Comparison of Survival After Breast-Conserving Therapy vs Mastectomy Among Patients With or Without the \textit{BRCA1/2} Variant in a Large Series of Unselected Chinese Patients With Breast Cancer

Qiting Wan, MD; Liming Su, MD; Tao Ouyang, MD; Jinfeng Li, MD; Tianfeng Wang, MD; Zhaoping Fan, MD; Tie Fan, MD; Benyao Lin, MD; Yuntao Xie, MD, PhD

Abstract

**IMPORTANCE** Whether patients with breast cancer who carry a \textit{BRCA1/2} variant can safely undergo breast-conserving therapy (BCT) remains controversial.

**OBJECTIVE** To compare survival rates after BCT vs mastectomy in \textit{BRCA1/2} variant carriers and noncarriers in a large series of unselected patients with breast cancer.

**DESIGN, SETTING, AND PARTICIPANTS** In this cohort study, a large consecutive series of 8396 unselected patients with primary breast cancer underwent either BCT, mastectomy with radiotherapy, or mastectomy alone from October 1, 2003, to May 31, 2015, at the Breast Center of Peking University Cancer Hospital in China. All patients were assessed for \textit{BRCA1/2} germline variant status. Statistical analysis was performed from May 1 to September 30, 2020.

**MAIN OUTCOMES AND MEASURES** The primary outcomes were breast cancer–specific survival (BCSS) and overall survival (OS); secondary outcomes included recurrence-free survival, distant recurrence–free survival, and ipsilateral breast tumor recurrence.

**RESULTS** Of these 8396 Chinese patients (8378 women [99.8% women]; mean [SD] age, 50.8 [11.4] years; 187 \textit{BRCA1} carriers, 304 \textit{BRCA2} carriers, and 7905 noncarriers), 3135 (37.3%) received BCT, 1511 (18.0%) received mastectomy with radiotherapy, and 3750 (44.7%) received mastectomy alone. After a median follow-up of 7.5 years (range, 0.3–16.6 years), both \textit{BRCA1} and \textit{BRCA2} variant carriers treated with BCT had similar rates of survival compared with those treated with mastectomy with radiotherapy (BCSS: hazard ratio [HR] for \textit{BRCA1}, 0.58 [95% CI, 0.16–2.10]; \(P = .41\); HR for \textit{BRCA2}, 0.46 [95% CI, 0.15–1.41]; \(P = .17\); OS: HR for \textit{BRCA1}, 0.61 [95% CI, 0.18–2.12]; \(P = .44\); HR for \textit{BRCA2}, 0.72 [95% CI, 0.26–1.96]; \(P = .52\)) or mastectomy alone (BCSS: HR for \textit{BRCA1}, 0.70 [95% CI, 0.22–2.20]; \(P = .54\); HR for \textit{BRCA2}, 0.59 [95% CI, 0.18–1.93]; \(P = .39\); OS: HR for \textit{BRCA1}, 0.77 [95% CI, 0.27–2.21]; \(P = .63\); HR for \textit{BRCA2}, 0.62 [95% CI, 0.22–1.73]; \(P = .37\)) after adjusting for clinicopathologic factors and adjuvant therapy. For noncarriers, patients receiving BCT had significantly better survival than those receiving mastectomy with radiotherapy (BCSS: HR, 0.45 [95% CI, 0.36–0.57]; \(P < .001\); OS: HR, 0.46 [95% CI, 0.37–0.58]; \(P < .001\)) or mastectomy alone (BCSS: HR, 0.71 [95% CI, 0.57–0.89]; \(P = .003\); OS: HR, 0.71 [95% CI, 0.58–0.87]; \(P < .001\)) in multivariable analyses.

**CONCLUSIONS AND RELEVANCE** This study suggests that \textit{BRCA1/2} variant carriers treated with BCT have survival rates at least comparable to those treated with mastectomy with radiotherapy or mastectomy alone and that BCT could be an option for \textit{BRCA1/2} variant carriers when the tumor is clinically appropriate for this procedure.

Key Points

**Question** Can patients with breast cancer who carry a \textit{BRCA1/2} variant safely undergo breast-conserving therapy (BCT)?

**Findings** In this cohort study, 8396 patients with operable primary breast cancer (187 \textit{BRCA1} carriers, 304 \textit{BRCA2} carriers, and 7905 noncarriers) underwent BCT, mastectomy with radiotherapy, or mastectomy alone. In multivariable analyses, patients with both the \textit{BRCA1} and \textit{BRCA2} variants who were treated with BCT had a survival rate at least comparable to those treated with mastectomy with radiotherapy or mastectomy alone.

**Meaning** This study suggests that BCT may be an option for patients who carry a \textit{BRCA1/2} variant when the tumor is clinically appropriate for this procedure.
Introduction

Early randomized clinical trials have demonstrated that breast-conserving therapy (BCT) with radiotherapy is equivalent to mastectomy in overall survival (OS) and breast cancer–specific survival (BCSS) among patients with early-stage breast cancer.1–5 Since then, BCT has been widely used for patients with early-stage breast cancer worldwide for more than 2 decades. Recent analyses based on population or registry studies involving many patients showed that BCT is associated with even better OS than mastectomy among patients with early-stage breast cancer.6–15 By contrast, it is still debated whether BCT could be safely used for BRCA1 (OMIM 113705) and BRCA2 (OMIM 600185) variant carriers with breast cancer. It is well documented that women carrying a germline variant in BRCA1/2 genes not only have a high risk of breast cancer but are also at increased risk of developing a second primary breast cancer, particularly in the contralateral breast.16–26 Although the results are not fully in concordance, many studies showed that BRCA1/2 variant carriers receiving BCT experienced a higher rate of ipsilateral breast cancer recurrence (especially second primary tumor) than did noncarriers.17,18,23,25,26 Therefore, the potential high risk of local recurrence after BCT and other unique features in BRCA1/2 variant carriers with breast cancer raised concerns about whether BCT is associated with survival compared with mastectomy.

