Clinicopathological Features of Breast Cancer in Relation to Exposure of Cycling Reproductive Hormones: A Multicenter Retrospective Study of 14 731 Patients Diagnosed with Invasive Breast Cancer

Jiazheng Sun, Jinxiang Tan, Hong Zheng, Jun Jiang, Tianning Zou, Hongyuan Li, Guosheng Ren, Dejuan Yang

Corresponding Authors: Dejuan Yang, e-mail: cyydj.200622@163.com; Guosheng Ren, e-mail: rengs726@126.com

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Background: The reproductive period for women begins at menarche and ends at menopause, representing the total time period of exposure to cycling reproductive hormones. The potential associations between clinicopathological features and exposure of cycling reproductive hormones has not been extensively studied. This retrospective study enrolled 14 731 patients diagnosed with invasive breast cancer and was designed to evaluate factors associated with the reproductive period on breast cancer type and patient outcomes.

Material/Methods: A total of 14 731 female breast cancer patients from the Western China Clinical Cooperation Group from January 1, 2008, to December 31, 2017, were enrolled. Unconditional logistic regression was performed to assess the associations between clinicopathological features and menarche age, menopause age, and reproductive years. The differences in risk factors between lower and higher number of reproductive years (<35 and ≥35 years) were examined with the chi-square test.

Results: First, patients with late menarche age were more likely to present with tumors of higher histological grade and larger size. Second, the findings suggested a higher likelihood of smaller tumor size in postmenopausal patients with a greater length of reproductive years. Conversely, higher histological grade was associated with this group of patients, compared with their counterparts with shorter reproductive years. Third, patients with luminal breast cancer with a greater length of reproductive years were more likely to present larger tumors.

Conclusions: Our findings indicated that several clinicopathologic factors, including tumor size and histological grade, were associated with the length of reproductive years in patients diagnosed with breast cancer.

Keywords: Breast Neoplasms • Menarche • Menopause

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Background

Breast cancer is the most common cancer type and the leading cause of cancer-related death in women. In 2020, a total of 2,261,419 new cases of breast cancer were diagnosed worldwide, accounting for 24.5% of all cancer types and 684,996 resulting deaths (representing 15.5% of all deaths) reported among female patients [1]. Breast cancer is widely acknowledged as a serious threat to female health in developing and developed countries worldwide [2]. In China, 268,625 new cases of breast cancer were diagnosed (accounting for 15.09% of all cancer types) in women and 69,495 resulting deaths (6.92% of all cancer-related deaths) were reported during 2015 [3]. Clarification of the epidemiological and clinicopathological characteristics of breast cancer is essential to improve treatment options.

Menarche and menopause are markers of onset and cessation, respectively, of ovarian and reproduction-correlated endocrine activity [4]. After menarche, the ovaries begin to produce steroid hormones that directly affect the development of the breasts. After menopause, when steroid hormone levels plummet, the breast begins to enter into recession [5]. Previous studies have proposed that the risk of breast cancer in women increases with time of exposure to reproductive hormones [6]. Early age at menarche and late age at menopause may therefore be associated with an increased risk of breast cancer [7]. The reliability of these associations has been supported by a meta-analysis conducted by the Collaborative Group on Hormonal Factors in Breast Cancer [8]. In early epidemiological studies, the duration of reproductive years was defined as the period between menarche and menopause and was considered as a risk factor of breast cancer [9,10]. To some extent, the length of reproductive years represents the length of exposure to cycling reproductive hormones, calculated from age at menarche to age at menopause. Cycling reproductive hormones are recognized as a causal factor in the etiology of breast cancer and play an important role in the initiation and promotion of neoplastic growth [11,12]. However, the potential associations between clinicopathological features and the exposure of cycling reproductive hormones has not been extensively studied. In addition, previous studies have mainly focused on the associations between menarche/menopause age and breast cancer risk; whereas, the correlations between tumor clinicopathological features and menarche and menopause age have rarely been reported [4]. Therefore, this retrospective study examined data on 14,731 patients diagnosed with invasive breast cancer between January 2008 and December 2017 from 23 breast cancer centers in 9 provinces of China and aimed to evaluate factors associated with the reproductive period on the development of breast cancer type and patient outcomes.

Material and Methods

Study Population

This multicenter retrospective study was supported by 23 breast cancer centers from 9 provinces of China (Chongqing, Yunnan, Sichuan, Guizhou, Gansu, Shanxi, Guangxi, Ningxia, and Xinjiang). On the basis of the exclusion criteria (Figure 1), a total of 14,731 female patients with invasive breast cancer diagnosed based on pathological examinations from January 1, 2008, to December 31, 2017, were enrolled. We restricted analyses comparing clinicopathological features of breast cancer in premenopausal and postmenopausal women with menarche from ages 11 to 18 years. Women who had natural menopause and had undergone bilateral oophorectomy were categorized as postmenopausal, otherwise they were categorized as premenopausal. In addition, women regularly using combined oral contraceptive pills and postmenopausal hormone replacement therapy were excluded. After screening, a total of 14,438 female patients were included and divided into 2 groups: premenopausal (n=8631) and postmenopausal (n=5807). All the study protocols were endorsed by the Ethics Committee of Chongqing Medical University and the other breast cancer centers.

Data Collection

Patients were queried about their pregnancies and outcomes, the time that each pregnancy was completed, whether the baby was breastfed, and the duration of breastfeeding. Additionally, patients were asked the age at first menstruation and whether they were postmenopausal. If so, they were queried to indicate the reason for menopause (natural, surgical, or other) and the age at which menopause happened. Records of other risk factors, initial disease symptoms and signs, clinical characteristics, pathological characteristics, and imageological features were obtained for all patients with invasive breast cancer from 23 breast cancer centers. Pre- and post-surgery pathological characteristics, including estrogen receptor (ER) expression, progesterone receptor (PR) expression, and human epidermal growth factor receptor 2 (HER2) expression were examined by pathologists with the aid of commercial immunohistochemistry (IHC) tests at the immunohistochemistry core laboratory of each breast cancer center.

Determination of Risk Factors

Data on risk factors of patients were obtained from electronic medical records by professional clinicians, following the same protocol. The reference time was the time of first diagnosis. All risk factors were classified based on China’s national conditions. Menopause status was evaluated on the basis of the
inquiry at the time of first diagnosis. Based on the median age of menarche and menopause, the patients were divided into different groups. Increased risk of breast cancer in women has been suggested with longer exposure to cycling reproductive hormones. Therefore, a combination of early menarche and late menopause could increase the risk of breast cancer [4]. To some extent, the length of reproductive years represents the period of exposure to the cycling reproductive hormones, calculated as age at menarche to age at menopause [10]. In the current study, postmenopausal patients were subdivided into 2 groups: reproductive years <35 years (n=2417) and reproductive years ≥35 years (n=2974). The average ages at diagnosis of the 2 groups were 57 and 60 years, respectively. Depending on the criteria set by the Chinese National Health and Family Planning Commission, body mass index was categorized into 4 grades: underweight (<18.5 kg/m²), normal weight (18.5-23.9 kg/m²), overweight (24-27.9 kg/m²), and obese (≥28 kg/m²) [13]. In addition, the demographic composition of the Chinese population was fully considered during categorization of other risk factors. The race/ethnicity of included patients was classified into 4 groups: Han, Uighur, Hui, and others (including Tujia, Manchu, Bouyi, and other groups). Concomitantly, the time of pregnancy and parity were categorized as 0, 1, 2, or ≥3. Ovariectomy, hysterectomy, and family history of cancer were binary variables, all of which were also considered.

