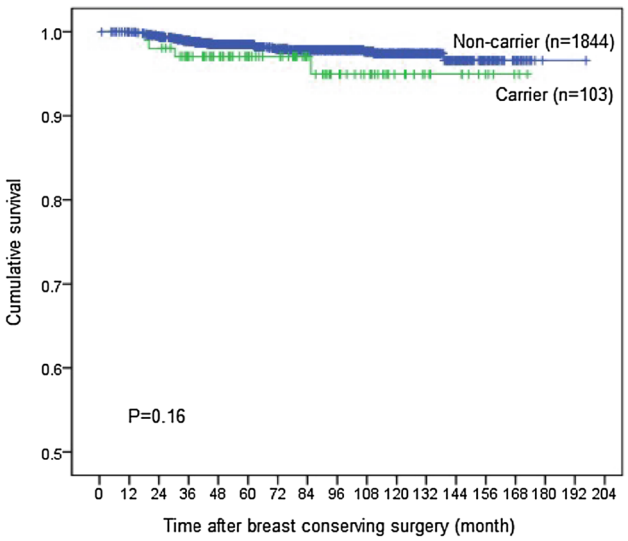

Fig. 1 Ipsilateral breast tumor recurrence-free survival after breast-conserving surgery estimated by *BRCA1/2* mutation status in univariate analysis

Table 2 Breast cancer-related events in *BRCA1/2* mutation carriers and non-carriers

Event	Carriers (*n* = 103)		Non-carriers (*n* = 1844)		P value
	N	%	*N*	%	
IBTR[a]	4	3.9	36	2.0	0.16
TR	0	0.0	22	1.2	0.63
NP	4	3.9	11	0.6	0.01
CBC	4	3.9	14	0.8	0.01
RR	2	1.9	25	1.4	0.65
Meta	9	8.7	100	5.4	0.18

IBTR ipsilateral breast tumor recurrence, *TR* true local recurrence, *NP* new primary tumor, *CBC* contralateral breast cancer, *RR* regional recurrence, *Meta* distant metastasis

[a]Three IBTR in non-carrier group emerged at the same location but IHC test was not performed

(HR = 6.39, $P = 0.001$). No other factors modified the risk significantly, but there was a borderline-significant increase in the risk of NP associated with lymph node positive (HR = 2.70, $P = 0.06$). After adjustment of all factors in univariate analysis, *BRCA1/2* mutation was still the only statistical risk factor of NP incidence (HR = 6.29, $P = 0.002$). Figure 2 shows the rate of NP according to the *BRCA1/2* mutation status.

Table 3 Risk of new primary tumors associated with patient characteristics

Factors	Univariate			Multivariate		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Age				ns		
≤35	1.0	–	–			
>35	1.37	0.18–10.43	0.76			
Tumor size (cm)				ns		
≤2	1.0	–	–			
>2	1.29	0.45–3.68	0.64			
Unknown	1.72	0.21–14.05	0.61			
Pathological type				ns		
IDC	1.0	–	–			
ILC	1.65	0.22–12.57	0.63			
Other	–	–	0.98			
HR status						
Negative	1.0	–	–	1.0	–	–
Positive	1.00	0.28–3.57	0.99	0.94	0.26–3.39	0.93
Unknown	6.98	0.73–67.25	0.09	6.91	0.72–66.67	0.10
HER2 status				ns		
Negative	1.0	–	–			
Positive	0.88	0.11–6.92	0.91			
Unknown	2.19	0.69–6.99	0.19			
Lymph node status						
Negative	1.0	–	–	1.0	–	–
Positive	2.70	0.96–7.59	0.06	2.70	0.96–7.62	0.06
BRCA1/2 status						
Non-carrier	1.0	–	–	1.0	–	–
Carrier	6.39	2.04–20.08	0.001	6.29	2.00–20.00	0.002

NP new primary tumor, *IDC* invasive ductal cancer, *ILC* invasive lobular cancer, *HR* hormone receptor, *HER2* human epidermal growth factor receptor-2, *ns* not significant

