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Original Article

The Impact of Reproductive Factors on the Risk of Breast Cancer by ER/PR and HER2: A Multicenter Case-Control Study in Northern and Eastern China

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Abstract

Background: Previous studies have suggested that reproductive factors are associated with breast cancer risk. Breast cancer subtypes have distinct natural characteristics and may also have unique risk profiles. The purpose of this study was to determine whether reproductive factors affect the risk of breast cancer by estrogen receptor (ER)/progesterone receptor (PR) and HER2 status.

Methods: A multicenter, case-control study was conducted. There were 1170 breast cancer patients and 1170 age- and hospital-matched females included in the analysis. Self-reported data were collected about lifestyle behaviors, including reproductive factors. Breast cancer cases were categorized subtypes according to ER, PR, and HER2 expression as HR- positive, HER2-enriched, and triple negative breast cancer (TNBC). Multivariable logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Having ≤1 child increased risk of HR-positive breast cancer (OR 1.882; 95%CI 1.29-2.74), especially in the premenopausal group (OR 2.212; 95%CI 1.23-3.99). Compared with women who first gave birth after age 30 years, earlier age at first birth decreased the risk of HR-positive breast cancer (≤23 years: OR 0.209; 95%CI 0.14-0.30; 24-29 years: OR 0.256; 95%CI 0.18-0.36; $P < .001$). Compared with those who had an average breastfed/birth period of more than 2 years, those with an average period less than 6 months had an elevated risk of all subtypes (HR positive: OR 2.690; 95%CI 1.71-4.16, $P < .001$; HER2-enriched: OR 3.779; 95%CI, 1.62-8.79, $P = .001$; TNBC: OR 2.564; 95%CI 1.11-5.94, $P = .022$). For postmenopausal patients, shorter period of lifetime menstrual cycles (≤30 years) had an obviously decreased risk in HR-positive cases (OR 0.397; 95%CI 0.22-0.71), while there was no similar appearance in other molecular subtypes.

Conclusion: The results suggest that reproductive behaviors affect risk of breast cancer differently according to ER/PR and HER2 status.

Key words: reproductive factor, breast cancer, risk, molecular subtype.

Implications for Practice

Results of this multicenter, case-control study revealed that reproductive behaviors affected risk of breast cancer differently according to estrogen receptor/progesterone receptor (ER/PR) and HER2 status. A total of 1170 breast cancer patients and 1170 age- and hospital-matched females were included. The results showed that having ≤1 child increased risk of HR-positive breast cancer, especially in the premenopausal group. Compared with women who first gave birth after age 30 years, earlier age at first birth decreased the risk of HR-positive breast cancer. Compared with those who had an average breastfed/birth period of more than 2 years, those with an average period less than 6 months had an elevated risk of all subtypes. For postmenopausal patients, shorter period of lifetime menstrual cycles (≤30 years) had an obviously decreased risk in HR-positive cases, while there was no similar appearance in other molecular subtypes.

Introduction

Breast cancer is the most common female cancer around the world, with an age-adjusted incidence of 43.3 cases per 100 000 women.[1] Although the incidence of breast cancer is lower in China compared with Western countries, there has been a rising trend in recent years, with an age-standardized rate (ASR) of 22.1 cases per 100 000 women according to GLOBOCAN.[1] Cases in China account for 12.2% of all newly diagnosed breast cancers and 9.6% of all deaths from breast cancer worldwide.[2] According to the Chinese National Central Cancer Registry, The ASR is twice as high in urban areas (34.3 cases per 100 000 women) as in rural areas (17.0 cases per 100 000 women).[3]

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The cause of breast cancer is multifactorial and complicated. Previous studies have found a number of lifestyle factors that are associated with breast cancer,[4] some of which are associated with reproductive and hormonal factors. Long menstrual life, nulliparity, late age at first live-birth, and limited breastfeeding may be associated with a modestly increased risk of breast cancer.[5-7] Besides that, age, family history, and obesity are also reported to be associated with breast cancer.[8,9] However, the majority of these studies were conducted among Western women. The patterns of breast cancer risk for Chinese women have their own features. The mean age at diagnosis of breast cancer in China is 45-55 years, which is considerably younger than for Western women.[2] That might be due to a birth cohort effect, resulting from changes in menstrual and reproductive patterns, such as the "one child policy" and other lifestyle and environmental factors that are prevalent in more recent birth cohorts.[10]

