De-escalation of five-year adjuvant endocrine therapy in patients with estrogen receptor-low positive (immunohistochemistry staining 1%-10%) breast cancer: Propensity-matched analysis from a prospectively maintained cohort

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BACKGROUND: The standard 5 years of endocrine therapy has demonstrated additional benefits compared with short-term (2-3 years) treatment in patients with estrogen receptor (ER)-positive breast cancer; however, data specific to ER-low positive breast cancer (1%-10% by immunohistochemistry) are limited, and it is unclear whether long-term treatment is still necessary for this subgroup. METHODS: The authors used the prospectively maintained Breast Surgery Database of Fudan University Shanghai Cancer Center for this propensity-matched analysis. The primary end point was disease-free survival. Multivariate Cox regression analysis and propensity score-matching methods were used to minimize bias. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. All statistics were 2-sided. RESULTS: From 2012 to 2017, 22,768 consecutive women had pathologically confirmed, early stage breast cancer, and 1013 (4.45%) were identified with ER-low positive disease. Among these, 634 patients met the inclusion criteria and were divided into 3 groups: those who received no endocrine therapy (n = 89), those who received 2 to 3 years of endocrine therapy (n = 185), and those who received approximately 5 years of endocrine therapy (n = 360). At a median follow-up of 65 months, there was no significant difference in disease-free survival between patients who received 2 to 3 years and 5 years of endocrine therapy (HR, 0.82; 95% CI, 0.51-1.33; P = .43). The findings were consistent after multivariate Cox analysis of the propensity score-matched samples (5 vs 2-3 years of treatment: HR, 0.74; 95% CI, 0.41-1.31; P = .30). CONCLUSIONS: Short-term endocrine therapy for 2 to 3 years might be an alternative for patients who have ER-low positive breast cancer instead of the standard 5 years of treatment. Cancer 2022;128:1748-1756. © 2022 The Authors. Cancer published by Wiley Periodicals LLC on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: breast cancer, endocrine therapy, estrogen receptor low-positive, short-term.

INTRODUCTION
According to updated global cancer statistics, breast cancer has now surpassed lung cancer as the most commonly diagnosed female cancer globally.1 The treatment recommendation for patients with breast cancer is mainly based on estrogen receptor (ER) status determined by immunohistochemistry.2 Historically, tumors with ≥10% nuclear staining by immunohistochemistry were considered ER-positive and thus were eligible for endocrine therapy.2,3 However, the 2010 guidelines of the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP)4 recommended dropping this threshold from 10% to 1% because of limited data exploring the benefits of endocrine therapy for tumors with ER expression from 1% to 10%, which were termed ER-low positive in the later 2020 ASCO/CAP guidelines.5 Currently, different multigene tools (such as 21-gene and 70-gene panels) have been developed to stratify patients with early, ER-positive, human epidermal receptor 2 (HER2)-negative breast cancer into different risk groups to guide the use of chemotherapy. It seems that the dichotomous ER status (as negative or positive) limited predictive and prognostic values, and ER-low positive status might provide additional information among ER-positive patients.6

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See editorial on pages 1724-1726, this issue.

This study was presented as an abstract at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting I; June 4-8, 2021; online.

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.34155, Received: September 8, 2021; Revised: November 7, 2021; Accepted: November 30, 2021, Published online February 25, 2022 in Wiley Online Library (wileyonlinelibrary.com)
The proportion of the population with ER-low positive disease among all patients who have breast cancer is not high, ranging from 3% to 9%. Current treatment guidelines for this subgroup are the same as those for patients who have ER-high expression, i.e., the standard endocrine therapy. However, the available data exploring the benefits of endocrine therapy for ER-low positive breast cancer have reported conflicting results. The Early Breast Cancer Trialists’ Collaborative Group performed a patient-level meta-analysis, and the subgroup analysis showed a significant benefit for patients who had ER-weakly positive breast cancer (10-19 fmol/mg cytosol protein) from tamoxifen (risk ratio ± standard error, 0.67 ± 0.08). However, in 2 other retrospective studies, endocrine therapy did not have a significant impact on outcomes among patients with ER-low positive breast tumors. Reasons for the inconsistency are unclear. Further data specific to ER-low positive breast tumors are urgently needed to confirm the rationality of current treatment guidelines for this subgroup.

