Comparison of epidemiological features, clinicopathological features, and treatments between premenopausal and postmenopausal female breast cancer patients in western China: a retrospective multicenter study of 15,389 female patients

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Abstract

Premenopausal and postmenopausal breast cancers are considered different types. Thus, this study aimed to explore differences in risk factors, epidemiological features, clinicopathological features, and treatment modes of premenopausal breast cancer compared to postmenopausal patients in western China. This was a hospital-based, retrospective, multicenter epidemiological study of patients with breast cancer. Using the Western China Clinical Cooperation Group database, we obtained the records of 15,389 female breast cancers between January 2010 and April 2017. These patients were divided into premenopausal and postmenopausal groups, and their risk factors, epidemiological feature, clinicopathological features, and treatment modes were compared. Chi-square tests, t-test, and the multivariate logistic regression analysis were applied for statistical analysis. A total of 8395 patients were categorized as premenopausal, and 6994 patients were categorized as postmenopausal. Their risk factors, epidemiological features, clinicopathological features, and treatment modes were compared. Premenopausal patients with breast cancer had a greater tumor diameter at diagnosis ($P = 0.008$); higher rates of estrogen receptor (ER) expression ($P < 0.0001$), progesterone receptor (PR) expression ($P < 0.0001$), negative human epidermal growth factor receptor 2 (HER2) expression ($P = 0.015$), and negative P53 expression ($P < 0.0001$); and higher proportions of receiving breast-conserving surgery and breast reconstruction ($P < 0.0001$), chemotherapy ($P < 0.0001$), radiotherapy ($P < 0.0001$), and endocrine therapy ($P < 0.0001$). The ethnicity, age at menarche, marital status, number of pregnancies, and number of births were the risk factors for age at diagnosis of breast cancer before or after menopause in western China. We found that the fall in the fertility rate, early menarche age, married, and less breastfeeding might have increased the possibility of premenopausal breast cancer. Significant differences exist in the tumor size, hormone receptor state, HER2 expression, epidemiological features, and treatment modes between premenopausal and postmenopausal female breast cancer patients in western China. Its further implementation requires prospective clinical testing.
Comparison of pre- and postmenopausal breast cancer

Introduction
Breast cancer is the most common cancer in women, and its incidence is increasing annually worldwide [1, 2]. Breast cancer is also a heterogeneous disease, divisible into various clinical subtypes, and the pathogenesis is not clear [3]. As early as the 1970s, De Waard proposed the concept that breast cancers develop by two distinct pathways, each with a different age-specific incidence rate curve [4, 5]. The first pathway results in mainly premenopausal tumors with peak occurrence early in life. The second pathway results in predominantly postmenopausal cancers with peak incidence later in life, similar to late-onset estrogen receptor(ER)-positive cancers.

In China, the data from both Shanghai and Beijing showed two breast cancer age peaks, one at 45–55 years and the other at 70–74 years [6]. The mean age at diagnosis of breast cancer in China is 45–55 years, which is considerably younger than that for western women, with 57.4% of women diagnosed before the age of 50 years and 62.9% of women diagnosed while still premenopausal; the peak incidence occurred after menopause in developed countries [7]. This result suggests the possibility that certain differences in the pathogenesis of breast cancer may exist between Chinese women and women in Western populations.

Few studies have investigated the risk factors that may influence the age at diagnosis of breast cancer. The difference in the clinicopathologic features and treatment modes between premenopausal and postmenopausal patients with breast cancer is not known. Some scholars have predicted that the incidence of hormone receptor-positive breast cancer is affected by the menopause transition [8, 9]. Nonetheless, and somewhat paradoxically, it has been reported that menopause significantly affects the incidence of ER-negative breast cancer but not that of ER-positive breast cancer [10, 11]. Presently, this issue is controversial.

Currently, no study has compared the difference between premenopausal and postmenopausal breast cancers in China. Therefore, the main objective of this study was to assess the epidemiological characteristics, clinicopathologic features, and treatment modes between premenopausal and postmenopausal breast cancers to make treatment decisions and improve patient prognoses, as well as to provide valuable insights into what may influence the age at diagnosis of breast cancer in western China.

Materials and Methods
Study design
The Western China Clinical Cooperation Group (WCCCG) was established in 2008 and includes 23 breast cancer centers in nine provinces in western China. A total of 18,000 patients with breast cancer are included in the database. Male patients and female patients without menopausal status and age at diagnosis were excluded from the study. In total, 15,389 patients with breast cancer who were diagnosed between 1 January 2009 and 30 April 2017 were included in the retrospective multicenter database analysis. Among them, 8395 patients (54.55%) were divided into premenopausal group, and 6994 patients (45.45%) were divided into postmenopausal group. This observational study was based entirely on data extracted from patient medical records and was approved by the ethics committee of each participating center.

Patients
The data for this study, including demographic data and tumor data, were extracted from the medical records of the patients included herein by trained data collectors at each center and were analyzed anonymously.