**Determination of Biological Characteristics**

IHC tests were used to define ER, PR, and HER2 status. While HER2 results were generally defined based on IHC analyses, fluorescence in situ hybridization (FISH) was used in some cases, especially for patients with CerbB-2 (IHC) scores of 2+. Patients with CerbB-2 (IHC) scores of 3+ or FISH positivity were determined as HER2-positive and those with negative or 1+ CerbB-2 (IHC) scores or FISH negativity as HER2-negative. In cases in which CerbB-2 (IHC) and FISH data were inconsistent, FISH results were preferentially used. ER status and PR status were obtained from IHC analyses. In our study, ER status and PR status were successfully evaluated in nearly 95% of patients. Specifically, 7143 (49.47%) patients were determined as ER+ and PR+; 4294 (29.74%) as ER- and PR-; 1653 (11.45%) as ER+ and PR-; and 628 (4.35%) as ER- and PR-. Based on immunohistochemical staining of breast cancer tissues, postmenopausal patients were categorized as luminal (ER+/PR+), HER2-overexpressing (ER-/PR-/HER2+), and triple-negative (ER-/PR-/HER2-) subtypes [14-16]. The nuclear protein Ki67 and the tumor protein p53 (P53) labeling analyses were additionally included. According to the St. Gallen International Expert Consensus of 2013, the cutoff value of Ki67 was defined as 20% [17]. However, due to the significant amount of missing data on Ki67, both luminal A and B were classified as the luminal group. Compared with luminal tumors, triple-negative and HER2-overexpressing tumors...
are more aggressive subtypes related to poorer 5-year survival [18-20]. Subgroup analysis was based on 5391 patients, including 3201 luminal (59.38%), 396 HER2-overexpressing (7.35%), and 1139 triple-negative (21.13%) cases.

### Statistical Analysis

The differences in risk factors between groups with shorter length of reproductive years (<35 years) and greater length of reproductive years (≥35 years) were examined with the chi-square test. Case-case associations of clinicopathological features among early menarche (<14 years) vs late menarche (≥14 years) premenopausal and postmenopausal women were evaluated using a multivariate logistic regression model. Additionally, early menopause (<50 years) vs late menopause (≥50 years) and shorter length of reproductive years (<35 years) vs greater length of reproductive years (≥35 years) groups were evaluated among postmenopausal women via multivariate logistic regression. Subgroup analyses included triple-negative breast cancer, luminal, and HER2-overexpression breast cancer; multivariate logistic regression analyses were applied to each individual subgroup during subgroup analysis. The variables identified as significant with univariate analysis (P<0.05) were included in the multivariate model. All statistical analyses were performed using SAS 9.4.0. (SAS Institute Inc, Cary, NC, USA). The statistical significance of our findings was evaluated using 2-tailed tests and the significance level set at P<0.05.

### Results

#### Cohort Characteristics

A total of 14 438 female breast cancer patients (including 8631 premenopausal and 5807 postmenopausal patients) were enrolled. The distribution of menopause and menarche ages is shown in **Figure 2**. The median age at menarche was 14 years from all patients, and 52.4% had onset of menstruation at 13 or 14 years of age (**Figure 2A**). In postmenopausal patients, median age at menopause was 50 years, with 61.5% reporting menopause at 48 to 52 years of age (**Figure 2B**).

#### Menarche Age and Tumor Clinicopathological Features

In multivariate logistic regression analyses of the association between menarche age and tumor characteristics, more aggressive tumors were associated with late menarche age of patients with breast cancer. In particular, patients with late menarche
age were more likely to present with tumors of higher histological grade and later local staging ($P=0.0027$ and $P=0.0317$, respectively, Table 1). Multivariate logistic regression analyses conducted among premenopausal and postmenopausal patients consistently revealed higher histological grades in premenopausal patients with late menarche age. In contrast, no association between menarche age and clinicopathological features among postmenopausal patients was discovered (Table 1). The crude analyses suggested an extremely weak association between menarche age and clinicopathological features of breast cancer among postmenopausal patients.

**Menopause Age, Reproductive Year, and Tumor Clinicopathological Features**

Accordingly, we further assessed the relationships of menopause age and length of reproductive years with tumor characteristics. The results showed no association between menopause age and clinicopathological features of breast cancer, except the expression of PS3, but showed a definite correlation between length of reproductive years and tumor features. Similar to previous analyses of associations between menopause age and tumor features, our findings suggested a higher likelihood of smaller tumor size in postmenopausal patients with a greater length of reproductive years ($P=0.0105$, Figure 3). Conversely, higher histological grade was associated with this group of patients, compared with their counterparts with shorter reproductive years ($P=0.0218$, Figure 3). In view of these findings, we speculated that the duration of reproductive years was a more valuable predictor than menarche and menopause ages, especially in postmenopausal patients.

It is well known that breastfeeding history and number of full-term pregnancies impact the length of exposure to cycling reproductive hormones. To reduce the impact of heterogeneity, we conducted a comparison of hormonal risk factors, including parity and breastfeeding history, between the groups with different reproductive year lengths via the chi-square test. Analysis of the results indicated no differences in times of parity and breastfeeding of babies between the groups. While ethnic composition analysis suggested statistical differences between the 2 groups, the heterogeneity may have had no effect on the association between length of reproductive years and tumor characteristics, as more than 95% of patients were Han Chinese ($P=0.0003$, Table 2). In addition, the proportion of patients with ovariectomy or hysterectomy was higher in the shorter reproductive years group relative than in the greater length of reproductive years group (1.20% vs 0.64%, $P=0.0158$; 10.34% vs 2.69%, $P<0.0001$, Table 2).

**Subgroup Analysis**

Based on the categorization of postmenopausal patients with breast cancer, subgroup analysis was conducted. Most associations between length of reproductive years and tumor clinicopathological characteristics were observed for luminal and triple-negative breast cancer types. In analyses stratified by tumor subtype, a negative association between length of reproductive years and tumor size was detected specifically in luminal breast cancer ($P=0.0328$, Table 3). In triple-negative breast cancer, a greater number of reproductive years was associated with lower detection rate of calcification and reduced expression of PS3, compared with the group with shorter length of reproductive years ($P=0.0052$ and $P=0.0034$, respectively, Figure 4). Multivariate logistic regression analyses suggested an association between patients with more reproductive years and advanced axillary lymph node metastasis ($P=0.0429$, Figure 4).

**Discussion**

Menarche, a marker of the onset of puberty, signifies the beginning of the female reproductive years. After menarche, the ovaries begin to produce steroid hormones that directly affect development of the breast. Conversely, menopause is the symbol of perpetual cessation of menstrual cycles. After menopause, circulating hormone levels are altered and various changes occur in the reproductive organs, such as ovarian aging, vulvovaginal atrophy, and breast atrophy [21-25].

Our hospital-based study involved 14 438 female breast cancer patients, including 8631 premenopausal and 5807 postmenopausal patients. We analyzed the differences in clinicopathological features between patients with different menarche and menopause ages and length of reproductive years. In multivariate logistic regression analyses, female breast cancer patients with late menarche age were more likely to have a higher histological grade and larger tumor size. By multivariate analysis, we indicated that patients with higher menarche age were more likely to have higher histological grade and larger size tumor. Similar to our study, a study by Song et al showed that a number of reproductive factors, including older age at menarche, shorter time since the last birth, and greater number of offspring, were correlated with poorer survival, with significant associations among hormone receptor and human epidermal growth factor 2-positive breast cancer cases [26]. Meanwhile, the study by Ritte et al showed women with an early menarche age (<13 years) had a 2-fold increased risk of ER+/PR+ breast cancer relative to those with late menarche age (≥13 years) [27]. Although our study lacked prognostic evaluation, higher histological grade and larger tumor size are clearly suggestive of poor prognosis in breast cancer [28-31]. However, menarche age is not universally beneficial for prognosis. Analyses of premenopausal and postmenopausal patients showed that premenopausal patients with a late menarche age also had tumors with a higher histological grade.