The optimal duration of endocrine therapy for ER-low positive breast cancer has not been established. The superiority of 5 years of adjuvant tamoxifen versus short-term treatment (2 years) for ER-positive, early breast cancer was first demonstrated in a multicenter, randomized trial initiated by the Swedish Breast Cancer Cooperative Group in the 1980s. Overview analyses have also demonstrated better outcomes associated with 5 years of tamoxifen compared with 2 years in patients with early breast cancer. However, data on endocrine therapy duration specific to ER-low positive breast cancer were not provided, and whether the long-term 5 years of endocrine therapy is necessary for patients who have ER-low positive breast cancer was not confirmed. In a study aiming to determine the intrinsic subtype of ER-low tumors, >60% of tumors were classified as basal-like. Similar results were also reported in another study, and approximately 50% of the ER-low tumors were identified as basal-like. Therefore, greater than one-half of ER-low tumors might be ER-negative in the molecular essence, and short-term endocrine therapy might be enough for such patients. Of note, the appropriate de-escalation of endocrine therapy might reduce the toxicities induced by long-term therapy (eg, the cumulative incidence of endometrial cancer) that cannot be ignored. It seems difficult to perform large-scale clinical trials in patients with ER-low positive breast cancer because of the small proportion of this subgroup. Instead, a real-world, prospective cohort study might be a more appropriate strategy. Therefore, we performed the current propensity-matched analysis to confirm the rationality of endocrine therapy and explore the feasibility of short-term therapy (2-3 years) for patients with ER-low positive breast cancer.

MATERIALS AND METHODS

Study Design and Participants

The Independent Institutional Review board of Fudan University Shanghai Cancer Center approved the study protocol. All patients provided written informed consent. This study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. The STROBE recommendation was developed by a group of researchers, methodologists, and editors, taking both theoretical considerations and empirical evidence into account, to improve the quality of reporting of observational studies. The STROBE checklist includes a description of methodological items and instructions on how to use them to transparently report observational studies. The STROBE checklist is available online at https://www.strobe-statement.org on 10 February, 2022. For the current propensity-matched analysis, we searched the prospectively maintained Breast Surgery Database of Fudan University Shanghai Cancer Center for data on all female patients who were diagnosed with invasive breast cancer from January 2012 to December 2017. We included consecutive patients who had operable, unilateral, pathologically confirmed, ER-low positive breast cancer. Patients who had carcinoma in situ or advanced disease were excluded. Of note, according to the American Joint Committee on Cancer staging system, advanced breast cancer included metastatic breast cancer and locally advanced breast cancer (stage III disease, except T3N1M0), which are not initially operable.

The data extracted included age, menopausal status, pathologic tumor size, lymph node status, tumor grade, HER2 status, duration of endocrine therapy, and whether adjuvant chemotherapy or radiotherapy was received. Endocrine therapy included tamoxifen (mainly for premenopausal women) and an aromatase inhibitor (anastrozole, letrozole, or exemestane, for postmenopausal women). Patients were divided into 3 groups: patients who received no endocrine therapy, those who received approximately 5 years of endocrine therapy. Patients who received an unknown duration of endocrine therapy, 1 year of endocrine therapy, or >5 years of adjuvant endocrine therapy were excluded from the analysis. A minority of patients who received ovarian function suppression also were excluded because the evidence on ovarian function-suppression treatment in patients with
ER-low breast cancer is lacking. According to the SOFT and TEXT trial protocol (ClinicalTrials.gov identifiers NCT00066690 and NCT00066703, respectively), tumors should express ER in at least 10% of cells. Patients who received neoadjuvant chemotherapy were excluded. Adjuvant chemotherapy, radiotherapy, and anti-HER2 treatment were all given in accordance with the corresponding clinical guidelines.

**Immunohistology**
ER, progesterone receptor (PgR), and HER2 status in on tumor sections was assessed using immunohistochemistry. The immunohistochemical cutoff for ER-negative/PgR-negative status was <1% staining in nuclei according to the 2010 ASCO/CAP test guideline. HER2 status was assessed by immunohistochemistry and fluorescence in situ hybridization when necessary according to the ASCO/CAP guideline. In the current study, breast cancer with weakly positive ER expression from 1% to 10% was termed ER-low positive breast cancer.