Data collection
Demographic data included information regarding the age at diagnosis, race, age at menarche, marital status, and number of pregnancies, number of births, breastfeeding history, and body mass index. Clinical characteristics consisted of tumor laterality, location in the breast, axillary and supraclavicular lymph node status, and size in cm. The tumors were classified according to initial disease symptoms and signs and whether there was distant metastasis in the body. The following pathologic characteristics were evaluated in the study: tumor histological types, axillary lymph node metastases, numbers of positive axillary lymph nodes, the presence of lymph vascular invasion, tumor grade, ER and PR status, HER2 and P53 expression, and Ki67 status. Data regarding treatments were also collected and included the chemotherapy regimens, radiotherapy regimens, anti-HER2 therapy regimens, endocrine therapy regimens, types of surgeries, and axillary lymph node dissection procedures.

Pathological grading and staging criteria
The tumor was graded according to the Bloom–Richardson classification (Nottingham grading) [12]. Staging of breast cancer size was performed according to the American Joint Committee on Cancer (AJCC) TNM staging system (from 1997 and 2002) [13]. All centers use the same criteria.

Statistical analyses
Statistical analyses were performed using the Statistical Package for the Social Sciences, version 22.0 (SPSS Inc.,
Chicago, IL, USA). The differences in the demographic, clinical, and pathological characteristics and in treatments between the two groups were analyzed using Student’s t-test in the case of quantitative variables and chi-square tests and Fisher’s exact test in the case of categorical variables. Multivariate logistic regression analyses were performed to assess the associations between menopausal status and several variables, and odds ratios (ORs) were calculated based on 95% confidence intervals. Variables with univariate results of \( P < 0.05 \) were included in the multivariate model. All statistical tests were considered significant when \( P < 0.05 \).

## Results

### Comparison of the baseline characteristics

The comparison of the baseline characteristics of premenopausal and postmenopausal groups is summarized in Table 1. The mean ages at diagnosis of the patients in premenopausal and postmenopausal groups were 42.8 and 58.2 years, respectively, and there was a difference in the distributions of the ages at which patients were diagnosed between the two groups (\( P < 0.0001 \)). The proportion of patients of Han ethnicity was lower in premenopausal group than in postmenopausal group (94.69% vs. 96.61%, respectively, \( P < 0.0001 \)). Most of the patients in the two groups experienced menarche at 13–14 years \([n = 4396 (52.36\%) \text{ and } n = 3456 (49.41\%), \text{respectively}]\). Patients in premenopausal group were younger at the time of menarche (younger than 12 years) than patients in postmenopausal group. In addition, more patients in postmenopausal group experienced menarche at an age older than 15 years (\( P < 0.0001 \)). We also observed differences in the marital status (\( P < 0.0001 \)), number of pregnancies (\( P < 0.0001 \)), number of births (\( P = 0.002 \)), and breastfeeding history (\( P < 0.0001 \)) between the two groups. The mean body mass indexes (BMI) of the patients in premenopausal and postmenopausal groups were 23.1 and 23.6, respectively. An analysis of BMI showed that premenopausal group included more patients who had a BMI <25.0 compared with that postmenopausal group \([n = 3693 (43.99\%) \text{ and } n = 2825 (40.39\%), \text{respectively}]\) (\( P < 0.0001 \)).

### Comparison of clinical characteristics

Table 2 shows significant differences in the occurrence of breast pain (8.33% vs. 9.75%, \( P = 0.002 \)), nipple discharge (2.30% vs. 2.83%, \( P = 0.037 \)), and nipple inversion (1.21% vs. 2.04%, \( P < 0.0001 \)). Patients in premenopausal group were more likely to have a positive axillary lymph node status (29.40% vs. 27.95%, \( P = 0.031 \)) and supraclavicular lymph node status (5.85% vs. 4.93%, \( P = 0.007 \)). No significant difference in the incidence of distant metastases was observed between the two groups (1.70% vs. 2.10%, \( P = 0.073 \)). Regarding the tumor size, most patients in the two groups had a tumor size between 2 and 5 cm, whereas significantly more patients in premenopausal group had large tumors (8.1% vs. 7.55%, \( P = 0.008 \)).

### Clinical outcomes

Comparison of pathological characteristics

Pathological characteristics are displayed in Table 3. Regarding ER, PR, human epidermal growth factor receptor-2 (HER-2), P53 status and Ki67, with which the patients receiving immunohistochemistry testing presented, we found that patients in premenopausal group were more likely to show positive expression of ER (59.14% vs. 54.86%, \( P < 0.0001 \)) and PR (55.76% vs. 43.78%, \( P < 0.0001 \)) than postmenopausal group. Premenopausal patients also had higher proportions of double-positive expression of ER and PR (i.e., ER+/PR+; 50.46% vs. 40.43%, \( P < 0.0001 \)) and single-positive expression of PR (i.e., ER−/PR--; 5.28% vs. 3.33%, \( P < 0.0001 \)). Conversely, patients in postmenopausal group presented with double-negative expression of ER and PR (i.e., ER-/PR--; 35.72% vs. 31.40%, \( P < 0.0001 \)) and single-positive expression of ER (i.e., ER+/PR--; 14.20% vs. 8.29%, \( P < 0.0001 \)) more frequently. Moreover, the proportion of patients with a positive HER2 status (14.46% vs. 13.48%, \( P = 0.015 \)) and P53 status (29.47% vs. 25.63%, \( P < 0.0001 \)) was higher in postmenopausal group. However, no significant difference in the incidence of triple-negative or Ki67 was observed between the two groups.