Several studies have addressed this issue and found no significant difference in survival rates between BRCA1/2 variant carriers who underwent BCT and those who underwent mastectomy.27–30 These studies, in general, have been limited to a relatively small number of variant carriers, especially BRCA2 variant carriers. In this study, therefore, we compared the survival rates between patients who underwent BCT and patients who underwent mastectomy with or without radiotherapy from a relatively large number of BRCA1/2 variant carriers and noncarriers who were drawn from a large series of unselected patients with breast cancer.

Methods

Study Design

We conducted a retrospective cohort study to compare the survival rates of BRCA1/2 variant carriers and noncarriers who underwent BCT, mastectomy with radiotherapy, or mastectomy alone at the Breast Center of Peking University Cancer Hospital from October 1, 2003, to May 31, 2015, in a large consecutive series of patients with operable primary invasive breast cancer who were unselected for age at diagnosis and family history of breast cancer. We also investigated the risk of recurrence in the ipsilateral breast and the risk of contralateral breast cancer in BRCA1/2 variant carriers and noncarriers when they underwent different surgical procedures. Follow-up was censored on May 1, 2020.

Written informed consent was obtained from all participants whose blood samples could be used for research, including genetic testing. We detected BRCA1/2 germline variants for research purposes. Therefore, the patients and physicians were unaware of the BRCA1/2 variant status when the patients were treated at the breast center. This study was approved by the research and ethics committee of Peking University Cancer Hospital. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Patients and Procedures

A total of 10,269 consecutive patients with primary breast cancer were treated at the breast center, among whom 9,822 patients had sufficient and qualified genomic DNA for BRCA1/2 germline variant sequencing. The following patients were excluded from this study: patients with stage IV disease at diagnosis, follow-up time less than 3 months or loss of follow-up after surgery, distant metastasis within 3 months after primary diagnosis, noninvasive breast cancer, no operation was performed, patients receiving breast-conserving surgery who refused to receive radiotherapy, and whether radiotherapy was applied or not was unknown after surgery. The final sample for this retrospective
study included 8396 Chinese patients with operable primary invasive breast cancer (stages I-III) (eFigure 1 in the Supplement).

Clear margins were required for BCT; a frozen section diagnosis was performed to judge whether the margins were clear. Patients who underwent BCT and those who underwent mastectomy who have a large tumor (ie, >5 cm) and/or 4 positive lymph nodes are referred for radiotherapy, whereas patients with 1 to 3 positive lymph nodes may receive radiotherapy if they have other high-risk factors. Patients may receive neoadjuvant or adjuvant chemotherapy or endocrine therapy depending on tumor clinicopathologic characteristics and clinical stage.

**BRCA1/2 Variant**

Germline DNA extracted from peripheral blood samples was tested for the **BRCA1/2** variant with multigene panel sequencing31 and/or Sanger sequencing32 or multiplex ligation–dependent probe amplification33 as described in previous studies. Only variants with definite pathogenicity were included. Of these 8396 patients, 187 (2.2%) carried a **BRCA1** variant, 304 (3.6%) carried a **BRCA2** variant, and 7905 (94.2%) were noncarriers.

**Statistical Analysis**

Statistical analysis was performed from May 1 to September 30, 2020. The common clinicopathologic characteristics and the types of adjuvant therapy were compared among **BRCA1** variant carriers, **BRCA2** variant carriers, and noncarriers receiving different types of surgery. Continuous variables were compared using a t test, and categorical variables were compared using the Pearson χ² test.

Follow-up started at the time of pathologic diagnosis from core needle biopsy or surgery. The primary outcomes included BCSS and OS, and the secondary outcomes were recurrence-free survival (RFS) and distant recurrence–free survival (DRFS). Breast cancer–specific survival was defined as the time from the date of diagnosis to death from breast cancer. Overall survival was calculated from the date of diagnosis to death from any cause. Recurrence-free survival was defined as the time from the date of pathologic diagnosis to the date of ipsilateral, regional, or distant recurrence or death from any cause but not including contralateral breast cancer. Distant recurrence–free survival was calculated from the date of diagnosis to distant recurrence or death from any cause. For patients who are alive, the latest date of follow-up was the last time they visited the physician or received a telephone call from the follow-up office of Peking University Cancer Hospital. Survival analyses were conducted using the Kaplan-Meier method, and the log-rank test was used to test differences between survival curves. Univariate and multivariable Cox proportional hazards regression models were used to assess the association between surgery procedures and survival. Multivariable adjustments were conducted for common clinicopathologic characteristics that are clinically relevant, including age at first breast cancer diagnosis; family history of breast and ovarian cancer; year of diagnosis; estrogen receptor, progesterone receptor, and ERBB2 status; nodal status; tumor size and grade; and adjuvant therapy.

Other secondary end points included ipsilateral breast tumor recurrence (IBTR) and contralateral breast cancer. Ipsilateral breast tumor recurrence was defined as a recurrence in the ipsilateral breast or chest wall no matter whether it was true tumor recurrence or a second primary tumor. Contralateral breast cancer was defined as developing invasive breast cancer or ductal carcinoma in situ in the contralateral breast at least 3 months after the primary breast cancer.

Tests were considered statistically significant at a 2-sided P < .05. All statistical analyses were completed in SPSS, version 23.0 software (SPSS Inc).
Results

Cohort Description
A total of 8396 patients (mean [SD] age, 50.8 [11.4] years) with primary invasive breast cancer (stages I-III), including 491 BRCA1/2 variant carriers (5.8%) (187 BRCA1 carriers [2.2%] and 304 BRCA2 carriers [3.6%]) and 7905 noncarriers (94.2%), were included in the final analyses. The detailed clinicopathologic characteristics and treatment information are presented in Table 1.

A total of 3135 patients (37.3%) received BCT, 1511 (18.0%) received mastectomy with radiotherapy, and 3750 (44.7%) received mastectomy alone. The percentages of patients who underwent BCT, mastectomy with radiotherapy, and mastectomy alone were similar among the BRCA1 variant carriers, BRCA2 variant carriers, and noncarriers (Table 1).