**Outcomes**
The primary outcome was disease-free survival (DFS). DFS events included local, regional, or distant recurrences of invasive and noninvasive breast cancer, second primary breast cancer, cancers other than cutaneous basal/squamous cell carcinoma and cervical carcinoma in situ, and death from any cause. The secondary outcomes were overall survival (OS) and the annual recurrence rate. OS was defined as the time from randomization to death from any cause.

**Re-Biopsy of Recurrent Lesions**
The recurrent lesions were re-biopsied for patients who developed to relapsed disease, although the re-biopsy was not mandatory. A core-needle biopsy was performed under ultrasound or computed tomography guidance. When necessary, open biopsy by surgical operation was performed. Biopsy samples were immediately fixed in 10% formalin. Malignancy was confirmed by hematoxylin and eosin staining; and ER, PgR, HER2, and Ki-67 status was evaluated in all re-biopsies. GATA3, mamoglobin, and GCDFP15 were tested to confirm the breast origin of the metastatic tumor. Two pathologists independently reviewed the pathologic specimens.

**Statistical Analysis**
Survival curves were generated using the Kaplan-Meier method, and outcomes were compared using a pooled log-rank test. Median follow-up time was estimated by using the reverse Kaplan-Meier method.

*Propensity score matching* is a statistical matching technique that attempts to reduce the bias caused by differences in covariates in the study. In the analysis of observational data, bias could arise because of lack of randomization. Propensity score matching creates a sample of units in different groups that are comparable on all observed covariates to mimic randomization and reduce potential bias. In our study, propensity score matching was performed between patients who received 2 to 3 years of endocrine therapy and those who received 5 years of endocrine therapy (patients who did not receive endocrine therapy were excluded from the matching). Matching was done based upon age, menopausal status (premenopausal vs postmenopausal), pathologic tumor size (T1 vs T2-T3), lymph node status (negative vs positive), tumor grade (1 and 2 vs 3), HER2 status (negative vs positive), receipt of chemotherapy (yes vs no), and receipt of radiotherapy (yes vs no) using a 1:1 nearest-neighbor method without replacement. The balance of propensity-matched groups was assessed and confirmed using mean standardized differences, and absolute values >.2 were considered unacceptably imbalanced.

Univariate and multivariate Cox proportional regressions were subsequently performed to explore the correlates of DFS for both nonmatched and matched comparisons. Hazard ratios (HRs) with 95% confidence intervals (CIs) were also calculated using the Cox model. Annual hazard rate curves were obtained using the *smoothed hazard estimate* function in the STATA software package. All of the data processing described above was performed using IBS SPSS (Statistics 26.lnk) and STATA (version 16, Stata SE). All tests were 2-sided, and P values <.05 were considered statistically significant.

**RESULTS**
Between January 2012 and December 2017, 22,768 consecutive women were newly diagnosed with early stage breast cancer, and 1013 (4.45%) of these women had ER-low positive breast cancers. In total, 634 patients with ER-low positive breast cancer met the inclusion criteria and were included in the analysis (Fig. 1). Representative immunohistology staining images of ER expression are provided in Figure 2A. Among these, 89 patients (14.0%) received no endocrine therapy, 185 (29.2%) received short-term (2-3 years) endocrine therapy, and 360 (56.8%) received the standard 5 years of treatment (Table 1).

At a median follow-up of 65 months (interquartile range, 44-72 months), the estimated 5-year DFS
rate was 85.3% (95% CI, 82.1%-87.9%) for the whole study cohort: 78.3% (95% CI, 67.7%-85.8%) for patients who received no endocrine therapy, 84.2% (95% CI, 77.7%-89.0%) for those who received endocrine therapy from 2 to 3 years, and 87.7% (95% CI, 83.6%-90.8%) for those who received 5 years of endocrine therapy.

The results demonstrated that patients who received 5 years of endocrine therapy had a better DFS than those who received no endocrine therapy in both univariate analysis (HR, 0.57; 95% CI, 0.33-0.98; \( P = 0.04 \)) (see Supporting Table 1) and multivariate analysis (HR, 0.54; 95% CI, 0.32-0.94; \( P = 0.03 \)) (Table 2). In contrast, there was no statistically significant difference in DFS between patients who received 2 to 3 years and 5 years of endocrine therapy in either univariate analysis (HR, 0.82; 95% CI, 0.51-1.33; \( P = 0.43 \)) (see Supporting Table 1) or multivariate analysis (HR, 0.77; 95% CI, 0.47-1.26, \( P = 0.30 \)) (Table 2).