### Comparison of treatment modes

We found that most patients received chemotherapy and that patients in premenopausal group received chemotherapy (85.06% vs. 75.72%, \( P < 0.0001 \)), radiotherapy (20.31% vs. 13.14%, \( P < 0.0001 \)), and endocrine therapy (29.77% vs. 22.79%, \( P < 0.0001 \)) more frequently. Of the 15,389 patients included in the study, 14,521 patients underwent surgery. Patients in premenopausal group were more likely to undergo breast-conserving surgery, simple mastectomy, and breast reconstruction and were less likely to undergo modified radical mastectomy than patients in postmenopausal group (\( P < 0.0001 \)). The comparison of the treatment characteristics between the two groups is presented in Table 4.

### Multivariate logistic regression analysis of premenopausal breast cancer-related risk factors among all breast cancer patients

Multivariate logistic regression analysis indicated following risk factors were related to premenopausal breast cancer:

\[ \text{OR} = 1.50, \text{CI} = 1.20-1.86, \text{P} < 0.0001 \]
ethnicity, age at menarche, marital status, number of pregnancies, and number of births. Compared with referent (Han; age at menarche ≤10; married; absence of a history of pregnancy and birth): (1) other ethnicities and number of pregnancy ≥1 were associated with elevated premenopausal breast cancer possibility (OR > 1, \( P < 0.05 \)); (2) and increase in age at menarche, never married, widowed/divorced, and number of birth ≥1 were associated with decreased premenopausal breast cancer possibility (OR < 1, \( P < 0.05 \)) among all breast cancer patients. All the results of multivariate logistic regression analysis are listed in Table 5.

### Table 1. Baseline characteristics of the patients with breast cancer.

| Characteristics                  | Total (N = 15,389) | Premenopausal (N = 8395) | Postmenopausal (N = 6994) | \( P \) value |
|----------------------------------|--------------------|--------------------------|---------------------------|--------------|
| **Age**                          |                    |                          |                           |              |
| Mean ± SD                        | 49.6 ± 11.1        | 42.8 ± 7.0               | 58.2 ± 8.5                | <0.0001\(^1\) |
| Race/ethnicity                   |                    |                          |                           |              |
| Han                              | 14,706             | 7949                     | 6757                      | 96.11        | <0.0001\(^2\) |
| Other                            | 683                | 446                      | 237                       | 3.39         |              |
| **Age at menarche (years)**      |                    |                          |                           |              |
| ≤10                              | 30                 | 20                       | 10                        | 0.14         | <0.0001\(^2\) |
| 11–12                            | 1844               | 1191                     | 653                       | 9.34         |              |
| 13–14                            | 7852               | 4396                     | 3456                      | 49.41        |              |
| 15–16                            | 3981               | 2089                     | 1892                      | 27.05        |              |
| 17–18                            | 1349               | 583                      | 766                       | 10.95        |              |
| ≥19                              | 284                | 98                       | 186                       | 2.66         |              |
| **Missing data**                 | 49                 | 18                       | 31                        | 0.44         |              |
| **Marital status**               |                    |                          |                           |              |
| Married                          | 14,960             | 8188                     | 6772                      | 96.83        | <0.0001\(^3\) |
| Never married                    | 138                | 110                      | 28                        | 0.40         |              |
| Widowed/divorced                 | 276                | 89                       | 187                       | 2.67         |              |
| Missing data                     | 15                 | 8                        | 7                         | 0.10         |              |
| **Number of pregnancies**        |                    |                          |                           |              |
| 0                                | 3239               | 1790                     | 1449                      | 20.72        | <0.0001\(^2\) |
| 1                                | 3848               | 2216                     | 1632                      | 23.33        |              |
| 2                                | 3228               | 1807                     | 1421                      | 20.32        |              |
| 3                                | 2228               | 1230                     | 998                       | 14.27        |              |
| 4                                | 1408               | 715                      | 693                       | 9.91         |              |
| ≥5                               | 1413               | 623                      | 790                       | 11.30        |              |
| **Missing data**                 | 15                 | 8                        | 7                         | 0.10         |              |
| **Number of births**             |                    |                          |                           |              |
| 0                                | 2753               | 1584                     | 1169                      | 16.71        | <0.0001\(^2\) |
| 1                                | 7086               | 4404                     | 2682                      | 38.35        |              |
| 2                                | 3579               | 1887                     | 1692                      | 24.19        |              |
| 3                                | 1198               | 378                      | 820                       | 11.72        |              |
| 4                                | 468                | 97                       | 371                       | 5.30         |              |
| ≥5                               | 282                | 32                       | 250                       | 3.57         |              |
| **Missing data**                 | 23                 | 13                       | 10                        | 0.14         |              |
| **Breastfeeding history**        |                    |                          |                           |              |
| No                               | 1543               | 900                      | 643                       | 9.19         | 0.002\(^2\) |
| Yes                              | 5050               | 2685                     | 2365                      | 33.81        |              |
| Missing data                     | 8796               | 4810                     | 3986                      | 56.99        |              |
| **BMI**                          |                    |                          |                           |              |
| Mean ± SD                        | 23.3 ± 2.5         | 23.1 ± 2.4               | 23.6 ± 2.7                |              |
| <18.5                            | 442                | 252                      | 190                       | 2.72         |              |
| 18.5–24.9                        | 6076               | 3441                     | 2635                      | 37.68        |              |
| 25.0–29.9                        | 2184               | 983                      | 1201                      | 17.17        |              |
| ≥30.0                            | 308                | 129                      | 179                       | 2.56         |              |
| **Missing data**                 | 6379               | 3590                     | 2789                      | 39.88        |              |