Comparison of Survival Among BRCA1 and BRCA2 Variant Carriers and Noncarriers in the Entire Cohort
After a median follow-up of 7.5 years (range, 0.3-16.6 years) in the entire cohort, there were no significant differences in BCSS among BRCA1 variant carriers (88.8%), BRCA2 variant carriers (92.1%), and noncarriers (92.4%; log-rank, P = .22; eFigure 2 in the Supplement). Among the 187 BRCA1 variant carriers, 73 (39.0%) underwent BCT, 30 (16.0%) underwent mastectomy with radiotherapy, and 84 (44.9%) underwent mastectomy alone; the clinicopathologic characteristics of the 3 groups are presented in Table 1 in the Supplement. The Kaplan-Meier survival curves of RFS, DRFS, BCSS, and OS in the 3 treatment subgroups of BRCA1 variant carriers are presented in Figure 1. Multivariable analyses showed that BRCA1 variant carriers treated with BCT had similar survival compared with those treated with mastectomy with radiotherapy (BCSS: hazard ratio [HR], 0.58 [95% CI, 0.16-2.10]; P = .41; OS: HR, 0.61 [95% CI, 0.18-2.12]; P = .44) or mastectomy alone (BCSS: HR, 0.70 [95% CI, 0.22-2.20]; P = .54; OS: HR, 0.77 [95% CI, 0.27-2.21]; P = .63) after adjusting for age at diagnosis, family history of breast and ovarian cancer, year of diagnosis, tumor size, tumor grade, lymph node, estrogen receptor, progesterone receptor, ERBB2, and adjuvant therapy (Table 2). The detailed data of multivariable analyses regarding RFS and DRFS among BRCA1 variant carriers are presented in Table 2.

Among the 304 BRCA2 variant carriers, 106 (34.9%) underwent BCT, 67 (22.0%) underwent mastectomy with radiotherapy, and 131 (43.1%) underwent mastectomy alone; the clinicopathologic characteristics of the 3 groups are presented in eTable 2 in the Supplement. The Kaplan-Meier survival curves of RFS, DRFS, BCSS, and OS in the 3 treatment subgroups of BRCA2 variant carriers are presented in Figure 2. Multivariable analyses showed that BRCA2 variant carriers treated with BCT had similar survival compared with those treated with mastectomy with radiotherapy (BCSS: HR, 0.46 [95% CI, 0.15-1.41]; P = 17; OS: HR, 0.72 [95% CI, 0.26-1.96]; P = .52) or mastectomy alone (BCSS: HR, 0.59 [95% CI, 0.18-1.93]; P = .39; OS: HR, 0.62 [95% CI, 0.22-1.73]; P = .37) (Table 2). The details of RFS and DRFS are presented in Table 2.

Among the 7905 noncarriers, 2956 (37.4%) underwent BCT, 1414 (17.9%) underwent mastectomy with radiotherapy, and 3535 (44.7%) underwent mastectomy alone; the clinicopathologic characteristics of the 3 groups are presented in eTable 3 in the Supplement. The Kaplan-Meier survival curves of RFS, DRFS, BCSS, and OS in the 3 treatment subgroups of noncarriers are presented in Figure 3. Noncarriers receiving BCT had a significantly better survival than those receiving mastectomy with radiotherapy (BCSS: HR, 0.45 [95% CI, 0.36-0.57]; P < .001; OS: HR, 0.46 [95% CI, 0.37-0.58]; P < .001) or mastectomy alone (BCSS: HR, 0.71 [95% CI, 0.57-0.89]; P = .003; OS: HR, 0.71 [95% CI, 0.58-0.87]; P < .001) in multivariable analyses (Table 2). The details of RFS and DRFS are presented in Table 2.
Table 1. Clinicopathologic Characteristics of *BRCA1* and *BRCA2* Variant Carriers and Noncarriers in the Entire Cohort