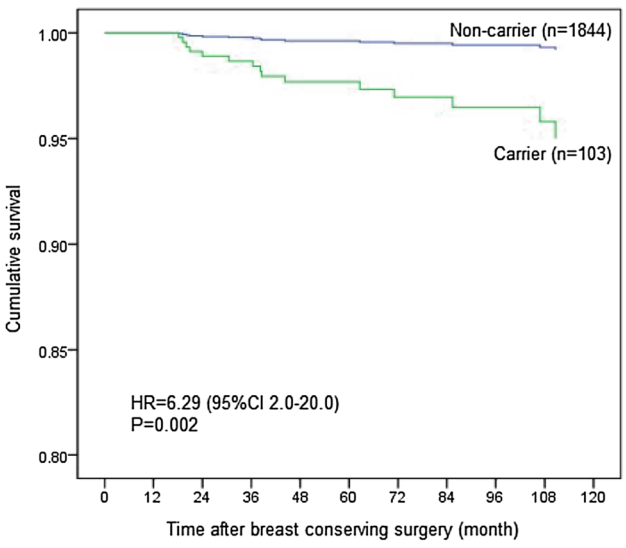

Fig. 2 New primary tumor-free survival after breast-conserving surgery estimated by *BRCA1/2* mutation status in multivariate analysis

Discussion

In this retrospective study, we enrolled 1947 consecutive breast cancer patients who had confirmed their *BRCA1/2* mutation status and undergone BCS from our *BRCA1/2* mutation screening database, in which 8085 unselected Chinese women with breast cancer were contained. To our knowledge, this is the largest *BRCA1/2* germline mutation database in China to date. The prevalence of *BRCA1/2* mutation in this cohort was only 5.3% (103/1947) that was equal to the incidence of overall database (5.3%, not reported in publications). There may exist a different genetic mechanism in Chinese breast cancer occurrence compared with Western patients.

After 80 mouths of follow-up, a total of 194 events occurred in 156 patients. The incidence of NP was significantly higher in carrier group than non-carrier group. But the same result was detected neither in IBTR nor TR. However, the incidence rate is much lower than the finding of meta-analysis implement by Valachis and colleagues, in which ten studies (6 cohort and 4 case–control)

investigated the risk for IBTR after BCS in *BRCA* mutation carriers and non-carriers [17]. The pooled rate of IBTR was 17.3% in 526 *BRCA* mutations and 11% in 2320 controls (RR 1.45, 95% CI 0.98–2.14, $P = 0.07$). No significant difference was found between the two groups. Only two of the ten studies separated their IBTR into NP and TR. The authors found no significant increase in TR but a trend for higher NP in *BRCA* mutation carriers compared with non-carriers. This trend may lead to the increased rate of IBTR in *BRCA* mutation carriers versus non-carriers when the follow-up period was over 7 years in 5 studies, 1634 patients (23.7% vs. 15.9%. RR 1.51, 95% CI 1.15–1.98, $P < 0.003$). In a relatively recent study, Nilsson and colleagues [22] reported 45 *BRCA1/2* mutation breast cancers who underwent BCS. 11 cases (24.4%) identified IBTR at a mean time of 7.6 years after breast cancer diagnosis.

The increased risk of contralateral breast cancer associated with *BRCA1/2* mutation was found in the majority of published studies [23–29]. We also found 3.9% CBC incidence in mutation carriers and 0.8% in non-carriers, respectively ($P = 0.013$). The date of CBC incidence in this study will be analyzed combined with mastectomy patients in our *BRCA1/2* mutation database and reported in later article.

In another study, we had reported that the cumulative breast cancer risk of *BRCA1* and *BRCA2* mutation carriers by age 70 years was 37.9% and 36.5% for Chinese women [30], respectively. It was dramatically higher (approximately tenfold) than that in general population in Chinese women. These findings are in agreement with those of previous studies in Korean, Ashkenazi Jews, and other ethnic groups [1, 5, 6, 31–36]. But the mean age of Chinese patients diagnosed with breast cancer in this study was younger than Western patients, even in the subgroup of *BRCA1/2* mutation carriers [5, 6]. So we defined 35 years as the upper limit of young breast cancer and put this factor into multivariate analysis. However, the result indicated that age is not risk factor for NP, TR, or CBC (TR and CBC were not listed in result), which is different from the previous studies [26, 27].

Some studies had reported that the IBTR in *BRCA* mutation carriers after BCS was significantly higher than that of non-carriers [22, 37]. But in our study, the IBTR incidence rate was only 3.9% for *BRCA1/2* mutation carriers with breast cancers in Chinese women. No significant difference was found between the incidence of *BRCA1/2* mutation carriers and non-carriers. According to our data, BCS may be a reasonable choice for *BRCA1/2* mutation carriers, especially considering the fact that BCS is becoming increasingly acceptable by Chinese women.

In summary, this study suggests that the rate of NP incidence after BCS for *BRCA1/2* mutation carriers in Chinese women is significantly higher than non-carriers. But the rate of IBTR has no statistical significance between the two groups. BCS is a rational option for Chinese *BRCA1/2* mutation carriers according to the analysis in this study.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent A broad informed consent was obtained from all individual participants included in the study. But due to the retrospective nature of the study, specified informed consent was waived.

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