**Table 1**

| Characteristics | Premenopausal | Postmenopausal | P-value |
|-----------------|--------------|---------------|---------|
| Menarche age    |              |               |         |
| Menopause age   |              |               |         |
| Reproductive year |             |               |         |

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Table 1. Comparison of clinicopathologic characteristics between menarche age <14 yrs and ≥14 yrs breast cancer patients.

| Tumor characters          | All patients | Premenopausal patients | Postmenopausal patients |
|---------------------------|--------------|------------------------|-------------------------|
|                           | No. of menarche age <14/≥14 (ref) patients | Odds ratio (95% CI) | P-value | No. of menarche age <14/≥14 (ref) patients | Odds ratio (95% CI) | P-value | No. of menarche age <14/≥14 (ref) patients | Odds ratio (95% CI) | P-value |
| Special type breast cancer| No           | 5129/7933              | 1.0                    |         | 3283/4500              | 1.0                  |         | 1846/3433              | 1.0                  |         |
|                           | Yes          | 202/292                | 1.11 (0.65, 1.92)      | 0.7014  | 132/176                | 1.21 (0.57, 2.57)    | 0.611   | 70/116                  | 1.05 (0.44, 2.49)   | 0.9192 |
|                           | Unknown      | 375/507                |                       |         | 257/283                |                       |         | 118/224                 |                       |         |
| Tumor histology           | Ductal carcinoma | 4155/6718              | 1.0                    |         | 2654/3896              | 1.0                  |         | 1501/2822              | 1.0                  |         |
|                           | Lobular carcinoma | 123/191                | 0.59 (0.33, 1.03)      | 0.0622  | 84/107                | 0.51 (0.23, 1.12)    | 0.0948  | 39/84                  | 0.75 (0.33, 1.71)   | 0.4939 |
|                           | Medullary carcinoma | 72/115                | 1.23 (0.32, 4.78)      | 0.768   | 56/77                | 1.34 (0.19, 9.54)    | 0.7702  | 16/38                  | 1.29 (0.17, 9.55)   | 0.8044 |
|                           | Mucinous carcinoma | 128/176                |                       |         | 74/99                |                       |         | 54/77                  |                       |         |
|                           | Mix           | 90/148                 | 0.39 (0.04, 3.50)      | 0.3977  | 63/98                | 0.40 (0.04, 3.97)    | 0.4322  | 27/50                  | <0.001 (0.001, >999.999) | 0.9915 |
|                           | Unknown       | 1138/1348              |                       |         | 741/682              |                       |         | 397/702                |                       |         |
| Nerve invasion            | No            | 3119/4408              | 1.0                    |         | 1938/2371              | 1.0                  |         | 1181/2037              | 1.0                  |         |
|                           | Yes           | 14/23                  | 1.35 (0.19, 9.69)      | 0.7641  | 10/14                | 0.95 (0.06, 15.39)   | 0.9711  | 4/9                    | 2.22 (0.12, 41.56)   | 0.5949 |
|                           | Unknown       | 2573/4301              |                       |         | 1724/2574              |                       |         | 849/1727               |                       |         |
| Vascular invasion         | No            | 3047/4254              |                       |         | 1896/2286              |                       |         | 1151/1968              |                       |         |
|                           | Yes           | 92/179                 | 0.98 (0.55, 1.73)      | 0.945   | 59/106                | 1.62 (0.73, 3.57)    | 0.2361  | 33/73                  | 0.55 (0.21, 1.43)    | 0.2205 |
|                           | Unknown       | 2567/4299              |                       |         | 1708/2567              |                       |         | 859/1732               |                       |         |
| Calcification             | No            | 1618/2153              | 1.0                    |         | 993/1111              | 1.0                  |         | 625/1042              | 1.0                  |         |
|                           | Yes           | 1401/2102              | 0.92 (0.79, 1.08)      | 0.3057  | 852/1171              | 0.87 (0.71, 1.07)    | 0.1903  | 549/931                | 0.96 (0.76, 1.21)    | 0.6976 |
|                           | Unknown       | 2687/4477              |                       |         | 1827/2677              |                       |         | 860/1800               |                       |         |
| Histological grade       | I             | 231/300                | 1.0                    |         | 140/169                | 1.0                  |         | 91/131                 | 1.0                  |         |
|                           | II            | 2248/3195              | 0.92 (0.75, 1.13)      | 0.4083  | 1387/1716              | 0.74 (0.57, 0.98)    | 0.0348  | 861/1479               | 1.28 (0.93, 1.77)    | 0.1351 |

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Table 1 continued. Comparison of clinicopathologic characteristics between menarche age <14 yrs and ≥14 yrs breast cancer patients.