| Characteristic | No. (N = 8396) | No. (%) | P value | BRCA1 carriers vs noncarriers | BRCA2 carriers vs noncarriers | BRCA1 carriers vs BRCA2 carriers |
|----------------|--------------|---------|---------|-----------------------------|--------------------------------|---------------------------------|
| Surgery        |              |         |         |                             |                                |                                 |
| BCT            | 3135         | 73 (39.0) | 106 (43.9) | 2956 (37.4) | .79                             |                                |
| Mastectomy plus RT | 1511     | 30 (16.0) | 67 (22.0)  | 1414 (17.9) | .18                             |                                |
| Mastectomy alone | 3750    | 84 (44.9) | 131 (43.1) | 3535 (44.7) | .25                             |                                |
| Follow-up, y   |              |         |         |                             |                                |                                 |
| Mean (SD)      | 8.1 (3.2)    | 8.1 (3.5) | 7.9 (3.2)  | 8.1 (3.2)   | .76                             | .50                             | .52                             |
| Median (range) | 7.5 (0.3-16.6) | 7.7 (0.8-15.6) | 7.3 (0.4-16.0) | 7.5 (0.3-16.6) |                                |                                 |
| Age, y         |              |         |         |                             |                                |                                 |
| Mean (SD)      | 50.8 (11.4)  | 44.8 (10.0) | 47.6 (10.4) | 51.0 (11.4) | <.001                           | <.001                           | .004                             |
| Median (range) | 50 (19-90)   | 43 (27-81) | 47 (21-75) | 51 (19-90)  |                                |                                 |
| ≤45            | 2913         | 110 (58.8) | 130 (42.8) | 2673 (33.8) | <.001                           | .001                            | <.001                             |
| >45            | 5483         | 77 (41.2)  | 174 (57.2) | 5232 (66.2) |                                |                                 |
| Year of diagnosis |        |         |         |                             |                                |                                 |
| 2003-2009      | 3480         | 87 (46.5)  | 111 (36.5) | 3282 (41.5) | .17                             | .08                             | .03                             |
| 2010-2015      | 4916         | 100 (53.5) | 193 (63.5) | 4623 (58.5) |                                |                                 |
| Family history of any cancer |       |         |         |                             |                                |                                 |
| Yes            | 2632         | 112 (59.9) | 166 (54.6) | 2354 (29.8) | <.001                           | <.001                           | <.001                             |
| No             | 5764         | 75 (40.1)  | 138 (45.4) | 5551 (70.2) |                                |                                 |
| Family history of breast and/or ovarian cancer |       |         |         |                             |                                |                                 |
| Yes            | 799          | 71 (38.0)  | 100 (32.9) | 628 (7.9)   | <.001                           | <.001                           | .25                             |
| No             | 7597         | 116 (62.0) | 204 (67.1) | 7277 (92.1) |                                |                                 |
| ER status*     |              |         |         |                             |                                |                                 |
| Positive       | 6071         | 59 (31.7)  | 242 (79.6) | 5770 (73.0) | <.001                           | .01                             | <.001                             |
| Negative       | 2295         | 127 (68.3) | 62 (20.4)  | 2106 (26.6) |                                |                                 |
| Unknown        | 30           | 1          | 0         | 29                        |                                |                                 |
| PR status*     |              |         |         |                             |                                |                                 |
| Positive       | 5475         | 55 (29.6)  | 224 (73.7) | 5196 (65.7) | <.001                           | .06                             | <.001                             |
| Negative       | 2886         | 131 (70.4) | 80 (26.3)  | 2675 (33.8) |                                |                                 |
| Unknown        | 35           | 1          | 0         | 34                        |                                |                                 |
| ERBB2 status*  |              |         |         |                             |                                |                                 |
| Positive       | 1986         | 13 (7.0)   | 35 (11.5)  | 1938 (24.6) | <.001                           | <.001                           | .10                             |
| Negative       | 6369         | 173 (93.0) | 269 (88.5) | 5927 (75.4) |                                |                                 |
| Unknown        | 41           | 1          | 0         | 40                        |                                |                                 |
| Molecular type*|              |         |         |                             |                                |                                 |
| ER positive, PR positive, and ERBB2 negative | 5197     | 58 (31.2)  | 225 (74.0) | 4914 (62.5) | <.001                           | <.001                           | <.001                             |
| ER negative, PR negative, and ERBB2 negative | 1171     | 115 (61.8) | 44 (14.5)  | 1012 (12.9) |                                |                                 |
| ERBB2 positive | 1986         | 13 (7.0)   | 35 (11.5)  | 1938 (24.6) |                                |                                 |
| Unknown        | 42           | 1          | 0         | 41                        |                                |                                 |
| Stage*         |              |         |         |                             |                                |                                 |
| I              | 2490         | 60 (32.4)  | 83 (27.8)  | 2347 (30.5) | .20                             | .22                             | .05                             |
| II             | 4664         | 110 (59.5) | 169 (56.5) | 4385 (57.0) |                                |                                 |
| III            | 1027         | 15 (8.1)   | 47 (15.7)  | 965 (12.5)  |                                |                                 |
| Unknown        | 215          | 2          | 5         | 208                       |                                |                                 |
| Grade*         |              |         |         |                             |                                |                                 |
| I and II       | 6170         | 104 (61.2) | 221 (81.5) | 5845 (84.8) | <.001                           | .15                             | <.001                             |
| III            | 1165         | 66 (38.8)  | 50 (18.5)  | 1049 (15.2) |                                |                                 |
| Unknown        | 1061         | 17        | 33        | 1011                     |                                |                                 |

(continued)
Comparison of Survival Among BRCA1 and BRCA2 Variant Carriers and Noncarriers With Early-Stage Disease

Patients with early-stage disease (ie, stages I and II) may be suitable for either BCT or mastectomy. Therefore, in this cohort, we compared the survival rates between patients with stage I and II disease (T3N0M0 excluded) who underwent BCT and those who underwent mastectomy with or without radiotherapy. Multivariable analyses still showed that BRCA1/2 variant carriers treated with BCT had a similar survival to those treated with mastectomy with radiotherapy (BCSS: HR for BRCA1, 1.31 [95% CI, 0.12-14.49]; \textit{P} = .83; HR for BRCA2, 0.76 [95% CI, 0.13-4.50]; \textit{P} = .77; OS: HR for BRCA1, 1.31 [95% CI, 0.13-13.33]; \textit{P} = .82; HR for BRCA2, 0.98 [95% CI, 0.18-5.21]; \textit{P} = .98) or mastectomy alone (BCSS: HR for BRCA1, 1.12 [95% CI, 0.30-4.22]; \textit{P} = .87; HR for BRCA2, 0.90 [95% CI, 0.23-3.60]; \textit{P} = .89; OS: HR for BRCA1, 1.29 [95% CI, 0.39-4.24]; \textit{P} = .68; HR for BRCA2, 0.60 [95% CI, 0.16-2.20]; \textit{P} = .44) (eTable 4 in the Supplement). Regarding noncarriers, we found that those who underwent BCT had significantly better survival than those who underwent mastectomy with radiotherapy (BCSS: HR, 0.56 [95% CI, 0.40-0.79]; \textit{P} = .001; OS: HR, 0.58 [95% CI, 0.43-0.80]; \textit{P} = .001) and those who underwent mastectomy alone (BCSS: HR, 0.69 [95% CI, 0.54-0.90]; \textit{P} = .006; OS: HR, 0.68 [95% CI, 0.54-0.85]; \textit{P} = .001) in multivariable analyses (eTable 4 in the Supplement).