Gene expression microarray profiles have identified breast cancer into at least five intrinsic molecular subtypes with distinct tumor characteristics, treatment responses, and prognosis.[11] There is increasing evidence that the etiology of breast cancer may differ according to intrinsic molecular subtypes, which can be classified by clinical markers such as estrogen receptors (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2).[12] Previous studies have shown that the strongest and most consistent relationship between reproductive risk factors and breast cancer are seen in ER-positive subtypes.[13,14] Some studies suggested that parity may be associated with an increased risk of triple negative tumors.[13,15-17] However, the distribution of molecular subtypes of breast cancer in China is slightly different from that in Western countries. For example, prevalence of hormone-receptor-positive breast cancer is bout 50% to 60% in China, which is lower than that in Western women (>70%).[2]

To better understand the reproductive and other lifestyle risk factors for breast cancer in Chinese women by subtypes, we conducted a large 1:1 case-control study of 2 978 women from 21 hospitals in northern and eastern China and investigated parity, age at first live birth, breastfeeding, menstruation situation, oral contraceptive use, along with other known risk factors. The present study was approved by the Ministry of Health of the People's Republic of China.

Material and Methods

Study Participants

A multicenter, case-control study that has enrolled 1489 breast cancer female patients and 1489 females was conduct from April 1, 2012 to March, 31, 2013. Participants were recruited from 21 hospitals in 9 provinces in northern and eastern China (Beijing, Hebei, Heilongjiang, Henan, Jilin, Shandong, Shanxi, Tianjin, Shenyang). The inclusion criteria for breast cancer cases was as follows: (1) women with newly diagnosed and histologically confirmed invasive breast cancer; (2) aged from 25 to 70 years old; (3) Han ethnic group. For control group, the inclusion criteria was: (1) women without any history of cancer; (2) physical examination and imaging examination (ultrasound scans and/or mammographic screening) were negative; (3) matched age with the cases (±3 years); (4) women who had been hospitalized or had a regular physical examination in the same hospital with matched case in the same time period (±2 months); (5) Han ethnic group. The paired controls were recruited from the same hospital. The study protocol and procedures were approved by the institutional review boards at the Second Hospital of Shandong University and the other hospitals involved in this study. Written informed consent was obtained from all participants. Breast cancer patients whose histological diagnosis was available and whose ER, PR, and HER2 status were confirmed were selected. Patients cases with either unknown ER(n = 129), PR(n = 138), HER2(n = 132) information were excluded. Finally, 1170 breast cancer patients and 1170 paired control women were included in the analyses.

Data Collection and Lifestyle Factor Assessment

Face to face interview was carried out in hospital immediately after breast cancer diagnosis. The paper questionnaire included the following information: (1) basic demographic characteristics including age, birthplace, height, weight, income, and education; (2) reproductive factors such as age at menarche, age at menopause, menopause status, number of births, and breast feeding; (3) family history of cancer, including first- and second-degree relatives; (4) lifestyle factors such as smoking, alcohol intake, physical exercise, and dietary habits; Menopause was defined as ≥60, or prior bilateral oophorectomy or ovary radical radiotherapy, amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression. The Body Mass Index (BMI) cutoff points of more than 24.0 kg/m^2 for overweight and more than 28.0 kg/m^2 for obesity was used according to Chinese data.[18]

Definition of Tumor Subtypes and Their Assessment

All the breast cancer patients' medical records were reviewed. Estrogen receptor, PR, and HER2 expression were confirmed from the original pathological reports. Estrogen receptor, PR, and HER2 status were assessed according to the ASCO/CAP guideline.[19,20] Tumors were considered HER2-positive if they were either staining scored 3+ by immunohistochemical (IHC) staining, or 2+ by IHC and were confirmed HER2 amplified by fluorescence in situ hybridization (FISH). Breast cancer cases were divided into three major subtypes according to the ER, PR, and HER2 expression: hormone receptor (HR) -positive subtype was defined as ER or PR positive; HER2-enriched subtype was defined as ER and PR negative and HER2 enriched; triple negative breast cancer (TNBC) was defined as ER, PR, and HER2 negative.