| Tumor characters | All patients | Premenopausal patients | Postmenopausal patients |
|------------------|--------------|------------------------|-------------------------|
|                  | No. of menarche age <14/³14 (ref) patients | Odds ratio (95% CI) | P-value | No. of menarche age <14/³14 (ref) patients | Odds ratio (95% CI) | P-value | No. of menarche age <14/³14 (ref) patients | Odds ratio (95% CI) | P-value |
| III              | 760/1215     | 0.66 (0.50, 0.86)      | 0.0027 | 469/659 | 0.48 (0.33, 0.70) | 0.0001 | 291/556 | 1.07 (0.70, 1.64) | 0.7617 |
| Unknown          | 2467/4022    |                        |        | 1676/2415 |                      |    | 791/1607 |                        |        |
| Tumor size       |              |                        |        |          |                        |    |          |                        |        |
| T1 (≤20 mm)      | 1616/2190    | 1.0                    |        | 1002/1190 | 1.0                    |        | 614/1000 | 1.0                    |        |
| T2 (20 mm<d≤50 mm)| 2188/3390    | 0.92 (0.62, 1.37)      | 0.6851 | 1397/1873 | 1.01 (0.57, 1.80)     | 0.9625 | 791/1517 | 0.86 (0.49, 1.51)     | 0.5916 |
| T3 (>50 mm)      | 246/387      | 0.86 (0.49, 1.51)      | 0.6013 | 161/235 | 0.87 (0.40, 1.88)     | 0.7173 | 85/152 | 0.85 (0.36, 1.98)     | 0.7035 |
| T4               | 82/161       | 0.19 (0.04, 0.86)      | 0.0317 | 46/85 | 0.71 (0.12, 4.24)     | 0.7039 | 508/76 | 0.999 (0.001, >999.999) | 0.9716 |
| Unknown          | 1574/2604    |                        |        | 1066/1576 |                      |    | 508/1028 |                        |        |
| ALNM             |              |                        |        |          |                        |    |          |                        |        |
| N0               | 2441/3526    | 1.0                    |        | 1557/1947 | 1.0                    |        | 884/1579 | 1.0                    |        |
| N1               | 1151/1818    | 0.99 (0.83, 1.19)      | 0.9484 | 763/1062 | 0.95 (0.75, 1.21)     | 0.6879 | 388/756 | 1.00 (0.76, 1.31)     | 0.9817 |
| N2               | 456/717      | 1.09 (0.84, 1.42)      | 0.5119 | 294/402 | 0.96 (0.67, 1.36)     | 0.8002 | 162/315 | 1.26 (0.83, 1.91)     | 0.2863 |
| N3               | 281/400      | 0.97 (0.69, 1.36)      | 0.8533 | 154/218 | 0.68 (0.40, 1.15)     | 0.1487 | 127/182 | 1.42 (0.90, 2.24)     | 0.1316 |
| Unknown          | 1377/2271    |                        |        | 904/1330 |                      |    | 473/941 |                        |        |
| Distant metastasis|            |                        |        |          |                        |    |          |                        |        |
| M0               | 4254/6362    | 1.0                    |        | 2723/3573 | 1.0                    |        | 1531/2789 | 1.0                    |        |
| M1               | 43/50        | 1.86 (0.60, 5.71)      | 0.2799 | 22/23 | 2.34 (0.37, 14.90)    | 0.3664 | 21/27 | 2.63 (0.58, 11.96)    | 0.2105 |
| Unknown          | 1409/2420    |                        |        | 927/1363 |                      |    | 482/957 |                        |        |
| Lymph nodes diameter (mm) |                  |                        |        |          |                        |    |          |                        |        |
| ≤15              | 798/1035     | 1.0                    |        | 494/585 | 1.0                    |        | 304/450 | 1.0                    |        |
| >15, ≤20         | 787/1095     | 1.11 (0.89, 1.38)      | 0.3774 | 484/563 | 1.31 (0.97, 1.78)     | 0.0836 | 303/352 | 0.92 (0.66, 1.28)     | 0.6109 |
| >20, ≤30         | 1135/1652    | 1.06 (0.69, 1.62)      | 0.8029 | 724/862 | 1.37 (0.75, 2.52)     | 0.3098 | 411/790 | 0.73 (0.39, 1.36)     | 0.3248 |
| >30              | 886/1358     | 1.14 (0.74, 1.76)      | 0.5599 | 550/761 | 1.28 (0.69, 2.37)     | 0.4361 | 336/597 | 0.90 (0.47, 1.70)     | 0.737 |
| Unknown          | 2100/3592    |                        |        | 1421/2188 |                      |    | 679/1404 |                        |        |
| ER               |              |                        |        |          |                        |    |          |                        |        |
| Negetive         | 1979/2975    | 1.0                    |        | 1230/1583 | 1.0                    |        | 749/1392 | 1.0                    |        |
| Tumor characters | All patients | Premenopausal patients | Postmenopausal patients |
|------------------|--------------|------------------------|------------------------|
|                  | No. of menarche age <14 yrs (ref) patients | Odds ratio (95% CI) | P-value | No. of menarche age <14 yrs (ref) patients | Odds ratio (95% CI) | P-value | No. of menarche age <14 yrs (ref) patients | Odds ratio (95% CI) | P-value |
| Positive         | 3487/5354 | 0.90 (0.72, 1.13) | 0.3726 | 2278/3134 | 0.81 (0.58, 1.13) | 0.2223 | 1209/2219 | 1.04 (0.75, 1.43) | 0.8225 |
| Unknown          | 240/403  | 1.00 | 1.00  | 164/242  | 0.97 (0.71, 1.32) | 0.834 | 76/162  | 1.00 | 1.00  |
| PR               |            |            |            |            |            |            |            |            |            |
| Negative         | 2336/3462 | 1.00 | 1.00  | 1340/1802 | 1.00 | 1.00  | 996/1840 | 1.00 | 1.00  |
| Positive         | 3125/4673 | 1.13 (0.91, 1.40) | 0.2753 | 2116/2906 | 1.15 (0.84, 1.58) | 0.3818 | 1009/1767 | 0.97 (0.71, 1.32) | 0.834 |
| Unknown          | 245/417 | 1.00 | 1.00  | 166/251 | 0.97 (0.71, 1.32) | 0.834 | 79/166 | 1.00 | 1.00  |
| HER2             |            |            |            |            |            |            |            |            |            |
| Negative         | 2988/4450 | 1.00 | 1.00  | 1931/2594 | 1.00 | 1.00  | 1056/1856 | 1.00 | 1.00  |
| Positive         | 1903/2829 | 1.06 (0.91, 1.24) | 0.4556 | 1179/1491 | 1.00 (0.81, 1.23) | 0.9819 | 724/1338 | 1.17 (0.92, 1.48) | 0.1936 |
| Unknown          | 815/1453 | 1.00 | 1.00  | 561/874 | 1.00 | 1.00  | 254/579 | 1.00 | 1.00  |
| Ki67             |            |            |            |            |            |            |            |            |            |
| ≤20%             | 1487/2076 | 1.00 | 1.00  | 911/1057 | 1.00 | 1.00  | 576/1009 | 1.00 | 1.00  |
| >20%             | 1321/1855 | 0.99 (0.84, 1.17) | 0.9147 | 853/1001 | 0.90 (0.72, 1.12) | 0.3569 | 468/864 | 1.03 (0.81, 1.32) | 0.8157 |
| Unknown          | 2898/4801 | 1.00 | 1.00  | 1908/2901 | 1.00 | 1.00  | 990/1900 | 1.00 | 1.00  |
| P53              |            |            |            |            |            |            |            |            |            |
| Negative         | 1210/1488 | 1.00 | 1.00  | 700/768 | 1.00 | 1.00  | 510/720 | 1.00 | 1.00  |
| Positive         | 1749/2365 | 0.93 (0.79, 1.09) | 0.3874 | 1095/1267 | 0.94 (0.75, 1.17) | 0.5568 | 654/1098 | 0.91 (0.71, 1.15) | 0.4145 |
| Unknown          | 2747/4879 | 1.00 | 1.00  | 1877/2924 | 1.00 | 1.00  | 870/1955 | 1.00 | 1.00  |

However, no associations were evident between menarche age and clinicopathological features among postmenopausal patients. To ascertain why menarche age was not related to tumor features and to identify the associated hormonal risk factors in postmenopausal patients, we further examined the correlations among menopause age, length of reproductive years, and tumor characteristics. Interestingly, our data indicated no associations between menopause age, histological grade, and tumor size. Notably, greater length of reproductive years was correlated with lower tumor size but higher histological grade. In postmenopausal female patients with breast cancer, the length of reproductive years, defined as the period between menarche and menopause ages, may be a more valuable prognostic factor of clinical outcome than either menarche or menopause age. Several studies reported some reproductive factors on risk of breast cancer, such as early menarche, nulliparity and late menopause, which is consistent with the findings from our study [32]. Furthermore, Olsson et al reported that cyclic hormonal stimulation of breast tissue is likely the most significant hormonal factor contributing to breast cancer. Additionally, the first full-term pregnancy affects the long-term hormonal levels including increased sex hormone-binding globulin and decreased prolactin and estrogen, which probably provide further protection against breast cancer [33]. Hormonal risk factors of breast cancer include late menopause, low and/or late parity, early menarche, postmenopausal hormone replacement therapy, and use of combined oral contraceptive pills, all of which affect survival [8,34–36]. In this study, all hormonal risk factors, except menopause and menarche age (times of parity and breastfeeding baby), were confounders. To assess heterogeneity, we analyzed the differences in population characteristics between postmenopausal...
### A. Correlated of late menopause age

| Tumor characters          | No. of menopause age ≥50/<35 (ref) patients | Odds ratio (95% CI) | P-value |
|---------------------------|--------------------------------------------|---------------------|---------|
| Special type breast cancer|                                            |                     |         |
| No                        | 2387/1244                                  | 1.24 (0.54, 2.85)   | 0.6115  |
| Yes                       | 98/88                                      |                     | 2168/2612 |
| Tumor histology           |                                            |                     |         |
| Ductal carcinoma          | 2350/1973                                  | 0.8124              | 0.94 (0.34, 2.59) |
| Lobular carcinoma         | 67/56                                      | 0.4368              | 25/29   |
| Medullary carcinoma       | 31/23                                      | 0.18 (0.02, 1.82)   |         |
| Mucinous carcinoma        | 67/64                                      | 0.45 (0.33, 0.55)   |         |
| Mix                       | 39/38 (<0.001 <0.001, >999.999)             | 0.9781              | 62/94   |

### B. Correlated of more length of reproductive years

| Lymph nodes diameter (mm) | No. of reproductive years ≥35/<35 yrs (ref) patients | Odds ratio (95% CI) | P-value |
|---------------------------|------------------------------------------------------|---------------------|---------|
| ≤20                       | 1722/1491                                            | 0.95 (0.06, 15.79)  | 0.9699  |
| >20                       | 67/56                                                |                     | 1819/1367 | 16/5 |
| ≤30                       | 1684/1435                                            | 0.69 (0.31, 1.53)   | 0.3572  |
| >30                       | 50/56                                                |                     | 52/62   |
| ≤40                       | 899/768                                              | 1.02 (0.81, 1.28)   | 0.8654  |
| >40                       | 827/653                                              |                     | 512/719 |
| ≤50                       | 121/101                                              | 1.01 (0.74, 1.37)   | 0.9657  |
| >50                       | 1277/1063                                            |                     | 872/1002 |
| ≤60                       | 443/405                                              | 0.97 (0.64, 1.45)   | 0.8711  |
| >60                       | 454/405                                              |                     | 348/414 |