IBTR and Contralateral Breast Cancer

The rates of IBTR were 2.1% for BRCA1 variant carriers (4 of 187), 4.6% for BRCA2 variant carriers (14 of 304), and 3.1% for noncarriers (249 of 7905) in the entire cohort (eTable 5 in the Supplement). The IBTR rates among BRCA1 variant carriers were 1.4% for BCT (1 of 73). 0.0% for mastectomy with radiotherapy (0 of 30), and 3.6% for mastectomy alone (3 of 84). The IBTR rates among BRCA2 variant carriers were 7.5% for BCT (8 of 106), 1.5% for mastectomy with radiotherapy (1 of 67), and 3.8% for mastectomy alone (5 of 131). The IBTR rates among noncarriers were 3.9% for BCT (115 of 2956), 2.7% for mastectomy with radiotherapy (38 of 1414), and 2.7% for mastectomy alone (96 of 3535) (eTable 5 in the Supplement). BRCA2 variant carriers who underwent BCT showed a...
nonsignificantly higher IBTR rate than BRCA1 variant carriers and noncarriers who underwent BCT (odds ratio, 2.02 [95% CI, 0.96-4.25]; \( P = .07 \); eTable 6 in the Supplement).

The rates of contralateral breast cancer among BRCA1 and BRCA2 variant carriers were significantly higher than that among noncarriers (BRCA1 vs noncarriers, 13.9% [26 of 187] vs 2.5% [198 of 7905]; \( P < .001 \); BRCA2 vs noncarriers, 13.5% [41 of 304] vs 2.5% [198 of 7905]; \( P < .001 \) (eTable 7 in the Supplement). The rates of contralateral breast cancer among BRCA1 variant carriers were 13.7% for those receiving BCT (10 of 73), 20.0% for those receiving mastectomy with radiotherapy (6 of 30), and 11.9% for those receiving mastectomy alone (10 of 84), whereas the rate of contralateral breast cancer was significantly higher among BRCA2 variant carriers treated with mastectomy alone than among those treated with BCT (19.8% [26 of 131] vs 6.6% [7 of 106]; \( P = .003 \)) and was nonsignificantly higher than among those treated with mastectomy with radiotherapy (19.8% [26 of 131] vs 11.9% [8 of 67]; \( P = .16 \)).

**Discussion**

In this cohort study of a large, consecutive series of 8396 Chinese patients with primary invasive breast cancer in a single center, we investigated whether BRCA1/2 variant carriers could safely undergo BCT when the breast tumor was suitable for this procedure. We found that BRCA1/2 variant carriers receiving BCT exhibited survival rates at least comparable to that of patients receiving mastectomy with or without radiotherapy after adjusting for clinicopathologic characteristics and adjuvant therapy. As expected,

---

**Figure 1. Survival of BRCA1 Variant Carriers Receiving Breast-Conserving Therapy (BCT), Mastectomy With Radiotherapy (RT), or Mastectomy Alone**

### (A) Recurrence-free survival for BRCA1 carriers

- **Mastectomy alone**
- **Mastectomy + RT**
- **BCT**

Log-rank \( P = .04 \)

| No. at risk | BCT | 73 | 68 | 56 | 38 | 28 | 10 | 3 | 0 |
|-------------|-----|----|----|----|----|----|----|---|---|
| Mastectomy + RT | 30 | 24 | 21 | 11 | 6 | 2 | 0 | 0 |
| Mastectomy alone | 84 | 76 | 69 | 44 | 24 | 4 | 0 | 0 |

### (B) Distant recurrence-free survival for BRCA1 carriers

Log-rank \( P = .009 \)

| No. at risk | BCT | 73 | 68 | 57 | 39 | 29 | 10 | 3 | 0 |
|-------------|-----|----|----|----|----|----|----|---|---|
| Mastectomy + RT | 30 | 25 | 21 | 11 | 6 | 2 | 0 | 0 |
| Mastectomy alone | 84 | 77 | 70 | 46 | 26 | 6 | 1 | 0 |

### (C) Breast cancer–specific survival for BRCA1 carriers

Log-rank \( P = .21 \)

| No. at risk | BCT | 73 | 69 | 58 | 41 | 30 | 12 | 4 | 0 |
|-------------|-----|----|----|----|----|----|----|---|---|
| Mastectomy + RT | 30 | 26 | 22 | 13 | 7 | 3 | 0 | 0 |
| Mastectomy alone | 84 | 81 | 71 | 46 | 27 | 7 | 1 | 0 |

### (D) Overall survival for BRCA1 carriers

Log-rank \( P = .15 \)

| No. at risk | BCT | 73 | 69 | 58 | 41 | 30 | 12 | 4 | 0 |
|-------------|-----|----|----|----|----|----|----|---|---|
| Mastectomy + RT | 30 | 26 | 22 | 13 | 7 | 3 | 0 | 0 |
| Mastectomy alone | 84 | 81 | 71 | 46 | 27 | 7 | 1 | 0 |
BCT was associated with significantly better survival than mastectomy with or without radiotherapy among noncarriers after adjusting for all confounding factors.

In this large, consecutive series of unselected patients with breast cancer, all of the patients and physicians were not aware of the BRCA1/2 variant status when they selected BCT or mastectomy, largely depending on the tumor characteristics per se and the preferences of patients and physicians. Therefore, the percentage of patients who underwent BCT was similar throughout the subgroups (39.0% of BRCA1 carriers, 34.9% of BRCA2 carriers, and 37.4% of noncarriers). In addition, the BRCA1/2 variant status was assessed for all of the participants. All of these features largely decreased selection bias. Therefore, our data represent the real world of clinical practice. Several previous studies also compared the survival rates of BRCA1/2 variant carriers who underwent BCT or