\(^1\) Student’s \( t \)-test.  
\(^2\) Chi-square test.  
\(^3\) Fisher’s exact test.
Discussion

Overall, it is of great interest that a significant difference exists between premenopausal and postmenopausal female breast cancer patients and we found some factors that are associated with elevated or decreased premenopausal breast cancer possibility. The related research is rare.

Consistent with the results of other scholars in China [6, 14], the median age at diagnosis was 49.6 years for all breast cancer patients in this study. The premenopausal patients accounted for 54.55% of the total breast cancer cases, the proportion was significantly higher than that of postmenopausal patients, and that differed from the corresponding proportion in a Western population [15]. This finding suggests the possibility that certain differences in the pathogenesis of breast cancer, considered to be related to ethnicity, age at menarche, marital status, number of pregnancies, number of births, and breastfeeding history [16–19], may exist between premenopausal and postmenopausal patients.

Table 2. Clinical characteristics of the tumors.

| Characteristics                        | Total (N = 15,389) | PREMENOPAUSAL (N = 8395) | POSTMENOPAUSAL (N = 6994) | P value |
|----------------------------------------|-------------------|--------------------------|--------------------------|---------|
|                                        | N     | %     | N     | %     | N     | %     |        |        |
| Breast lump                            |       |       |       |       |       |       |        |        |
| Yes                                    | 14,485| 94.07 | 7913  | 94.26 | 6572  | 93.97 | 0.4821 |        |
| No                                     | 904   | 5.87  | 483   | 5.75  | 421   | 6.02  |        |        |
| Breast pain                            |       |       |       |       |       |       |        |        |
| Yes                                    | 1381  | 8.97  | 699   | 8.33  | 682   | 9.75  | 0.0021 |        |
| No                                     | 14,008| 90.97 | 7697  | 91.69 | 6311  | 90.23 |        |        |
| Nipple discharge                       |       |       |       |       |       |       |        |        |
| Yes                                    | 391   | 2.54  | 193   | 2.30  | 198   | 2.83  | 0.0371 |        |
| No                                     | 14,998| 97.40 | 8203  | 97.71 | 6795  | 97.15 |        |        |
| Nipple inversion                       |       |       |       |       |       |       |        |        |
| Yes                                    | 254   | 1.65  | 111   | 1.32  | 143   | 2.04  | <0.0001|        |
| No                                     | 15,135| 98.29 | 8285  | 98.69 | 6850  | 97.94 |        |        |
| Tumor location in breast               |       |       |       |       |       |       |        |        |
| 3 o'clock                              | 385   | 2.50  | 214   | 2.55  | 171   | 2.44  | <0.0001|        |
| 6 o'clock                              | 259   | 1.68  | 138   | 1.64  | 121   | 1.73  |        |        |
| 9 o'clock                              | 475   | 3.08  | 254   | 3.03  | 221   | 3.16  |        |        |
| 12 o'clock                             | 813   | 5.28  | 478   | 5.69  | 335   | 4.79  |        |        |
| Upper inner quadrant                   | 1975  | 12.83 | 1190  | 14.18 | 785   | 11.22 |        |        |
| Lower inner quadrant                   | 577   | 3.75  | 326   | 3.88  | 251   | 3.59  |        |        |
| Upper outer quadrant                   | 5637  | 36.61 | 3238  | 38.57 | 2399  | 34.30 |        |        |
| Lower outer quadrant                   | 1119  | 7.27  | 624   | 7.43  | 495   | 7.08  |        |        |
| Nipple–areola                          | 910   | 5.91  | 449   | 5.25  | 461   | 6.59  |        |        |
| Missing data                           | 3239  | 21.04 | 1484  | 17.68 | 1755  | 25.09 |        |        |
| Axillary lymph node status             |       |       |       |       |       |       |        |        |
| Positive                               | 4402  | 28.59 | 2346  | 27.95 | 2056  | 29.40 | 0.0312 |        |
| Negative                               | 10,097| 65.57 | 5578  | 66.44 | 4519  | 64.61 |        |        |
| Missing data                           | 890   | 5.78  | 471   | 5.61  | 419   | 5.99  |        |        |
| Supraclavicular lymph node status      |       |       |       |       |       |       |        |        |
| Positive                               | 823   | 5.34  | 414   | 4.93  | 409   | 5.85  | 0.0072 |        |
| Negative                               | 13,557| 88.04 | 7480  | 89.10 | 6077  | 86.89 |        |        |
| Missing data                           | 1009  | 6.55  | 501   | 5.97  | 508   | 7.26  |        |        |
| Tumor size (cm)                        |       |       |       |       |       |       |        |        |
| ≤1                                     | 820   | 5.33  | 485   | 5.78  | 335   | 4.79  | 0.0081 |        |
| >1, ≤2                                 | 4456  | 28.94 | 2370  | 28.23 | 2086  | 29.83 |        |        |
| >2, ≤5                                 | 7158  | 46.49 | 3907  | 46.54 | 3251  | 46.48 |        |        |
| >5                                     | 1208  | 7.85  | 680   | 8.10  | 528   | 7.55  |        |        |
| Missing data                           | 1747  | 11.35 | 953   | 11.35 | 794   | 11.35 |        |        |
| Distant metastasis                     |       |       |       |       |       |       |        |        |
| Positive                               | 290   | 1.88  | 143   | 1.70  | 147   | 2.10  | 0.0731 |        |
| Negative                               | 14,951| 97.10 | 8165  | 97.26 | 6786  | 97.03 |        |        |
| Missing data                           | 148   | 0.96  | 87    | 1.04  | 61    | 0.87  |        |        |