Propensity score matching was performed between patients who received 2 to 3 years versus 5 years of endocrine therapy. In total, 360 patients were finally matched successfully, and 180 patients were assigned to each cohort. Baseline characteristics were adequately balanced between the 2 cohorts after propensity matching. For the matched samples, basic information on characteristics is provided in Supporting Table 2. In univariate analysis, DFS was not significantly better for patients who received 5 years of endocrine therapy versus those who received 2 to 3 years of treatment (HR, 0.74; 95% CI, 0.41-1.31; \( P = 0.30 \)) (Table 2).

Kaplan-Meier curves for DFS before and after propensity score matching are shown in Figure 2B and Figure 2C, respectively. Annual recurrence rate curves for the 634 patients before propensity matching are presented in Figure 2D. Patients who received 5 years versus 2 to 3 years of endocrine therapy had comparable recurrence rates at approximately 2 years of follow-up. Those who received no endocrine therapy had a higher recurrence peak at 2 to 3 years after surgery.

The exploratory subgroup analyses of DFS before (Fig. 3A) and after (Fig. 3B) propensity score matching are illustrated in Figure 3. None of the explored variates
were found to interact with the duration (5 years vs 2-3 years) of endocrine therapy on DFS. Kaplan-Meier curves for OS before and after propensity score matching are shown in Supporting Figure 1. It appeared that the short-term duration of endocrine therapy did not compromise OS.

We also checked changes in the ER status of ER-low positive breast cancers in the recurrence lesions. There were 89 women who had a relapse during follow-up, and 37 recurrence lesions (including lesions of the lung, liver, bone, thoracic wall, lymph node, and skin) were further re-biopsied. ER status was re-tested in the recurrence lesions, with 2 tumors (5.4%) displaying ER staining in \( \geq 10\% \) of nuclei, 16 tumors (43.2%) remaining ER-low positive (ER staining in \( 1\%-9\% \) of nuclei), and 19 tumors (51.4%) changing to ER-negative disease. The loss of ER expression was mostly observed in patients who had distant recurrences, such as liver and lung metastasis.

**DISCUSSION**

The findings of our analysis suggest that there is no statistically significant DFS benefit of 5 years versus 2 to 3 years (short-term) of endocrine therapy in patients with ER-low positive breast cancer. The analysis of propensity score-matched samples further confirmed the robustness of outcomes.

The 2020 ASCO/CAP guidelines acknowledged that data are limited on the benefits of endocrine therapy for patients with ER-low positive breast cancer. Is this population still eligible for endocrine therapy the same as those with ER-high positive breast cancer? Will the magnitude of endocrine therapy benefit be the same regardless of therapy duration? Unfortunately, currently available...
data could not provide clear answers to these critical questions. Previous studies mainly focused on the difference in survival outcomes between patients with ER-low positive and those with ER-high positive/ER-negative breast cancer. Findings on ER-low positive breast cancer mainly came from the subgroup analyses of these studies, and the sample size of the ER-low positive subgroup was usually small. Moreover, a randomized controlled trial to explore the effect of endocrine therapy in patients with ER-low positive breast cancer is challenging to conduct because cases are rare. In addition, some patients would not want to be randomized to 2 to 3 years versus 5 years of endocrine therapy (ie, patients have preferences about what they want), and the results would be difficult to interpret because some patients might not complete their course of treatment because of side effects. Therefore, we searched our prospectively maintained database to examine the value of endocrine therapy in this population, especially the effect on DFS. Although patients who received 5 years of endocrine therapy were found to have a significantly better DFS than those who received no endocrine therapy, there was no significant difference in DFS between 5 years and 2 to 3 years (short-term) of endocrine treatment, both before and after adjustment of