| Survival, Surgery | Univariate analysis | Multivariable analysis a |
|-------------------|---------------------|-------------------------|
|                   | HR (95% CI)         | P value                 | HR (95% CI)         | P value                 |
| **BRCA1 carriers**|                     |                         |                       |
| RFS               |                     |                         |                       |
| BCT vs mastectomy plus RT | 0.41 (0.18-0.92) | .03                     | 0.55 (0.21-1.44) | .23                     |
| BCT vs mastectomy alone   | 0.97 (0.45-2.07) | .94                     | 1.04 (0.46-2.35) | .93                     |
| DRFS              |                     |                         |                       |
| BCT vs mastectomy plus RT | 0.38 (0.17-0.86) | .02                     | 0.59 (0.22-1.61) | .31                     |
| BCT vs mastectomy alone   | 1.20 (0.53-2.70) | .67                     | 1.20 (0.50-2.89) | .68                     |
| BCSS               |                     |                         |                       |
| BCT vs mastectomy plus RT | 0.43 (0.14-1.27) | .13                     | 0.58 (0.16-2.10) | .41                     |
| BCT vs mastectomy alone   | 0.81 (0.29-2.18) | .69                     | 0.70 (0.22-2.20) | .54                     |
| OS                 |                     |                         |                       |
| BCT vs mastectomy plus RT | 0.42 (0.15-1.15) | .09                     | 0.61 (0.18-2.12) | .44                     |
| BCT vs mastectomy alone   | 0.87 (0.34-2.26) | .78                     | 0.77 (0.27-2.21) | .63                     |
| **BRCA2 carriers**|                     |                         |                       |
| RFS               |                     |                         |                       |
| BCT vs mastectomy plus RT | 0.42 (0.22-0.80) | .009                    | 0.71 (0.34-1.49) | .37                     |
| BCT vs mastectomy alone   | 0.96 (0.49-1.86) | .90                     | 0.73 (0.36-1.48) | .38                     |
| DRFS              |                     |                         |                       |
| BCT vs mastectomy plus RT | 0.39 (0.20-0.76) | .006                    | 0.66 (0.31-1.44) | .30                     |
| BCT vs mastectomy alone   | 1.06 (0.51-2.19) | .88                     | 0.83 (0.39-1.79) | .64                     |
| BCSS               |                     |                         |                       |
| BCT vs mastectomy plus RT | 0.31 (0.11-0.83) | .02                     | 0.46 (0.15-1.41) | .17                     |
| BCT vs mastectomy alone   | 0.96 (0.32-2.87) | .95                     | 0.59 (0.18-1.93) | .39                     |
| OS                 |                     |                         |                       |
| BCT vs mastectomy plus RT | 0.37 (0.15-0.92) | .03                     | 0.72 (0.26-1.96) | .52                     |
| BCT vs mastectomy alone   | 0.99 (0.38-2.56) | .98                     | 0.62 (0.22-1.73) | .37                     |
| **Noncarriers**    |                     |                         |                       |
| RFS               |                     |                         |                       |
| BCT vs mastectomy plus RT | 0.35 (0.30-0.40) | <.001                   | 0.63 (0.54-0.74) | <.001                   |
| BCT vs mastectomy alone   | 0.87 (0.76-1.00) | .05                     | 0.84 (0.73-0.97) | .02                     |
| DRFS              |                     |                         |                       |
| BCT vs mastectomy plus RT | 0.27 (0.24-0.32) | <.001                   | 0.49 (0.42-0.59) | <.001                   |
| BCT vs mastectomy alone   | 0.77 (0.66-0.90) | .001                    | 0.75 (0.64-0.88) | <.001                   |
| BCSS               |                     |                         |                       |
| BCT vs mastectomy plus RT | 0.22 (0.18-0.28) | <.001                   | 0.45 (0.36-0.57) | <.001                   |
| BCT vs mastectomy alone   | 0.75 (0.61-0.93) | .009                    | 0.71 (0.57-0.89) | .003                    |
| OS                 |                     |                         |                       |
| BCT vs mastectomy plus RT | 0.25 (0.21-0.31) | <.001                   | 0.46 (0.37-0.58) | <.001                   |
| BCT vs mastectomy alone   | 0.70 (0.58-0.85) | <.001                   | 0.71 (0.58-0.87) | <.001                   |

Abbreviations: BCSS, breast cancer-specific survival; BCT, breast-conserving therapy; DRFS, distant recurrence-free survival; HR, hazard ratio; OS, overall survival; RFS, recurrence-free survival; RT, radiotherapy.

* Hazard ratio adjusted for clinicopathologic characteristics and treatment factors including age at first breast cancer diagnosis (≤45 vs >45 years), family history of breast and ovarian cancer (with vs without), year of diagnosis (2003-2009 vs 2010-2015), estrogen receptor status, progesterone receptor status, ERBB2 status, lymph node status (positive vs negative), tumor size (>3 vs ≤3 cm), grade (III vs I and II; unknown vs I and II), and adjuvant therapy (chemotherapy vs endocrine therapy or no therapy).
mastectomy and found no difference in BCSS and OS between BCT and mastectomy.\textsuperscript{27-30} However, the sample size of some studies was relatively small, particularly for BRCA2 variant carriers.\textsuperscript{28-30} Therefore, these studies could not comprehensively analyze the survival of the BRCA2 subgroup, especially for multivariable analyses.\textsuperscript{27-30} Our present study comprised a relatively large number of BRCA1/2 variant carriers to date, particularly BRCA2 variant carriers (304 cases). These advantages enabled us to analyze survival among the BRCA1 and BRCA2 subgroups in univariate and multivariable analyses. The results of our present study in combination with previous studies suggest that the survival rate among BRCA1/2 variant carriers who underwent BCT and the survival rate among BRCA1/2 variant carriers who underwent mastectomy were comparable.

On the other hand, we also noted that patients who received mastectomy with radiotherapy usually had a large tumor or more positive lymph nodes involved compared with those who received BCT or mastectomy alone. In the univariate analyses, we found that BCT showed significantly favorable survival compared with mastectomy with radiotherapy among BRCA1/2 variant carriers and noncarriers, but these differences in BRCA1/2 variant carriers did not reach significance in multivariable analyses. The main reason for these differences not reaching significance was the relatively small sample size of BRCA1/2 variant carriers when stratified by 3 subgroups, particularly for BRCA1 variant carriers. In contrast, BCT showed significantly favorable survival compared with mastectomy with radiotherapy among noncarriers after adjusting for clinicopathologic factors and adjuvant therapy.