1 Chi-square test.
2 Fisher’s exact test.
Table 3. Pathological characteristics of the tumors.

| Characteristics                        | Total (N = 15,389) | Premenopausal (N = 8395) | Postmenopausal (N = 6994) | P value |
|----------------------------------------|--------------------|--------------------------|---------------------------|--------|
|                                        | N  | %     | N  | %     | N  | %     |        |
| Tumor histology                        |    |       |    |       |    |       |        |
| Carcinoma in situ                      | 801| 5.20  | 413| 4.92  | 388| 5.55  | 0.053 |
| Invasive carcinoma                     | 14,008| 90.97 | 7712| 91.86 | 6296| 90.02 |        |
| Missing data                           | 580| 3.77  | 270| 3.22  | 310| 4.43  |        |
| Axillary lymph nodes metastasis        |    |       |    |       |    |       |        |
| Yes                                    | 6584| 42.76 | 3612| 43.03 | 2972| 42.49 | 0.914 |
| No                                     | 7210| 46.82 | 3962| 47.19 | 3248| 46.44 |        |
| Missing data                           | 1595| 10.36 | 821 | 9.78  | 774 | 11.07 |        |
| No. of positive axillary lymph nodes   |    |       |    |       |    |       |        |
| 0 (N0)                                 | 7210| 46.82 | 3962| 47.19 | 3248| 46.44 | 0.068 |
| 1–3 (N1)                               | 4125| 26.79 | 2285| 27.22 | 1840| 26.31 |        |
| 4–9 (N2)                               | 1572| 10.21 | 877 | 10.45 | 695 | 9.94  |        |
| ≥10 (N3)                               | 887 | 5.76  | 450 | 5.36  | 437 | 6.25  |        |
| Missing data                           | 1595| 10.36 | 821 | 9.78  | 774 | 11.07 |        |
| Lymphovascular invasion                |    |       |    |       |    |       |        |
| Yes                                    | 270 | 1.75  | 155 | 1.85  | 115 | 1.64  | 0.099 |
| No                                     | 6873| 44.64 | 3594| 42.81 | 3279| 46.88 |        |
| Missing data                           | 8246| 53.55 | 4646| 55.34 | 3600| 51.47 |        |
| Tumor grade                            |    |       |    |       |    |       |        |
| I                                      | 554 | 3.60  | 292 | 3.48  | 262 | 3.75  | 0.588 |
| II                                     | 5384| 34.97 | 2776| 33.07 | 2608| 37.29 |        |
| III                                    | 1893| 12.29 | 1002| 11.94 | 891 | 12.74 |        |
| Uncertain                              | 1546| 10.04 | 785 | 9.35  | 761 | 10.88 |        |
| Missing data                           | 5988| 38.89 | 3527| 42.01 | 2461| 35.19 |        |
| ER+/PR+                                |    |       |    |       |    |       |        |
| Yes                                    | 7269| 50.46 | 4236| 40.43 | 2828| 41.25 | <0.001 |
| No                                     | 7324| 45.21 | 3795| 35.35 | 3731| 52.56 |        |
| Missing data                           | 796 | 4.34  | 364 | 6.22  | 435 | 6.19  |        |
| ER+/PR−                                |    |       |    |       |    |       |        |
| Yes                                    | 1722| 8.29  | 696 | 14.20 | 993 | 14.41 | <0.001 |
| No                                     | 12,871| 87.21 | 7321| 79.40 | 5553| 79.40 |        |
| Missing data                           | 796 | 4.50  | 378 | 6.41  | 448 | 6.19  |        |
| ER−/PR+                                |    |       |    |       |    |       |        |
| Yes                                    | 1722| 5.28  | 443 | 3.33  | 233 | 14.41 | <0.001 |
| No                                     | 12,871| 90.22 | 7574| 90.26 | 6313| 79.40 |        |
| Missing data                           | 796 | 4.50  | 378 | 6.41  | 448 | 6.19  |        |
| ER−/PR−                                |    |       |    |       |    |       |        |
| Yes                                    | 4916| 31.40 | 2636| 35.72 | 2498| 34.69 | <0.001 |
| No                                     | 9677| 64.26 | 5395| 58.06 | 4061| 59.12 |        |
| Missing data                           | 796 | 4.34  | 364 | 6.22  | 435 | 6.19  |        |
| HER2 status                            |    |       |    |       |    |       |        |
| Yes                                    | 2143| 13.92 | 1132| 13.48 | 1011| 14.46 | 0.015 |
| No                                     | 8063| 52.36 | 4496| 53.56 | 3567| 51.00 |        |
| Uncertain                              | 2475| 16.07 | 1257| 14.97 | 1218| 17.41 |        |
| Missing data                           | 2708| 17.59 | 1510| 19.99 | 1198| 17.13 |        |
| Triple-negative                        |    |       |    |       |    |       |        |
| Yes                                    | 2372| 15.40 | 1279| 15.24 | 1093| 15.63 | 0.502 |
| No                                     | 13,017| 84.54 | 7116| 84.76 | 5901| 84.37 |        |
| PS3 status                             |    |       |    |       |    |       |        |
| Yes                                    | 4213| 27.36 | 2152| 25.63 | 2061| 29.47 | <0.001 |
| No                                     | 2304| 14.96 | 1060| 12.63 | 1244| 17.79 |        |
| Missing data                           | 8872| 57.62 | 5183| 61.74 | 3689| 52.75 |        |
| Ki67                                   |    |       |    |       |    |       |        |
| ≥14                                    | 4772| 30.99 | 2534| 30.18 | 2238| 32.00 | 0.715 |
| 14                                     | 2712| 17.61 | 1452| 17.30 | 1260| 18.02 |        |
| Missing data                           | 7905| 51.34 | 4409| 52.52 | 3496| 49.99 |        |

