

# Parity association with clinicopathological factors in invasive breast cancer: a retrospective analysis

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**Abstract:** The aim of this study was to determine the relationship between parity and age at diagnosis, primary tumor size, axillary lymph node (ALN) metastasis, histological grade, and subtype classification in patients with breast cancer. Data from 392 patients with invasive breast cancer were collected and divided into four groups: nulliparous (parity 0), parity 1, parity 2, and parity  $\geq 3$ . The relationship between parity and age at diagnosis was assessed using post hoc Dunnett's T3 test, and tumor size, the number of ALN metastases, and histological grade were analyzed using Spearman's rho test. Breast cancer subtypes were analyzed using the chi-square ( $\chi^2$ ) test. The results showed that the mean age at diagnosis increased with increased parity, and the mean age of patients with parity  $\geq 3$  was significantly greater than that of patients with parity 0, parity 1, and parity 2. The mean age at diagnosis of patients with parity 2 was greater than that of patients with parity 1. There was no significant difference in the mean age between patients with parity 0 and parity 1 or parity 0 and parity 2. Parity was negatively correlated with ALN metastasis. Parity was not correlated with tumor size or histological grade and the proportion of the four subtypes in breast cancer. So, increased parity deferred the onset of breast cancer and inhibited the metastasis of ALN, but did not affect tumor size, histological grade, or the proportion of subtypes. Increased parity was a protective factor against breast cancer.

**Keywords:** parity, invasive breast cancer, clinicopathological factors, age

## Introduction

Parity is an important modulator of breast cancer risk and age at diagnosis.<sup>1,2</sup> Multiple last birth was found to be protective against breast cancer.<sup>3</sup> Late age at first full-term birth and low parity are high risk factors for breast cancer.<sup>4</sup> Giving birth before the age of 30 was shown to reduce breast cancer risk, and women with their first full-term birth before the age of 20 had a 50% reduced risk of developing breast cancer compared with nulliparous women. In contrast, those who gave birth after the age of 35 had a 22% increased risk of breast cancer compared to women giving first birth before age 30, and this risk was the same as that of nulliparous women, with no risk reduction with increased parity.<sup>5</sup> Indeed, increased parity was found to decrease the age at diagnosis of breast cancer.<sup>2</sup>

The morbidity of breast cancer was not very high (~40/10 million), but the rate of growth was dramatic in China. The family planning policy has been amended this year: one child policy was abrogated, and all couples were allowed to have two children. Many women would have parity  $\geq 2$  in the future; therefore, it was necessary to investigate the effect of parity on breast cancer.

The effect of parity on age of onset, primary tumor size, axillary lymph node (ALN) metastasis, histological grade, and the classification of breast cancer subtype has been seldom reported in breast cancer. The aim of our study was to analyze the effect of

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parity on the abovementioned clinicopathological factors in patients with breast cancer.

## Patients and methods

A total of 392 patients with primary invasive breast cancer from 2010 to 2015 were reviewed at Yuebei People's Hospital and divided into four groups: 15 nulliparous cases (parity 0), 165 cases with parity 1, 152 cases with parity 2, and 60 cases with parity  $\geq 3$ . There were no cases with pregnancy-associated breast cancer. All data were analyzed anonymously, and the information that could identify individual participants during or after data collection was preserved well and could be accessed. Breast cancer patients had no family history of cancer and had not undergone radiotherapy, chemotherapy, or hormone therapy before the pathological specimens were extracted. The samples were fixed with 10% neutral buffered formalin and then embedded in paraffin. According to the TNM stage criterion of the seventh edition of the AJCC,<sup>6</sup> tumor size was divided into three categories:  $\leq 2$  cm, 2–5 cm, and  $> 5$  cm; ALN metastasis was divided into four categories: no cancer metastasis, cancer metastasis in 1–3 lymph nodes, cancer metastasis in 4–9 lymph nodes, and cancer metastasis in  $\geq 10$  lymph nodes. Histological grade was divided into three categories based on the modified Nottingham criteria of Bloom and Richardson.<sup>7,8</sup> Breast cancer was classified into four subtypes according to the 13th St Gallen International Breast Cancer Conference.<sup>9</sup> All clinicopathological factors were analyzed retrospectively. Parity and age were defined at the time of breast cancer diagnosis.

## Statistical analysis

Data were analyzed using SPSS Version 20.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean  $\pm$  standard error of the mean (SEM). The relationship between parity and age was assessed using one-way analysis of variance (ANOVA) with post hoc Dunnett's T3 test. Tumor size, the number of ALN metastases, and histological grade were analyzed using Spearman's rho test, and breast cancer subtypes were analyzed using the chi-square ( $\chi^2$ ) test. All statistical analyses were two-sided with significance defined as a *P*-value of  $< 0.05$ .

## Ethical standards

The study complied with the current laws of China and was approved by the institutional review board of Southern Medical University; this institutional review board waived the need for patient consent to use patient data, due to the retrospective nature of the research.