We further performed an analysis among patients with clinical stage I and II disease (T3N0M0 excluded) who might be either suitable for BCT or mastectomy. We found that BCT showed a survival

Figure 2. Survival of BRCA2 Variant Carriers Receiving Breast-Conserving Therapy (BCT), Mastectomy With Radiotherapy (RT), or Mastectomy Alone

A. Recurrence-free survival for BRCA2 carriers

B. Distant recurrence-free survival for BRCA2 carriers

C. Breast cancer-specific survival for BRCA2 carriers

D. Overall survival for BRCA2 carriers
rate similar to mastectomy with or without radiotherapy among BRCA1/2 variant carriers in this subset of patients.

In this study, the IBTR rates were relatively low among the groups in the entire cohort, and there was no significant difference in the BRCA1 variant carrier, BRCA2 variant carrier, and noncarrier groups among the patients who underwent BCT, although BRCA2 variant carriers exhibited a nonsignificantly higher rate than noncarriers (7.5% vs 3.9%). These findings are in line with those of previous studies and indicate that the rates of IBTR were reasonably low among BRCA1/2 variant carriers treated with BCT.

In contrast to IBTR, the rate of contralateral breast cancer was significantly higher among BRCA1/2 variant carriers than among noncarriers regardless of BCT or mastectomy. The high risk of contralateral breast cancer may outweigh the benefits associated with BCT for BRCA1/2 variant carriers. Clinicians may discuss this issue with BRCA1/2 variant carriers who may face a high risk of contralateral breast cancer regardless of BCT or mastectomy. Therefore, a mastectomy and a contralateral prophylactic mastectomy with or without immediate reconstruction is an alternative option for BRCA1/2 variant carriers.

**Limitations and Strengths**

There are 2 limitations in our study. First, this was a retrospective study, and patients were not randomly assigned to treatment groups. Second, although the size of the entire cohort was large and the number of BRCA1/2 variant carriers was relatively large, the number of variant carriers (i.e., BRCA1/2) carriers was relatively small.

![Figure 3. Survival of Noncarriers Receiving Breast-Conserving Therapy (BCT), Mastectomy With Radiotherapy (RT), or Mastectomy Alone](image-url)
in the subgroups was relatively small. Thus, caution should be taken when estimating the rate of IBTR among BRCA1/2 variant carriers. This study also has some strengths, including the relatively large number of BRCA1/2 variant carriers and the comprehensive information on clinicopathologic characteristics and adjuvant therapy.

**Conclusions**

In this study, we found that BRCA1/2 variant carriers treated with BCT have a survival rate comparable to that of those treated with mastectomy with radiotherapy or mastectomy alone after adjusting for clinicopathologic factors and adjuvant therapy in this large, consecutive series of unselected patients with breast cancer. We also demonstrated that, with regard to survival rates, BCT is significantly superior to mastectomy with radiotherapy or mastectomy alone among noncarriers. Nevertheless, our present study clearly shows that BCT could be an option for BRCA1/2 variant carriers when the breast tumor is clinically appropriate for the procedure.

**ARTICLE INFORMATION**

Accepted for Publication: February 26, 2021.

Published: April 23, 2021. doi:10.1001/jamanetworkopen.2021.6259

Open Access: This is an open access article distributed under the terms of the CC-BY License. © 2021 Wan Q et al. JAMA Network Open.

Corresponding Author: Yuntao Xie, MD, PhD, Breast Center, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing 100142, China (zbyx2@bjmu.edu.cn).

Author Affiliations: Breast Center, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China.

Author Contributions: Dr Xie had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Wan and Su contributed equally to this study.

Concept and design: Xie.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Wan, Xie.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Wan, Su.

Obtained funding: Xie.

Administrative, technical, or material support: Ouyang, Li, Wang, Z. Fan, T. Fan, Lin, Xie.

Supervision: Xie.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by grants 81372832, 81672625, and 81772824 from the National Natural Science Foundation of China.

Role of the Funder/Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We are thankful to all patients who participated in this study.

**REFERENCES**

1. Jacobson JA, Danforth DN, Cowan KH, et al. Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. *N Engl J Med*. 1995;332(14):907-911. doi:10.1056/NEJM199504063321402

2. van Dongen JA, Voogd AC, Fentiman IS, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst*. 2000;92(14):1143-1150. doi:10.1093/jnci/92.14.1143
3. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med*. 2002;347(16):1227-1232. doi:10.1056/NEJMoa020989

4. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347(16):1233-1241. doi:10.1056/NEJMoa022152

5. Litière S, Werutsky G, Fentiman IS, et al. Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. *Lancet Oncol*. 2012;13(4):412-419. doi:10.1016/S1470-2045(12)70042-6

6. Hwang ES, Lichtensztajn DY, Gomez SL, Fowble B, Clarke CA. Survival after lumpectomy and mastectomy for early stage invasive breast cancer: the effect of age and hormone receptor status. *Cancer*. 2013;119(7):1402-1411. doi:10.1002/cncr.27795

7. Agarwal S, Pappas L, Neumayer L, Kokeny K, Agarwal J. Effect of breast conservation therapy vs mastectomy on disease-specific survival for early stage breast cancer. *JAMA Surg*. 2014;149(3):267-274. doi:10.1001/jamasurg.2013.3049

8. Fisher S, Gao H, Yasui Y, Dabbs K, Winget M. Survival in stage I-III breast cancer patients by surgical treatment in a publicly funded health care system. *Ann Oncol*. 2015;26(6):1161-1169. doi:10.1093/annonc/mdv107

9. Hartmann-Johansen OJ, Kåresen R, Schlichting E, Nygård JF. Survival is better after breast conserving therapy than mastectomy for early stage breast cancer: a registry-based follow-up study of Norwegian women primary operated between 1998 and 2008. *Ann Surg Oncol*. 2015;22(12):3836-3845. doi:10.1245/s10434-015-4441-3

10. Hofvind S, Holen Å, Aas T, Roman M, Sebuødegård S, Akslen LA. Women treated with breast conserving surgery do better than those with mastectomy independent of detection mode, prognostic and predictive tumor characteristics. *Eur J Surg Oncol*. 2015;41(10):1417-1422. doi:10.1016/j.ejso.2015.07.002