(Continued)
The onset of the premenopausal peak is considered related to a birth cohort effect, resulting from changes in the menstrual and reproductive patterns and other lifestyle changes [20, 21]. Further research results in our study supported this possibility. First, multivariate logistic regression analysis indicated that other ethnicities and

### Table 4. Treatments of the patients with breast cancer.

| Characteristics          | Total (N = 15,389) | Premenopausal (N = 8395) | Postmenopausal (N = 6994) | P value |
|--------------------------|--------------------|--------------------------|---------------------------|---------|
|                          | N                  | %                        | N                         | %       | N                      | %                        |                    |
| **Chemotherapy**         |                    |                          |                           |         |                        |                          |                    |
| Yes                      | 12,437             | 80.77                    | 7141                      | 85.06   | 5296                   | 75.72                    | <0.0001 \(^1\) |
| No                       | 2294               | 14.90                    | 960                       | 11.44   | 1334                   | 19.07                    |         |
| Missing data             | 668                | 4.34                     | 294                       | 3.50    | 374                    | 5.35                     |         |
| **Radiotherapy**         |                    |                          |                           |         |                        |                          |                    |
| Yes                      | 2624               | 17.04                    | 1705                      | 20.31   | 919                    | 13.14                    | <0.0001 \(^1\) |
| No                       | 12,058             | 78.31                    | 6373                      | 75.91   | 5685                   | 81.28                    |         |
| Missing data             | 707                | 4.59                     | 317                       | 3.78    | 390                    | 5.58                     |         |
| **Anti-HER2 therapy**    |                    |                          |                           |         |                        |                          |                    |
| Yes                      | 136                | 0.88                     | 75                        | 0.89    | 61                     | 0.87                     | 0.978 \(^1\) |
| No                       | 14,571             | 94.63                    | 8018                      | 95.51   | 6553                   | 93.69                    |         |
| Missing data             | 682                | 4.43                     | 302                       | 3.60    | 380                    | 5.43                     |         |
| **Endocrine therapy**    |                    |                          |                           |         |                        |                          |                    |
| Yes                      | 4093               | 26.58                    | 2499                      | 29.77   | 1594                   | 22.79                    | <0.0001 \(^1\) |
| No                       | 10,584             | 73.42                    | 5574                      | 70.23   | 5406                   | 77.29                    |         |
| Missing data             | 712                | 4.62                     | 322                       | 3.84    | 390                    | 5.58                     |         |
| **Type of surgery**      |                    |                          |                           |         |                        |                          |                    |
| Modified radical mastectomy | 11,467           | 74.47                    | 6061                      | 72.20   | 5406                   | 77.29                    | <0.0001 \(^1\) |
| Breast-conserving surgery | 1582              | 10.27                    | 986                       | 11.75   | 596                    | 8.52                     |         |
| Simple mastectomy        | 793                | 5.15                     | 451                       | 5.37    | 342                    | 4.89                     |         |
| Radical mastectomy       | 196                | 1.27                     | 115                       | 1.37    | 81                     | 1.16                     |         |
| Extensive radical mastectomy | 103              | 0.67                     | 58                        | 0.69    | 45                     | 0.64                     |         |
| Breast reconstruction    | 380                | 2.47                     | 314                       | 3.74    | 66                     | 0.94                     |         |
| Missing data             | 868                | 5.64                     | 410                       | 4.88    | 458                    | 6.55                     |         |
| **Axillary lymph node dissection** |       |                          |                           |         |                        |                          |                    |
| Yes                      | 13,065             | 84.85                    | 7145                      | 85.11   | 5920                   | 84.64                    | 0.058 \(^1\) |
| No                       | 1575               | 10.23                    | 901                       | 10.73   | 674                    | 9.64                     |         |
| Missing data             | 749                | 4.66                     | 349                       | 4.16    | 400                    | 5.27                     |         |
| **Level of axillary lymph node dissection** | |                          |                           |         |                        |                          |                    |
| Level I, II              | 9504               | 61.72                    | 5220                      | 62.18   | 4284                   | 61.25                    | 0.485 \(^1\) |
| Level III                | 1867               | 12.12                    | 1009                      | 12.02   | 858                    | 12.27                    |         |
| Missing data             | 4018               | 26.09                    | 2166                      | 25.80   | 1852                   | 26.28                    |         |