### ALNM

| ALNM          | No. of reproductive years ≥35/<35 yrs (ref) patients | Odds ratio (95% CI) | P-value |
|---------------|------------------------------------------------------|---------------------|---------|
| N0            | 1316/1147                                            | 1.03 (0.79, 1.34)   | 0.8353  |
| N1            | 61/533                                                |                     | 437/556 |
| N2            | 263/214                                              | 0.79 (0.52, 1.19)   | 0.2522  |
| N3            | 173/136                                              | 0.86 (0.55, 1.34)   | 0.5029  |

### Distal metastasis

| Distal metastasis | No. of reproductive years ≥35/<35 yrs (ref) patients | Odds ratio (95% CI) | P-value |
|-------------------|------------------------------------------------------|---------------------|---------|
| M0                | 2333/1897                                            | 0.13 (0.02, 0.12)   | 0.0637  |
| M1                | 19/29                                                |                     | 1643/2048 |

### Lymph nodes diameter (mm)

| Lymph nodes diameter | No. of reproductive years ≥35/<35 yrs (ref) patients | Odds ratio (95% CI) | P-value |
|----------------------|------------------------------------------------------|---------------------|---------|
| ≤15                  | 409/346                                              | 1.14 (0.82, 1.58)   | 0.4558  |
| >15, ≤20             | 459/376                                              | 1.22 (0.67, 2.24)   | 0.5176  |
| >20, ≤30             | 637/564                                              | 1.60 (0.86, 2.98)   | 0.1376  |
| >30                  | 520/413                                              | 1.60 (0.86, 2.98)   | 315/431 |

### ER

| ER                | No. of reproductive years ≥35/<35 yrs (ref) patients | Odds ratio (95% CI) | P-value |
|------------------|------------------------------------------------------|---------------------|---------|
| Negative         | 1163/978                                             | 0.98 (0.72, 1.35)   | 0.9087  |
| Positive         | 1826/1600                                            |                     | 900/1081 |

### PR

| PR                | No. of reproductive years ≥35/<35 yrs (ref) patients | Odds ratio (95% CI) | P-value |
|------------------|------------------------------------------------------|---------------------|---------|
| Negative         | 1557/1279                                            | 0.86 (0.64, 1.16)   | 0.3343  |
| Positive         | 1428/1298                                            |                     | 1123/1427 |

### HER2

| HER2              | No. of reproductive years ≥35/<35 yrs (ref) patients | Odds ratio (95% CI) | P-value |
|------------------|------------------------------------------------------|---------------------|---------|
| Negative         | 1523/1389                                            | 1.18 (0.94, 1.49)   | 0.1429  |
| Positive         | 1158/924                                             | 1.18 (0.94, 1.49)   | 1576/1992 |

### Ki67

| Ki67              | No. of reproductive years ≥35/<35 yrs (ref) patients | Odds ratio (95% CI) | P-value |
|------------------|------------------------------------------------------|---------------------|---------|
| ≤20%             | 867/719                                              | 0.94 (0.74, 1.19)   | 0.5993  |
| >20%             | 700/631                                              | 0.94 (0.74, 1.19)   | 715/981 |

### PS3

| PS3              | No. of reproductive years ≥35/<35 yrs (ref) patients | Odds ratio (95% CI) | P-value |
|-----------------|------------------------------------------------------|---------------------|---------|
| Negative        | 683/547                                              | 0.77 (0.61, 0.98)   | 0.0321  |
| Positive        | 927/825                                              | 0.77 (0.61, 0.98)   | 374/593 |

**Figure 3.** Correlates of clinicopathologic features with late menopause age and more length of reproductive years. (A) Menopause age; (B) the length of reproductive years. Data are for postmenopausal female patients with breast cancer. OR = odds ratio; ALNM = axillary lymph node metastasis; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2. SAS 9.4.0. (SAS Institute Inc, Cary, NC, USA) and Adobe Illustrator (25.4.1, USA) were used for figure creation.
### Table 2. Comparison of baseline characteristics between reproductive years <35 years and ≥35 years in patients with breast cancer.

| Baseline characteristics | <35 yrs | ≥35 yrs | Chi-square | P-value |
|--------------------------|---------|---------|------------|---------|
|                          | N       | Percent | N          | Percent |
| **Race/ethnicity**       |         |         |            |         |
| Han                      | 2306    | 95.41%  | 2882       | 96.91%  |
| Uighur                   | 45      | 1.86%   | 20         | 0.67%   |
| Others                   | 66      | 2.73%   | 72         | 2.42%   |
| Unknown                  | 0       | 0.00%   | 0          | 0.00%   |
| **Total**                | 2417    | 100%    | 2974       | 100%    |
| **Height**               |         |         |            |         |
| ≤150                     | 188     | 7.78%   | 266        | 8.94%   |
| 151-160                  | 1013    | 41.91%  | 1277       | 42.94%  |
| 161-170                  | 349     | 14.44%  | 383        | 12.88%  |
| >170                     | 7       | 0.29%   | 13         | 0.44%   |
| Unknown                  | 860     | 35.58%  | 1035       | 34.80%  |
| **Total**                | 2417    | 100%    | 2974       | 100%    |
| **Weight**               |         |         |            |         |
| ≤50                      | 350     | 14.48%  | 430        | 14.46%  |
| 51-60                    | 763     | 31.57%  | 949        | 31.91%  |
| 61-70                    | 463     | 19.16%  | 603        | 20.28%  |
| >70                      | 180     | 7.45%   | 215        | 7.23%   |
| Unknown                  | 661     | 27.35%  | 777        | 26.13%  |
| **Total**                | 2417    | 100%    | 2974       | 100%    |
| **BMI**                  |         |         |            |         |
| <18.5                    | 89      | 3.68%   | 80         | 2.69%   |
| 18.5-23.9                | 781     | 32.31%  | 991        | 33.32%  |
| 24-27.9                  | 499     | 20.65%  | 644        | 21.65%  |
| ≥28                      | 185     | 7.65%   | 223        | 7.50%   |
| Unknown                  | 863     | 35.71%  | 1036       | 34.84%  |
| **Total**                | 2417    | 100%    | 2974       | 100%    |
| **Marital status**       |         |         |            |         |
| Married                   | 2348    | 97.15%  | 2874       | 96.64%  |
| Married/Single            | 7       | 0.29%   | 10         | 0.34%   |
| Divorced/Widow            | 57      | 2.36%   | 88         | 2.96%   |
| Unknown                   | 5       | 0.21%   | 2          | 0.07%   |
| **Total**                | 2417    | 100%    | 2974       | 100%    |
Table 2 continued. Comparison of baseline characteristics between reproductive years <35 years and ≥35 years in patients with breast cancer.