## Results

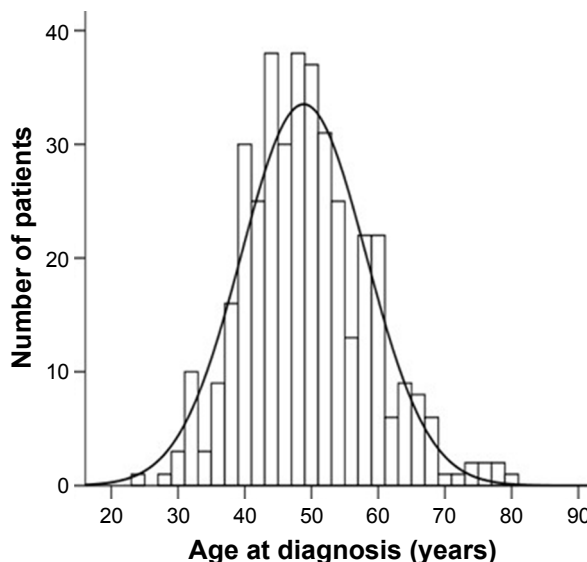
The age distribution is shown in Figure 1. The age range was from 24 to 80 years; the median age was 48 years; and the mean age was  $48.8 \pm 9.3$  years. The mean age at diagnosis increased with increased parity (Figure 2), and the mean age of patients with parity  $\geq 3$  was significantly greater than that of patients with parity 0 ( $P=0.005$ ), parity 1 ( $P<0.001$ ), and parity 2 ( $P<0.001$ ). The mean age of patients with parity 2 was greater than that of patients with parity 1 ( $P=0.021$ ). There was no significant difference in the mean age of patients with parity 0 and parity 1 ( $P=0.997$ ) or between patients with parity 0 and parity 2 ( $P=0.539$ ), the result may be due to the few nulliparous patients.

The clinicopathological data from all patients and the statistical analyses are summarized in Table 1. Parity was negatively correlated with ALN metastasis (correlation coefficient [CC] =  $-0.340$ ,  $P<0.001$ ), and the number of ALN metastases decreased with increased parity in patients with breast cancer.

Parity was not correlated with tumor size (CC =  $0.081$ ,  $P=0.109$ ) or histological grade (CC =  $0.024$ ,  $P=0.633$ ), and there was no obvious relationship between parity and the proportion of the four subtypes in breast cancer ( $\chi^2=10.184$ ,  $P=0.336$ ).

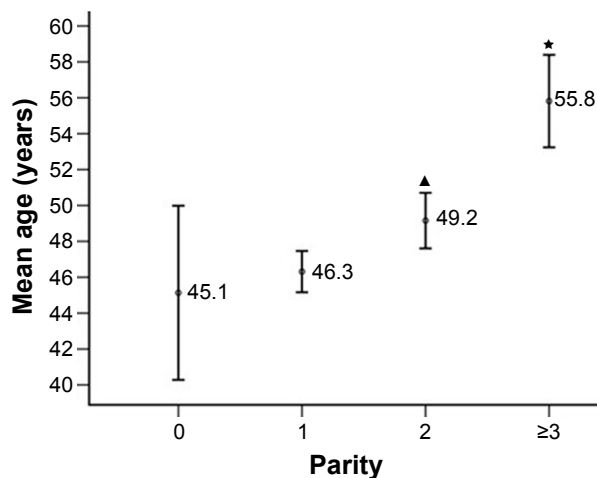
## Discussion

Breast cancer is the most common malignant tumor in females,<sup>10</sup> and its morbidity has been dramatically increasing by 3%–5% each year in China. The peak age of onset was previously estimated to be 45 years. While the peak



**Figure 1** Age distribution of 392 patients at diagnosis of breast cancer.

**Note:** The age of the patients from Shaoguan ranged from 24 to 80 years and was normal distribution, with the peak age of onset of breast cancer being 48 years.



**Figure 2** Mean age at diagnosis of breast cancer according to parity.

**Notes:** Mean age was marked at midpoint of vertical line. The relationship between parity and age was assessed using one-way analysis of variance with post hoc Dunnett's T3 test. The mean age at diagnosis increased with increased parity. \*Compared with parity 0 ( $P=0.005$ ), parity 1 ( $P<0.001$ ), and parity 2 ( $P<0.001$ ). ▲Compared with parity 1 ( $P=0.021$ ). There was no significant difference in the mean age of patients with parity 0 and parity 1 ( $P=0.997$ ) or between patients with parity 0 and parity 2 ( $P=0.539$ ).