\(^1\)Chi-square test.
Comparison of pre- and postmenopausal breast cancer

We found a significantly higher proportion of premenopausal breast cancer possibility (OR > 1, \( P < 0.05 \)). We also noted that a higher proportion of postmenopausal women had more than two births and a history of breastfeeding. A meta-analysis of 47 studies in 30 countries showed that breastfeeding could reduce the risk of breast cancer [25]. Bao concluded that increased numbers of births per woman were associated with a reduced risk of breast cancer for postmenopausal women [17]. We found the number of pregnancies was positively associated with risk of premenopausal breast cancer, but increased number of births decreased the risk of that. Because of the one-child policy and some other reasons, Chinese women may not to give a birth after pregnancy. Here come to a conclusion that only pregnancy but no childbirth might increase the risk of premenopausal breast cancer. We speculate that the fall in the fertility rate [26, 27], early menarche age, the married and less breastfeeding might have increased the possibility of premenopausal breast cancer.

A Westernized lifestyle, particularly an increase in the obesity prevalence and physical inactivity in recent decades, is likely to affect the observed rise in breast cancer incidence [28, 29]. Obesity was considered a mechanism of breast cancer in postmenopausal women [30]. These results guide postmenopausal women to adjust their diet, strengthen exercises, and reduce the risk factors of breast cancer that can be controlled artificially.

Breast cancer is age-dependent, and it is widely accepted that young women tend to present with a greater tumor size that is more advanced and with poorer prognostic features. Obesity is likely to affect the observed rise in breast cancer incidence [28, 29]. Obesity was considered a mechanism of breast cancer in postmenopausal women [30]. These results guide postmenopausal women to adjust their diet, strengthen exercises, and reduce the risk factors of breast cancer.

We further analyzed the difference in the pathological features between the two groups. The ER and PR status are important indicators to guide endocrine therapy in breast cancer. It is also an important factor affecting the prognosis of breast cancer [33, 34]. Wittliff studied the relationship between menopausal status and ER and reported that the positive expression of ER occurred at a rate of 45% in premenopausal women and at a rate of <63% in postmenopausal patients [35]. Anderson reported that ER-positive rates rose continuously irrespective of menopause [36]. However, we found the opposite. That is, the positive expression of ER occurred at a rate of 59% in premenopausal women and was higher than 55% in postmenopausal patients. We also found that postmenopausal patients had higher proportions of

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**Table 5. Multivariate logistic regression analysis of premenopausal breast cancer-related risk factors.**