| Baseline characteristics | <35 yrs |                   | ≥35 yrs |                   | Chi-square | P-value |
|--------------------------|---------|------------------|---------|------------------|------------|---------|
|                          | N       | Percent          | N       | Percent          |            |         |
| Breastfeeding baby       |         |                  |         |                  |            |         |
| 0                       | 1506    | 62.31%           | 1937    | 65.13%           | 5.16       | 0.1606  |
| 1                       | 345     | 14.27%           | 405     | 13.62%           |            |         |
| 2                       | 258     | 10.67%           | 288     | 9.68%            |            |         |
| ≥3                      | 283     | 11.71%           | 312     | 10.49%           |            |         |
| Unknown                  | 25      | 1.03%            | 32      | 1.08%            |            |         |
| Total                    | 2417    |                  | 2974    |                  |            |         |
| Times of pregnancy       |         |                  |         |                  | 13.89      | 0.0031  |
| 0                       | 574     | 23.75%           | 682     | 22.93%           |            |         |
| 1                       | 400     | 16.55%           | 608     | 20.44%           |            |         |
| 2                       | 467     | 19.32%           | 569     | 19.13%           |            |         |
| ≥3                      | 971     | 40.17%           | 1112    | 37.39%           |            |         |
| Unknown                  | 5       | 0.21%            | 3       | 0.10%            |            |         |
| Total                    | 2417    |                  | 2974    |                  |            |         |
| Times of parity          |         |                  |         |                  | 3.47       | 0.325   |
| 0                       | 487     | 20.15%           | 570     | 19.17%           |            |         |
| 1                       | 822     | 34.01%           | 1075    | 36.15%           |            |         |
| 2                       | 553     | 22.88%           | 686     | 23.07%           |            |         |
| ≥3                      | 553     | 22.88%           | 641     | 21.55%           |            |         |
| Unknown                  | 2       | 0.08%            | 2       | 0.07%            |            |         |
| Total                    | 2417    |                  | 2974    |                  |            |         |
| Age at first-time delivery (years) |         |                  |         |                  | 2.62       | 0.1052  |
| <25                      | 531     | 21.97%           | 524     | 17.62%           |            |         |
| ≥25                      | 378     | 15.64%           | 434     | 14.59%           |            |         |
| Unknown                  | 1508    | 62.39%           | 2016    | 67.79%           |            |         |
| Total                    | 2417    |                  | 2974    |                  |            |         |
| Age at menarche (years)  |         |                  |         |                  | 725.03     | <.0001  |
| ≤12                      | 140     | 5.79%            | 400     | 13.45%           |            |         |
| 13                       | 350     | 14.48%           | 941     | 31.64%           |            |         |
| 14                       | 477     | 19.74%           | 721     | 24.24%           |            |         |
| 15                       | 435     | 18.00%           | 531     | 17.85%           |            |         |
| 16                       | 389     | 16.09%           | 218     | 7.33%            |            |         |
| ≥17                      | 626     | 25.90%           | 163     | 5.48%            |            |         |
Table 2 continued. Comparison of baseline characteristics between reproductive years <35 years and ≥35 years in patients with breast cancer.

| Baseline characteristics | <35 yrs | ≥35 yrs | Chi-square | P-value |
|--------------------------|--------|--------|------------|---------|
|                          | N      | Percent | N          | Percent |
| Unknown                  | 0      | 0.00%   | 0          | 0.00%   |
| Total                    | 2417   |         | 2974       |         |
| Age at menopause (years) |        |        |            |         |
| ≤40                      | 287    | 11.87%  | 0          | 0.00%   |
| 41-45                    | 704    | 29.13%  | 1407       | 47.31%  |
| 46-50                    | 1320   | 54.61%  | 1412       | 47.48%  |
| 51-55                    | 106    | 4.39%   | 141        | 4.74%   |
| 56-60                    | 0      | 0.00%   | 14         | 0.47%   |
| >60                      | 0      | 0.00%   | 0          | 0.00%   |
| Unknown                  | 0      | 0.00%   | 0          | 0.00%   |
| Total                    | 2417   |         | 2974       |         |
| Ovariectomization        |        |        |            |         |
| No                       | 1526   | 63.14%  | 2019       | 67.89%  |
| Yes                      | 29     | 1.20%   | 19         | 0.64%   |
| Unknown                  | 862    | 35.66%  | 936        | 31.47%  |
| Total                    | 2417   |         | 2974       |         |
| Hysterectomy             |        |        |            |         |
| No                       | 1365   | 56.47%  | 1966       | 66.11%  |
| Yes                      | 250    | 10.34%  | 80         | 2.69%   |
| Unknown                  | 802    | 33.18%  | 928        | 31.20%  |
| Total                    | 2417   |         | 2974       |         |
| Family history of cancer |        |        |            |         |
| No                       | 1820   | 75.30%  | 2338       | 78.61%  |
| Yes                      | 199    | 8.23%   | 221        | 7.43%   |
| Unknown                  | 398    | 16.47%  | 415        | 13.95%  |
| Total                    | 2417   |         | 2974       |         |

patients of different reproductive years. Evaluation of the results suggested no differences in times of parity and breastfeeding of babies among the groups of postmenopausal patients with differences in reproductive years. Although ethnic composition analysis revealed statistical differences between the 2 groups, heterogeneity may not affect the associations between length of reproductive years and tumor characteristics, because more than 95% of patients were Han Chinese. The length of reproductive years is equivalent to the duration of lifetime endogenous estrogen exposure, especially after elimination of the confounding factors. Previous studies indicated that the effects of hormonal risk factors were mainly restricted to hormone receptor-positive tumors (ER+/PR+). For instance, multiple large case control and meta-analysis studies reported that the protection provided by parity was restricted to hormone receptor-positive tumors (ER+/PR+) [37-39]. Genetic studies suggested that polymorphisms within the ER
| Tumor characters          | Luminal                                                                 | HER2 overexpression                                      |
|--------------------------|--------------------------------------------------------------------------|----------------------------------------------------------------|
| No. of reproductive years ≥35/≤35 yrs (ref) patients | Odds ratio (95% CI) | P-value | No. of reproductive years ≥35/≤35 yrs (ref) patients | Odds ratio (95% CI) | P-value |
| Special type breast cancer | No. (1324) | 179 (192) | Yes (117) | 15 | 0.21 (0.01, 3.33) | 0.2654 |
| Tumor histology           | Ductal carcinoma (1209/1491)                                            | 169/174                                                   |
| Lobular carcinoma         | 39/44                      | 1.00 (0.31, 3.26) | 0.9988 | 0/0 | – | – |
| Medullary carcinoma       | 4/5                        | – | – | 2/3 | – | – |
| Mucinous carcinoma        | 38/41                      | 1.61 (0.51, 5.08) | 0.4154 | 0/2 | – | – |
| Mix                       | 0/0                        | – | – | 0/0 | – | – |
| Nerve invasion            | No. (609)                  | 92/93                                                   |
| Vascular invasion         | No. (595)                  | 90/88                                                   |
| Calcification             | No. (320)                  | 22/                                                     |
| Histological grade        | I (62/103)                 | 5/6                                                     |
| Tumor size                | T1 (≤20 mm)                | 370/464                                                 | 43/34 |
|                           | T2 (20 mm <d≤50 mm)        | 493/623                                                 | 84/91 | 0.15 (0.00, 5.73) | 0.304 |
|                           | T3 (>50 mm)                | 51/75                                                   | 8/15 | 0.60 (0.01, 53.61) | 0.8234 |
|                           | T4                         | 43/44                                                   | 0.07 (0.01, 0.81) | 0.0328 | 5/5 | <0.001 |
| ALNM                      | N0                         | 552/698                                                 | 79/81 |
|                           | N1                         | 275/340                                                 | 0.83 (0.51, 1.35) | 0.4469 | 49/46 | 0.93 (0.08, 10.69) | 0.9506 |
gene and other members of the ER signaling pathway are predominantly associated with age at natural menopause [40,41]. Consequently, we speculated that associations between the length of reproductive years and tumor features differ among various molecular subtypes of breast cancer. To examine this hypothesis, we conducted subgroup analysis according to various breast cancer molecular subtypes defined by hormone receptors status. In the luminal breast cancer subtype, postmenopausal patients with greater length of reproductive years were more likely to have smaller-sized tumors. Consistent with our findings, an earlier study by Song et al [42] suggested that hormone receptor-positive tumors are more significantly associated with higher duration of estrogen exposure. Spitale et al reported better survival in patients with hormone receptor-positive (ER+ and/or PR+) breast cancer than those with hormone receptor-negative breast cancer [43]. In addition, a study by Song et al involving 3430 breast cancer patients indicated better survival in patients with longer duration of estrogen exposure [26]. Similar to our study, Khalis et al reported that early menarche and nulliparity were remarkably associated to an increased risk of breast cancer [44]. Furthermore, an analysis based on 1126 patients diagnosed with invasive breast cancer and 2106 controls suggested that parity and extended breastfeeding were associated with decreased risks [45].