age of onset of breast cancer in our study was 48 years, with a mean age of 48.8 years now, representing an ~3 years peak age delay. The proportion of women giving childbirth in advanced age has increased (but seldom >35 years), and the age at the completion of the last pregnancy and lactation has increased. The cycle effect of hormones on the breast can be avoided during pregnancy or lactation (breast feeding is

common in China). Lower estrogen and higher progesterone are known to protect the breast from canceration.<sup>11,12</sup> In addition, the maternal serum alpha-fetoprotein (AFP) level was high during pregnancy, and the AFP had direct antibreast cancer activity.<sup>13,14</sup> Therefore, the age at diagnosis of breast cancer increased with increased parity. Albrektsen et al<sup>15</sup> found that women with multiparity had a slightly lower risk of breast cancer compared with women with parity 1. Nevertheless, the reduction in risk diminished with increasing parity. Furthermore, the risk elevated among women with parity  $\geq 3$ .<sup>15</sup> Woods et al<sup>2</sup> reported that the age at breast cancer diagnosis decreased with increased parity.<sup>16</sup> These contradictory results were attributed to a higher proportion of women who delivered after the age of 35, the lower rates of lactation in Western women, ethnic difference, and so on.

To date, the status of ALN is a very powerful prognostic factor for patients with breast cancer. The prognosis of patients with ALN metastasis was poorer than that of those without ALN metastasis.<sup>17</sup> Age at diagnosis of breast cancer is a predictor of ALN metastasis, younger patients have more ALN metastasis than older patients.<sup>18</sup> Our study showed that parity was correlated with ALN metastasis, and the number of ALN metastasis declined with increased parity. This was attributed to the increase in age at diagnosis with increased parity.

In breast cancer, tumor size is a powerful predictor for local recurrence and regional and systemic spread. Oppidan

**Table I** Associations between parity and clinicopathological factors in invasive breast cancer

Clinicopathological factors	Parity				Statistical analysis
	0	1	2	3	
Age, years (mean $\pm$ SD)	45.1 $\pm$ 2.4	46.3 $\pm$ 0.6	49.2 $\pm$ 0.8	55.8 $\pm$ 1.3	$F=18.117$ , $P<0.001$
Tumor size					CC =0.081, $P=0.109$
$\leq 2$ cm	5	74	52	22	
2–5 cm	8	87	93	33	
>5 cm	2	4	7	5	
ALN metastasis					CC =-0.340, $P<0.001$
0	5	87	67	28	
1–3	6	45	39	12	
4–9	4	18	21	10	
$\geq 10$	0	15	25	10	
Grade					CC =0.024, $P=0.633$
I	3	9	10	2	
II	8	117	100	45	
III	4	39	42	13	
Subtype					$\chi^2=10.184$ , $P=0.336$
Luminal A	3	50	37	11	
Luminal B	7	66	70	27	
HER2	0	21	18	12	
TN	5	28	27	10	

**Abbreviations:** ALN, axillary lymph node; CC, correlation coefficient; TN, triple-negative.

women seldom had parity  $\geq 1$ , while the women in rural area in China were often multiparous. Although breast mass was palpated easily in women with more parity and lactation, these women often acquired few health-care resources, did not pay more attention to their breast health, seldom performed self-examination and received physical examination, so their breast lesions were not detected early. Therefore, parity was not associated with tumor size at the time of breast cancer diagnosis.

Histological grade is an indicator of malignant degree.<sup>8</sup> A high histological grade indicated that the tumor grew fast and had strong invasion, resulting in a poor prognosis. Our study showed that there were no significant differences in histological grade in the four groups of patients. The result was consistent with the report of Somasegar et al<sup>19</sup> that there was no association of parity with breast cancer histological grade.

Each breast cancer subtype has its own biological characteristics, and treatment plan optimization is based on the subtype classification. The proportion of each subtype was not significantly different in the four groups of patients. Ursin et al<sup>20</sup> reported that parity reduced the risk of estrogen/progesterone receptor-positive breast cancer and lactation reduced the risk of both receptor-positive and -negative breast cancer. Lambertini et al<sup>21</sup> reported that parity reduced the risk of luminal subtype, lactation reduced the risk of both luminal and triple-negative (TN) subtypes. Besides, the subtype classification was involved in the expression status of HER2 and Ki67. Thus, the effect of only parity on the subtype classification was uncertain.

Based on our results, we can speculate that tumor initiation occurred at the end of the last parity and lactation and not before the first birth. In contrast, Woods et al<sup>2</sup> concluded that tumor growth was initiated before the first birth. Accordingly, the high levels of estrogen and progesterone during pregnancy would promote hormone-dependent tumor growth and decrease the age at diagnosis. However, our findings were in direct opposition to that conclusion.

## Conclusion

In our study, increased parity deferred the onset of breast cancer and inhibited metastasis of ALN, but did not affect tumor size, histological grade, and the proportion of the subtypes at diagnosis of breast cancer. Therefore, increased parity was a protective factor against breast cancer, and parity should be taken into account when we schedule the optimum age to screen for breast cancer.

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## Disclosure

The authors report no conflicts of interest in this work.

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