| Factors                        | B     | SE   | \( \chi^2 \) | P value | OR (95% CI) |
|-------------------------------|-------|------|--------------|---------|-------------|
| Ethnicity                     |       |      |              |         |             |
| Han‡                          | 0.87  | 0.091| 91.048       | <0.001  | 2.388       |
| Other                         |       |      |              |         |             |
| Age at menarche               |       |      |              |         |             |
| ≤10†                          |       |      |              |         |             |
| 11–12                         | −1.038| 0.413| 6.33         | 0.012   | 0.354       |
| 13–14                         | −1.013| 0.141| 51.852       | <0.001  | 0.363       |
| 15–16                         | −0.71 | 0.133| 28.356       | <0.001  | 0.492       |
| 17–18                         | −0.6  | 0.135| 19.673       | <0.001  | 0.549       |
| ≥19                           | −0.295| 0.143| 4.243        | 0.039   | 0.745       |
| Marital status                |       |      |              |         |             |
| Married¹                      | −0.88 | 0.138| 40.648       | <0.001  | 0.415       |
| Never married                 | −1.832| 0.256| 51.151       | <0.001  | 0.16        |
| Widowed/divorced              |       |      |              |         |             |
| Number of pregnancies         |       |      |              |         |             |
| 0†                            | 0.49  | 0.095| 26.637       | <0.001  | 1.632       |
| 2                             | 0.668 | 0.081| 67.892       | <0.001  | 1.95        |
| 3                             | 0.359 | 0.078| 21.342       | <0.001  | 1.432       |
| Number of births              |       |      |              |         |             |
| 0†                            | −2.895| 0.214| 183.38       | <0.001  | 0.055       |
| 2                             | −3.071| 0.204| 149.986      | <0.001  | 0.082       |
| 3                             | −4.296| 0.204| 225.333      | <0.001  | 0.036–0.084 |
| 4                             | −1.48 | 0.081| 50.452       | <0.001  | 0.228       |
| ≥5                            | −0.835| 0.228| 13.392       | <0.001  | 0.434       |

Legend:

†Referent.
positive HER2 expression and positive P53 expression. Scholars have reported a negative correlation between the positive expression of ER and positive HER2 status [37, 38]. We obtained similar results. Those results are similar to that in another article from the same database [32]. Additionally, higher proportion of (ER+/PR+) in premenopausal patients and higher proportion of (ER−/PR−) in postmenopausal patients suggested that the distribution of hormone receptors in western Chinese women is different from that in foreign countries. The reasons for the difference in the expression of hormone receptor may be as follows: (1) the proportion of premenopausal and postmenopausal women with breast cancer in China is opposite of that in foreign countries [15]; (2) the stimulation of different human populations and the external environment affect the expression of hormone receptor; and (3) pregnancy and childbirth lead to the fluctuation of estrogen and progesterone levels, which affect the expression of hormone receptor. The relationship between menopause and ER and PR remains controversial, and we need more large-scale studies to clarify their relationship.

Regarding treatment options, we compared the following five aspects between the two groups: surgery, chemotherapy, radiotherapy, endocrine therapy, and anti-HER2 therapy. First, we found that 94% of all patients underwent surgery. Regarding the choice of surgical approach, a higher proportion of premenopausal patients underwent advanced operation methods, such as breast-conserving surgery and breast reconstruction. A possible explanation was that younger patients have a greater desire to keep their original breasts and shapes and are more accepting of advanced operation methods compared to postmenopausal patients [39]. Second, we found that there are more premenopausal patients receiving chemotherapy. Chemotherapy is one of the most commonly used and most effective methods among adjuvant therapies for treating breast cancer. Premenopausal patients had a smaller average age, higher malignancy, and risk of recurrence of the tumors [32], and it was reported that chemotherapy can significantly reduce the risk of relapse of high malignant breast cancer [34, 40], so they could benefit more from chemotherapy. The discovery of more aggressive cancers found in premenopausal women is the fact that leads to more chemotherapy in this population. Third, we found that a higher proportion of premenopausal patients receiving radiotherapy, as radiotherapy is necessary after breast-conserving surgery, and that the proportion of premenopausal patients receiving breast-conserving surgery were higher. Additionally, adjuvant radiotherapy after surgery significantly reduces the local recurrence rate and increases the overall survival rate [41]. Similarly, the proportion of premenopausal patients receiving endocrine therapy was significantly higher than that of postmenopausal patients.

The increased use of endocrine therapy may be due to the fact that endocrine therapy is suitable for hormone receptor-positive breast cancer and significantly reduces the recurrence rate [42], and the proportion of (ER+/PR+) in premenopausal patients was significantly higher. Finally, this study showed that very few patients with a positive HER2 status accepted anti-HER2 therapy. The possible reason may be that the HER2 testing condition is deficient in local areas. Additionally, anti-HER2 therapy is not included in health care, indicating that it is a costly burden in western China.

Limitations

Our study had some limitations. First, all patients included were from nine provinces of western China; thus, the results may not be generalizable to all women in China. Second, data regarding some characteristics, such as HER2 status, BMI, breastfeeding history, tumor location, P53 status, and Ki67 status, were missing, which may have underpowered the study. Another limitation is that we failed to follow up the patients. As a result, we cannot analyze the relationship between prognosis and clinicopathologic features.

Conclusion

In this study, we found that the fall in the fertility rate, early menarche age, married, and less breastfeeding might have increased the possibility of premenopausal breast cancer. Significant differences exist in the tumor size, hormone receptor state, HER2 expression, epidemiological features, and treatment modes between premenopausal and postmenopausal female breast cancer patients in western China. The difference in breast cancer onset period remains to be investigated in the further studies.

Ethical Approval

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

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Conflict of Interest

The authors have no disclosures.
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