### TABLE 1. Characteristics of Patients With Estrogen Receptor Low-Positive Breast Cancer

| Characteristic                | Total, N = 634 | No ET, N = 89 | ET for 2-3 Years, N = 185 | ET for 5 Years, N = 360 | P^2 |
|------------------------------|----------------|---------------|---------------------------|------------------------|-----|
| Age: Median [IQR], y         |                |               |                           |                        |     |
| Menopausal status            |                |               |                           |                        |     |
| Premenopausal/perimenopausal | 261 (41.2)     | 41 (46.1)     | 78 (42.2)                 | 142 (39.4)             | .50 |
| Postmenopausal               | 373 (58.8)     | 48 (53.9)     | 107 (57.8)                | 218 (60.6)             |     |
| Pathologic tumor size <2 cm  | 390 (61.5)     | 54 (60.7)     | 112 (60.5)                | 224 (62.2)             | .92 |
| Pathologic tumor size >2 cm  | 244 (38.5)     | 35 (39.3)     | 73 (39.5)                 | 136 (37.8)             |     |
| Lymph node status            |                |               |                           |                        |     |
| Negative                     | 394 (62.1)     | 60 (67.4)     | 116 (62.7)                | 218 (60.6)             | .48 |
| Positive                     | 240 (37.9)     | 29 (32.6)     | 69 (37.3)                 | 142 (39.4)             |     |
| Grade 1/2                    | 236 (37.2)     | 36 (40.4)     | 73 (39.5)                 | 127 (35.3)             | .50 |
| Grade 3                      | 398 (62.8)     | 53 (59.6)     | 112 (60.5)                | 233 (64.7)             |     |
| PgR status                   |                |               |                           |                        |     |
| Negative                     | 438 (69.1)     | 58 (65.2)     | 133 (71.9)                | 247 (68.6)             | .51 |
| Positive                     | 196 (30.9)     | 31 (34.8)     | 52 (28.1)                 | 113 (31.4)             |     |
| HER2 status                  |                |               |                           |                        |     |
| Negative                     | 428 (67.5)     | 62 (70.0)     | 132 (71.4)                | 234 (65.0)             | .29 |
| Positive                     | 206 (32.5)     | 27 (30.0)     | 53 (28.8)                 | 126 (35.0)             |     |
| Adjuvant chemotherapy        |                |               |                           |                        |     |
| No                           | 95 (15.0)      | 16 (18.0)     | 34 (18.4)                 | 45 (12.5)              | .13 |
| Yes                          | 539 (85.0)     | 73 (82.0)     | 151 (81.6)                | 315 (87.5)             |     |
| Adjuvant radiation           |                |               |                           |                        |     |
| No                           | 352 (55.5)     | 55 (61.8)     | 97 (52.4)                 | 200 (55.6)             | .35 |
| Yes                          | 282 (44.5)     | 34 (38.2)     | 88 (47.6)                 | 160 (44.4)             |     |

**Abbreviations:** ET, endocrine therapy; HER2, human epidermal receptor 2; IQR, interquartile range; PgR, progesterone receptor.

^2P values are for heterogeneity.

### TABLE 2. Multivariate Analysis Before and After Propensity Score Matching

| Variable                      | Prematching Hazard Ratio [95% CI] | P     | Postmatching Hazard Ratio [95% CI] | P     |
|-------------------------------|-----------------------------------|-------|-----------------------------------|-------|
| Age (continuous)              | 1.01 [0.99-1.03]                  | .60   | 1.00 [0.97-1.02]                  | .69   |
| Pathologic tumor size <2 cm   | —                                 | —     | 2.19 [1.18-4.08]                  | .01   |
| Pathologic tumor size ≥2 cm   | 1.40 [0.91-2.17]                  | .13   | 3.54 [1.76-7.10]                  | <.01  |
| Lymph node status             | 3.08 [1.92-4.96]                  | <.01  | 3.54 [1.76-7.10]                  | <.01  |
| Grade 1/2                     | 1.24 [0.77-2.00]                  | .37   | 0.94 [0.50-1.78]                  | .85   |
| Grade 3                       | 0.62 [0.38-1.00]                  | .05   | 0.58 [0.29-1.17]                  | .13   |
| HER2 status                   | 0.91 [0.47-1.73]                  | .76   | 0.87 [0.37-2.07]                  | .75   |
| Adjuvant chemotherapy No (Ref)| 0.64 [0.40-1.02]                  | .06   | 0.68 [0.35-1.35]                  | .27   |
| Adjuvant chemotherapy Yes     | 0.70 [0.39-1.27]                  | .24   | 0.70 [0.39-1.27]                  | .24   |
| Duration of adjuvant ET 2-3 y vs none | 0.54 [0.32-0.94] | .03 | 0.77 [0.47-1.26] | .30 |
| Adjuvant chemotherapy 5 y vs none | 0.70 [0.39-1.27] | .24 | 0.70 [0.39-1.27] | .24 |
| Adjuvant chemotherapy 5 y vs 2-3 y | 0.77 [0.47-1.26] | .80 | 0.77 [0.47-1.26] | .80 |