11. Onitilo AA, Engel JM, Stankowski RV, Doi SA. Survival comparisons for breast conserving surgery and mastectomy revisited: community experience and the role of radiation therapy. *Clin Med Res*. 2015;13(2):65-73. doi:10.3121/cmr.2014.1245

12. van Maaren MC, de Munck L, de Bock GH, et al. 10 Year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study. *Lancet Oncol*. 2016;17(8):1158-1170. doi:10.1016/S1470-2045(16)30067-5

13. Lagendijk M, van Maaren MC, Saadatmand S, et al. Breast conserving therapy and mastectomy revisited: breast cancer-specific survival and the influence of prognostic factors in 129,692 patients. *Int J Cancer*. 2018;142(1):165-175. doi:10.1002/ijc.31034

14. Lazow SP, Riba L, Alapati A, James TA. Comparison of breast-conserving therapy vs mastectomy in women under age 40: national trends and potential survival implications. *Breast J*. 2019;25(4):578-584. doi:10.1111/tbj.13293

15. 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(2):914-919. doi:10.1245/s10434-020-08829-4

16. Mavaddat N, Peock S, Frost D, et al; EMBRACE. Cancer risks for *BRCA1* and *BRCA2* mutation carriers: results from prospective analysis of EMBRACE. *J Natl Cancer Inst*. 2013;105(11):812-822. doi:10.1093/jnci/djt095

17. Robson M, Levin D, Federici M, et al. Breast conservation therapy for invasive breast cancer in Ashkenazi women with *BRCA* gene founder mutations. *J Natl Cancer Inst*. 1999;91(24):2112-2117. doi:10.1093/jnci/91.24.2112

18. Haffty BG, Harrold E, Khan AJ, et al. Outcome of conservatively managed early-onset breast cancer by *BRCA1/2* status. *Lancet*. 2002;359(9316):1471-1477. doi:10.1016/S0140-6736(02)08434-9

19. Kirova YM, Stoppa-Lyonnet D, Savignoni A, Sigal-Zafrani B, Fabre N, Fourquet A; Institut Curie Breast Cancer Study Group. Risk of breast cancer recurrence and contralateral breast cancer in relation to *BRCA1* and *BRCA2* mutation status following breast conserving surgery and radiotherapy. *Eur J Cancer*. 2005;41(5):2304-2311. doi:10.1016/j.ejca.2005.02.037

20. Robson M, Shah SN, McCormick B, et al. Appropriateness of breast-conserving treatment of breast carcinoma in women with germ line mutations in *BRCA1* or *BRCA2*: a clinic-based series. *Can J Clin Oncol*. 2006;24(16):2437-2443. doi:10.1200/JCO.2005.02.7888
22. Brekelmans CT, Tilanus-Linthorst MM, Seynaeve C, et al. Tumour characteristics, survival and prognostic factors of hereditary breast cancer from BRCA2-, BRCA1- and non-BRCA1/2 families as compared to sporadic breast cancer cases. *Eur J Cancer*. 2007;43(5):867-876. doi:10.1016/j.ejca.2006.12.009

23. Garcia-Etienne CA, Barile M, Gentilini OD, et al. Breast-conserving surgery in BRCA1/2 mutation carriers: are we approaching an answer? *Ann Surg Oncol*. 2009;16(12):3380-3387. doi:10.1245/s10434-009-0638-7

24. Kirova YM, Savignoni A, Sigal-Zafrani B, et al. Is the breast-conserving treatment with radiotherapy appropriate in BRCA1/2 mutation carriers? Long-term results and review of the literature. *Breast Cancer Res Treat*. 2010;120(1):119-126. doi:10.1007/s10549-009-0685-6

25. Valachis A, Nearchou AD, Lind P. Surgical management of breast cancer in BRCA1/2-mutation carriers: a systematic review and meta-analysis. *Breast Cancer Res Treat*. 2014;144(3):443-455. doi:10.1007/s10549-014-2890-1

26. Cao W, Xie Y, He Y, et al. Risk of ipsilateral breast tumor recurrence in primary invasive breast cancer following breast-conserving surgery with BRCA1 and BRCA2 mutation in China. *Breast Cancer Res Treat*. 2019;175(3):749-754. doi:10.1007/s10549-019-05199-8

27. Pierce LJ, Phillips KA, Griffith KA, et al. Local therapy in BRCA1 and BRCA2 mutation carriers with operable breast cancer: comparison of breast conservation and mastectomy. *Breast Cancer Res Treat*. 2010;121(2):389-398. doi:10.1007/s10549-010-0894-z

28. Nilsson MP, Hartman L, Kristoffersson U, et al. High risk of in-breast tumor recurrence after BRCA1/2-associated breast cancer. *Breast Cancer Res Treat*. 2014;147(3):571-578. doi:10.1007/s10549-014-3115-3

29. Huang X, Cai XY, Liu JQ, et al. Breast-conserving therapy is safe both within BRCA1/2 mutation carriers and noncarriers with breast cancer in the Chinese population. *Gland Surg*. 2020;9(3):775-787. doi:10.21037/gs-20-531

30. Sun J, Meng H, Yao L, et al. Germline mutations in cancer susceptibility genes in a large series of unselected breast cancer patients. *Clin Cancer Res*. 2017;23(20):5713-5718. doi:10.1158/1078-0432.CCR-16-3227

31. Su L, Zhang J, Meng H, et al. Prevalence of BRCA1/2 large genomic rearrangements in Chinese women with sporadic triple-negative or familial breast cancer. *Clin Genet*. 2018;94(1):165-169. doi:10.1111/cge.13256

32. Brekelmans CT, Seynaeve C, Menke-Pluymers M, et al. Survival and prognostic factors in BRCA1-associated breast cancer. *Ann Oncol*. 2006;17(3):391-400. doi:10.1093/annonc/mdj095