Statistical Analysis

Only first-degree breast cancer family history was included in analysis. The accumulated breastfeeding time (month) was collected and average breastfeeding time for each birth (month) was calculated and used into statistical analysis. The lifetime menstrual period (year) was calculated to evaluate the estrogen effect time for postmenopausal women instead of menopausal age, since the accumulated estrogen effect time is more meaningful than the age of menopausal or menarche for postmenopausal women. Menstrual period (year) = age at menopause – age at menarche. The distribution of patient characteristics was quantified among all the subjects. All the variables were treated as categorical variables. We used the missing indicator method to handle missing data. Only 1.1% of women in control group and 1.9% in cases for age of menopausal had missing data.

Chi-squared tests were used to evaluate the significance of differences between cases and controls. Conditional logistic regression models were used to estimate odds ratios (OR) and

95% confidence intervals (95% CI) for the association between risk factors and each breast cancer subtype. Age, age at menarche, parity, age at first live birth, family history of breast cancer, breastfeeding history, breastfeeding duration/birth (month), oral contraceptive use, and overweight/obesity were included into the multivariable analysis. Logistic analyses were adjusted for parity (≤1 or ≥2). For postmenopausal women, menstrual period (year) was used instead of age at menopause. Data were analyzed using the Statistical Package for the Social Sciences for Windows (SPSS version 24.0) (Chicago, IL). All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Descriptive Characteristics

There were 1170 breast cancer patients and 1170 control women included in the analyses. Compared with the control subjects, cases had a significantly higher proportion of childlessness, a later age at first birth (≥30 years), a shorter average breastfeeding duration (≤6 months/birth), a higher proportion of long menstrual period (>30 years), and a higher proportion of overweight/obesity (Table 1).

In stratified analyses by menopause status, most of the same differences can be still observed in both pre- and postmenopausal groups. Cases had a lower proportion of breastfeeding history was still significant in both pre- (92.7% vs. 94.0%, $P < .001$) and postmenopausal (87.1% vs. 92.0%, $P < .001$) population. Shorter average breastfeeding duration (21.3% vs. 16.2%, $P < .001$) and higher proportion of overweight/obesity (38.7% vs. 33.1%, $P = .022$) was significant only in premenopausal population (Supplementary Table S1).

Impact of Reproductive Factors on Molecular Subtypes

The association between reproductive characteristics and breast cancer risk by tumor subtypes was also evaluated by conditional logistic regression. Among the 1170 cases, the positive rates of ER, PR, and HER2 were 75.3% (881/1170), 68.3% (799/1170), and 30.3% (354/1170), respectively. Nine hundreds and two (77.1%) patients were classified as HR positive, 132 (11.3%) as HER2-enriched, and 136 (11.6%) as triple negative subtype.

The proportion of early age of first birth (≤ 23 years) was obviously lower in HR-positive subtype, especially in premenopausal patients (14.2%^{HR} vs. 38.8%^{HER2}, 34.1%^{TNBC}, $P < .001$). Comparing with women who gave their first birth after 30 years old, early age at first birth decreased the risk of HR positive breast cancer (≤23 years: OR 0.209; 95%CI 0.144-0.302; 24-29 years: OR 0.256; 95%CI 0.184-0.356; $P < .001$; Table 3). Stratified analysis showed that early age of first birth was still a protective factor for HR-positive breast cancer in both pre- and postmenopausal patients, but not for other subtypes (Table 3).

HR-positive patients had a higher proportion of having ≤1 child than other subtypes in both pre-(96.1%^{HR} vs. 87.1%^{HER2} 91.5%^{TNBC}, $P = .008$) and postmenopausal patients (85.5%^{HR} vs. 78.7%^{HER2} 68.5%^{TNBC}, $P = .037$). Having ≤1 child increased risk of HR-positive breast cancer (OR 0.882; 95%CI 1.293-2.739) (Table 2), especially in premenopausal group (OR 2.212; 95%CI 1.226-3.990) (Table 3).