**Abbreviations:** CI, confidence interval; ET, endocrine therapy; HER2, human epidermal receptor-2; Ref, reference category.
confounding factors. Another interesting finding of our study was that 5 years of endocrine therapy was better than no endocrine treatment in terms of DFS, indicating that patients with ER-low breast cancer should always be considered for endocrine therapy. However, these patients were not propensity matched, and bias based on whatever reasons endocrine therapy was omitted may have influenced this result. Moreover, 50% cases recurred as ER-negative. This finding suggests that re-biopsy of recurrences is essential and needs to be done whenever possible. These patients with ER-low disease may not be as hormone-driven as those who have higher levels of ER positivity.

To further explore the rationality of de-escalating 5 years of endocrine therapy duration for patients with ER-low positive breast cancer, we used propensity score matching to adjust for the differences in baseline characteristics between patients receiving 5 years and those receiving 2 to 3 years (short-term) of endocrine therapy. As expected, even after matching, no superiority of 5 years of endocrine therapy was observed compared with 2 to 3 years of treatment, and the negative results persisted across all subgroups based on different variables. This finding is of great significance for optimizing the treatment strategy of patients with ER-low positive breast cancer: de-escalation of 5 years' duration might be considered for the ER-low positive population and not only may reduce the toxicities of long-term treatment but also may reduce the economic costs and improve patients' compliance.

Figure 3. Forest plots illustrate the exploratory subgroup analysis of disease-free survival (A) before and (B) after propensity score matching. ET indicates endocrine therapy; HER2, human epidermal receptor-2.
To our knowledge, the current study is the first propensity score-matching analysis specific to patients with ER-low positive breast cancer. We used data from a large number of patients who had accurate DFS data in a prospectively maintained database, and we used propensity score matching and multivariate Cox analyses to minimize inherent bias. In addition, there is huge potential for obtaining methodologically sound research proposals to use the prospectively maintained database of Fudan University Shanghai Cancer Center and to generate and report well designed observational studies that will have value for the literature.

However, there are still some limitations of our study. These include the retrospective design and the small sample size (particularly for the propensity-matched subsets), together with the inability to review and confirm individual data. Our database did not collect information on the persistence of adjuvant endocrine treatment, and the rate of persistence with adjuvant endocrine therapy might decrease over time. Moreover, although several steps have been taken to minimize selection bias, the reasons for different durations might introduce bias in treatment outcomes. For instance, patients with low compliance who intended to receive no endocrine therapy or to receive short-term therapy also may have had a low degree of cooperation at the examination during follow-up and thus may compromise survival findings. Therefore, when our findings are interpreted, the above limitations should be taken into account with full caution.

Conclusion
In conclusion, our results support the consideration of short-term endocrine therapy for 2 to 3 years for the treatment of ER-low positive early breast cancer. Further studies of more extensive scale and translational research on identifying endocrine-sensitive cases within this population are still needed.

FUNDING SUPPORT
This work was supported by grants from the National Natural Science Foundation of China (grants 81672600, 81722032, and 82072916), the 2018 Shanghai Youth Excellent Academic Leader, the Fudan ZHUOSHI Project, and the Chinese Young Breast Experts Research Project (CYBER-2021-A01).

CONFLICT OF INTEREST DISCLOSURES
The authors made no disclosures.

AUTHOR CONTRIBUTIONS
Yu-Wen Cai: Obtained the data; contributed to data analysis, interpretation of the data, and preparation and writing of the article; and approved of the final version for submission. Zhi-Ming Shao: Contributed to data analysis, interpretation of the data, and preparation and writing of the article and approved of the final version for submission. Ke-Da Yu: Was the principal investigator; obtained the data; contributed to data analysis, and interpretation of the data, and preparation and writing of the article; and approved of the final version for submission.

DATA AVAILABILITY
Individual participant data that underlie the results reported in this article will be shared after de-identification. Data will be available 3 months after publication. Researchers who provide a methodologically sound proposal might access the individual participant data. Proposals should be directed to yukeda@fudan.edu.cn. To gain access, data requestors will need to sign a data access agreement.

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