Accordingly, we propose that length of reproductive years is not a potential protective factor for triple-negative breast cancer,

Table 3 continued. Correlation of clinicopathologic features with longer reproductive years among luminal and HER2-overexpression breast cancer.

| Tumor characters | Luminal | HER2 overexpression |
|------------------|---------|---------------------|
|                  | No. of reproductive years ≥35/≤35 yrs (ref) patients | Odds ratio (95% CI) | P-value | No. of reproductive years ≥35/≤35 yrs (ref) patients | Odds ratio (95% CI) | P-value |
| N2               | 111/158  | 0.76 (0.38, 1.52)   | 0.4425 | 15/17  | 0.11 (0.00, 5.33)   | 0.2605 |
| N3               | 72/88    | 0.57 (0.22, 1.50)   | 0.2554 | 13/14  | 3.48 (0.06, 195.90) | 0.5444 |
| Distant metastasis |          |                     |       |        |                     |       |
| M0               | 988/1265 |                     |       | 152/155|                     |       |
| M1               | 16/10    | 1.09 (0.10, 11.93)  | 0.9470 | 4/0    |                     | 0.2626 |
| Lymph nodes diameter (mm) |       |                     |       |        |                     |       |
| ≤15              | 166/238  |                     |       | 18/12  |                     |       |
| >15, ≤20         | 166/212  | 1.15 (0.67, 1.97)   | 0.6166 | 25/19  | 0.23 (0.01, 10.72)  | 0.4513 |
| >20, ≤30         | 239/326  | 2.31 (0.78, 6.83)   | 0.1292 | 28/39  | 6.44 (0.25, 168.28) | 0.2633 |
| >30              | 172/240  | 2.55 (0.86, 7.56)   | 0.0924 | 40/46  |                     |       |
| Ki67             |          |                     |       |        |                     |       |
| ≤20%             | 467/657  |                     |       | 47/51  |                     |       |
| >20%             | 155/153  | 1.04 (0.51, 2.13)   | 0.9186 | 57/45  | 0.91 (0.09, 9.26)   | 0.9344 |
| PS3              |          |                     |       |        |                     |       |
| Negative         | 246/376  |                     |       | 20/24  |                     |       |
| Positive         | 248/375  | 0.89 (0.60, 1.32)   | 0.5546 | 38/44  | 1.86 (0.25, 13.98)  | 0.5488 |
## Tumor characters

| Character                           | No. of Reproductive Years | Odds Ratio (95% CI) | P-value |
|-------------------------------------|---------------------------|---------------------|---------|
| Special type breast cancer          |                           |                     |         |
| No                                  | 472/606                   | 2.78 (0.85, 9.07)   | 0.0909  |
| Yes                                 | 18/43                     |                     |         |
| Tumor histology                     |                           |                     |         |
| Ductal carcinoma                    | 413/535                   |                     |         |
| Lobular carcinoma                   | 3/8                       | 0.45 (0.05, 3.98)   | 0.4740  |
| Medullary carcinoma                 | 12/16                     | 0.09 (0.01, 1.03)   | 0.0530  |
| Mucinous carcinoma                  | 3/9                       | >999.999 (<0.001, >999.999) | 0.9909 |
| Mix                                 | 0/0                       |                     |         |
| Nerve invasion                      |                           |                     |         |
| No                                  | 253/363                   | 0.43 (0.23, 0.78)   | 0.0052  |
| Yes                                 | 4/0                       | <0.001 (<0.001, >999.999) | 0.9898 |
| Vascular invasion                   |                           |                     |         |
| No                                  | 245/353                   | 1.12 (0.15, 8.31)   | 0.9136  |
| Yes                                 | 10/14                     |                     |         |
| Calcification                       |                           |                     |         |
| No                                  | 115/169                   | 2.03 (0.97, 4.24)   | 0.0593  |
| Yes                                 | 128/164                   | 1.64 (0.61, 4.43)   | 0.3300  |
| Histological grade                 |                           |                     |         |
| I                                   | 15/17                     |                     |         |
| II                                  | 175/224                   | 2.03 (0.97, 4.24)   | 0.0593  |
| III                                 | 94/115                    | 1.64 (0.61, 4.43)   | 0.3300  |
| Tumor size                          |                           |                     |         |
| T1 (≤20 mm)                         | 127/170                   | 1.07 (0.27, 4.21)   | 0.9289  |
| T2 (20 mm<d ≤50 mm)                 | 191/237                   | 1.83 (0.27, 12.54)  | 0.5377  |
| T3 (>50 mm)                         | 20/24                     | 5.56 (0.02, 16.14)  | 0.7454  |
| ALNM                                |                           |                     |         |
| N0                                  | 216/265                   | 2.15 (1.03, 4.52)   | 0.0429  |
| N1                                  | 72/125                    | 0.71 (0.27, 1.83)   | 0.4739  |
| N2                                  | 49/52                     | 0.54 (0.17, 1.70)   | 0.2890  |
| N3                                  | 31/35                     |                     |         |
| Distant metastasis                  |                           |                     |         |
| M0                                  | 358/466                   | <0.001 (<0.001, <999.999) | 0.9907 |
| M1                                  | 4/3                       |                     |         |
| Lymph nodes diameter (mm)           |                           |                     |         |
| ≤50                                 | 54/82                     | 1.57 (0.67, 3.66)   | 0.3014  |
| >5, ≤20                             | 63/84                     | 1.50 (0.33, 6.85)   | 0.5981  |
| >20, ≤30                            | 89/121                    | 1.66 (0.37, 7.55)   | 0.5106  |
| >30                                 | 77/105                    |                     |         |
| Ki67                                 |                           |                     |         |
| ≤20%                                | 97/242                    | 0.56 (0.19, 1.63)   | 0.2856  |
| >20%                                | 139/75                    |                     |         |
| PS3                                 |                           |                     |         |
| Negative                            | 179/175                   | 0.39 (0.21, 0.74)   | 0.0034  |
| Positive                            | 61/168                    |                     |         |

**Figure 4.** Correlates of clinicopathologic features with longer reproductive years among triple-negative breast cancer. Data are for postmenopausal female patients with triple-negative breast cancer. OR – odds ratio; ALNM – axillary lymph node metastasis; ER – estrogen receptor; PR – progesterone receptor; HER2 – human epidermal growth factor receptor 2. SAS 9.4.0. (SAS Institute Inc, Cary, NC, USA) and Adobe Illustrator (25.4.1, USA) were used for figure creation.
and the mechanism is possibly associated with hormone receptors. However, due to the limitations in sample size, the reliability of our results remains open to debate.

To the best of our knowledge, the present study was the first to analyze the associations between length of exposure to cycling reproductive hormones and clinicopathological characteristics among women with breast cancer. To reduce heterogeneity, subgroup analysis was conducted according to various molecular subtypes of breast cancer, defined by hormone receptor status. The larger sample size should have provided greater statistical power, compared with previous studies. Information on most variables was obtained from the electronic medical records system in breast cancer centers and was therefore reliable. All missing data were removed during the analysis and should not have significantly impacted the interpretation of the results.

Our study had a number of limitations that should be considered when interpreting the results. First, the prognostic evaluation could not be carried out as a result of a lack of survival data. Additionally, some important confounding factors such as BRCA gene mutation status, status of Ki67 and P53, nuclear grade, socioeconomic status, and performance status, may have affected our results and resulted in bias to some extent. During the 10-year duration of the review, diagnostic methods and patient management have improved and affected patient outcome, which led to inevitable bias. Furthermore, because patients were registered from multiple hospitals, we cannot entirely control the quality of pathological diagnosis and primary data, which led to inevitable bias. Finally, for the correlations between clinicopathological features and menarche age, and menopause age and reproductive period, the cross-sectional analysis could not indicate that late menarche and greater length of reproductive years were the cause or consequence of these clinicopathologic features.

Conclusions

In conclusion, our data suggested that the length of reproductive years might present a positive association with histological grade but negative association with tumor size. Further research is warranted to ascertain the significance of the length of reproductive hormone exposure in breast cancer prognosis in the future.

Ethics Approval and Consent to Participate

All study protocols were approved by the ethics committee of each participating breast center, and all participants gave their written informed consent to participate.

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Declaration of Figures’ Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. Cancer J Clin. 2020;70:7-30
2. DeSantis CE, Ma J, Goding Sauer A, et al. Breast cancer statistics, 2017, released February 2017. CA Cancer J Clin. 2017;67:439-48
3. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. Cancer J Clin. 2016;66:11-32
4. Britt K. Menarche, menopause, and breast cancer risk. Lancet Oncol. 2012;13:1071-72
5. Sievert, Lynnette L. Menopause: A biocultural perspective. New Brunswick, N.J.: Rutgers University Press 2016,81
6. Kim J, Kuriita T, Bulum SE. Progesterone action in endometrial cancer, endometriosis, uterine fibroids, and breast cancer. Endocr Rev. 2013;34(1):130-62
7. Dall GV, Britt KL. Estrogen effects on the mammary gland in early and late life and breast cancer risk. Front Oncol. 2017;7:110
8. Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118,964 women with breast cancer from 117 epidemiological studies. Lancet Oncol. 2012;13:1141-51
9. Lane-Claypon J. A further report on cancer of the breast with special reference to its associated antecedent conditions. Reports on Public Health and Medical Subjects No. 32. 2016; London: HMSO
10. Wainwright JM. A comparison of conditions associated with breast cancer in Great Britain and America. Am J Cancer. 1931;15:10-45
11. Feng Y, Hong X, Wilker E, et al. Effects of age at menarche, reproductive years, and menopause on metabolic risk factors for cardiovascular diseases. Atherosclerosis. 2008;196:590-97
12. Wu X, Cai H, Kallianpur A, et al. Age at menarche and natural menopause and number of reproductive years in association with mortality: Results from a median follow-up of 11.2 years among 31,955 naturally menopausal Chinese women. PLoS One. 2014;9:e103673
13. Criteria of weight for adults. National Health and Family Planning Commission. Ongoing Since 2013;10 [in Chinese]
14. Phipps AI, Malone KE, Porter PL, et al. Body size and risk of luminal, HER2-overexpressing, and triple-negative breast cancer in postmenopausal women. Cancer Epidemiol Biomarkers Prev. 2008;17:2078-86
15. Phipps AI, Malone KE, Porter PL, et al. Reproductive and hormonal risk factors for postmenopausal luminal, HER2-overexpressing, and triple-negative breast cancer. Cancer. 2008;113:1221-26
16. Chen L, Cook LS, Tang M-TC, et al. Body mass index and risk of luminal, HER2-overexpressing, and triple negative breast cancer. Breast Cancer Res Treat. 2016;157:545-54
17. Goldhirsh A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: Highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol. 2013;24:2206-23
18. Onitilo AA, Engel JM, Greenlee RT, et al. Breast cancer subtypes based on ER/PR and Her2 expression: Comparison of clinicopathologic features and survival. Clin Med Res. 2009;7:4-13
19. Dawood S, Hu R, Hornes MD, et al. Defining breast cancer prognosis based on molecular phenotypes: Results from a large cohort study. Breast Cancer Res Treat. 2011;126:185-92
20. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA. 2006;295:2492-502
21. Koebele SV, Mennenga SE, Hiroi R, et al. Cognitive changes across the menopause transition: A longitudinal evaluation of the impact of age and ovarian status on spatial memory. Horm Behav. 2017;87:96-114
22. Desai S, Rajkovic A. Genetics of reproductive aging from gonadal dysgenesis through menopause. Semin Reprod Med. 2017;35:147-59
23. Wurz GT, Kao C-J, DeGregorio MW. Safety and efficacy of ospemifene for the treatment of dyspareunia associated with vulvar and vaginal atrophy due to menopause. Clim Interv Aging. 2014;9:1939-50
24. Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. Menopause. 2013;20:888-904
25. Bruyniks N, Biglia N, Palacios S, et al. Systematic indirect comparison of ospemifene versus local estrogens for vulvar and vaginal atrophy. Int J Cancer. 2013;132:2619-29
26. Song N, Choi J-Y, Sung H, et al. Tumor subtype-specific associations of hormone-related reproductive factors on breast cancer survival. PLoS One. 2015;10:e0123994
27. Ritte R, Lukanova A, Tjonneland A, et al. Height, age at menarche and risk of hormone receptor-positive and -negative breast cancer: A cohort study. Int J Cancer. 2013;132:2619-29
28. Lin C, Chien S-Y, Kuo S-I, et al. A 10-year follow-up of triple-negative breast cancer patients in Taiwan. Ipn J Clin Oncol. 2012;42:161-67
29. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer. 1989;63:181-87
30. Jayasinghe UW, Bilous AM, Boyages J. Is survival from infiltrating lobular carcinoma of the breast different from that of infiltrating ductal carcinoma? Breast J. 2007;13:479-85
31. Kadioğlu H, Özbaş S, Akcan A, et al. Comparison of the histopathology and prognosis of bilateral versus unilateral multifocal multicentric breast cancers. World J Surg Oncol. 2014;12:266
32. Parsa P, Parsa B. Effects of reproductive factors on risk of breast cancer: A literature review. Asian Pac J Cancer Prev. 2009;10(4):545-50
33. Olsson HL, Olsson ML. The menstrual cycle and risk of breast cancer: A review. Front Oncol. 2020;10:21-46
34. Breast cancer and hormone replacement therapy: Collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet. 1997;350:1047-59
35. Althuis MD, Brogan DR, Coates RJ, et al. Hormonal content and potency of oral contraceptives and breast cancer risk among young women. Br J Cancer. 2003;88:50-57
36. Ma H, Henderson KD, Sullivan-Halley I, et al. Pregnancy-related factors and the risk of breast carcinoma in situ and invasive breast cancer among post-menopausal women in the California Teachers Study cohort. Breast Cancer Res. 2010;12:R35
37. Ursin G, Bernstein L, Lord SJ, et al. Reproductive factors and subtypes of breast cancer defined by hormone receptor and histology. Br J Cancer. 2005;93:364-71
38. Ma H, Bernstein L, Pike MC, et al. Reproductive factors and breast cancer risk according to joint estrogen and progesterone receptor status: A meta-analysis of epidemiological studies. Breast Cancer Res. 2006;8:R43
39. Anderson KN, Schwab RB, Martinez ME. Reproductive risk factors and breast cancer subtypes: A review of the literature. Breast Cancer Res Treat. 2014;144:1-10
40. Weel AE, Uitterlinden AG, Westendorp IC, et al. Estrogen receptor polymorphism predicts the onset of natural and surgical menopause. J Clin Endocrinol Metab. 1999;84:3146-50
41. He L-N, Xiong D-H, Liu Y-J, et al. Association study of the oestrogen signalling pathway genes in relation to age at natural menopause. J Genet. 2007;86:269-76
42. Song N, Choi J-Y, Sung H, et al. Heterogeneity of epidemiological factors by breast tumor subtypes in Korean women: A case-case study. Int J Cancer. 2014;135:669-81
43. Spitalé A, Mazzola P, Soldini D, et al. Breast cancer classification according to immunohistochemical markers: Clinicopathologic features and short-term survival analysis in a population-based study from the South of Switzerland. Ann Oncol. 2014;20:628-35
44. Khalis M, Charbotel B, Chajès V, et al. Menstrual and reproductive factors and risk of breast cancer: A case-control study in the Fez region, Morocco. PLoS One. 2018;13(1):e0191333
45. Figueroa JD, Davis Lynn BC, Edusei L, et al. Reproductive factors and risk of breast cancer by tumor subtypes among Ghanaian women: A population-based case-control study. Int J Cancer. 2020;147(6):1535-47