Compared with those who had an average breastfed/birth period more than 2 years, those with an average period less than 6 months had an elevated risk of all subtypes (HR positive: OR 2.690; 95% CI 1.714-4.157, $P < .001$; HER2-enriched: OR 3.779; 95% CI, 1.624-8.792, $P = 0.001$; TNBC:

Table 1. Characteristics of breast cancer cases and controls.

	Control (n = 1170) (%)	Cases (n = 1170) (%)	P
Age (year)			
≤40	237 (20.3%)	237(20.3%)	.999
41-50	503 (43.0%)	501 (42.8%)	
51-60	316 (27.0%)	316 (27.0%)	
≥60	114 (9.7%)	116 (9.9%)	
Age at menarche (year)			
≤13	293 (25.0%)	302 (25.8%)	.034
14-17	798 (68.2%)	751 (64.2%)	.015[a]
≥18	66 (5.6%)	95 (8.1%)	
Unknown	13 (1.1%)	22 (1.9%)	
Menopausal status			.492
Premenopausal	735 (62.8%)	751 (64.2%)	
Postmenopausal	436 (37.2%)	419 (35.8%)	
Age at menopause (year)			
<45	37 (8.5%)	35 (8.4%)	.738
46-55	390 (89.4%)	373 (89.0%)	
≥56	9 (2.1%)	11 (2.6%)	
Parity			
0	1 (0.1%)	27 (2.3%)	<.001
1	1021 (87.3%)	1029 (87.9%)	<.001[b]
≥2	148 (12.6%)	114 (9.7%)	
Age at first live birth (year)			
≤23	313 (26.8%)	255 (22.3%)	<.001
24-29	797 (68.2%)	717 (62.8%)	.008[c]
≥30	59 (5.0%)	171 (14.9%)	
Family history of breast cancer			
No	1137 (97.2%)	1123 (96.0%)	.111
Yes	33 (2.8%)	47 (4.0%)	
Breastfeeding			
Yes	1091 (93.2%)	1061 (90.7%)	.023
No (Parous)	79 (6.8%)	109 (9.3%)	
Breastfeeding duration/birth (month)			
≤6	227 (19.4%)	276 (24.1%)	<.001
7-12	434 (37.1%)	416 (36.4%)	.006[d]
13-24	371 (31.7%)	369 (32.3%)	
≥25	137 (11.7%)	82 (7.2%)	
Oral contraceptive use			
Yes	94 (8.0%)	81 (6.9%)	.307
No	1076 (92.0%)	1089 (93.1%)	
Overweight/obesity			
Yes	424 (32.6%)	472 (40.3%)	.041
No	746 (63.8%)	698 (59.7%)	

Two-sided $P < .05$ is statistically significant.
[a]The P-value was calculated comparing menarche at ≥18 years old with others.
[b]The P-value was calculated comparing childlessness with others.
[c]The P-value was calculated comparing first birth at ≥30 years old with others.
[d]The P-value was calculated comparing breastfeeding time ≤6 months with others.

Table 2. Associations between reproductive factors and breast cancer risk by molecular subtype[a].

Characteristic	All cases (*n* = 1170)		HR positive (*n* = 902)		HER2-enriched (*n* = 132)		TBNC (*n* = 136)	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (year)								
≤40	1.010 (0.71-1.43)	.999	0.926 (0.64-1.35)	.793	1.066 (0.51-2.24)	.989	2.010 (0.85-4.76)	.055
41-50	1.018 (0.74-1.39)		0.956 (0.68-1.34)		1.087 (0.57-2.09)		1.495 (0.67-3.34)	
51-60	1.004 (0.73-1.39)		0.862 (0.61-1.22)		1.013 (0.52-1.99)		2.417 (1.10-5.34)	
≥61	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0(ref)	
Age at menarche (year)								
≤13	0.694 (0.48-1.01)	.054	0.722 (0.48-1.09)	.112	0.537 (0.26-1.12)	.116	0.709 (0.32-1.58)	.687
14-17	0.654 (0.46-0.92)		0.672 (0.46-0.98)		0.498 (0.26-0.96)		0.742 (0.36-1.53)	
≥18	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
Parity								
≤1	1.543(1.12-2.14)	.009	1.882 (1.29-2.74)	.001	1.266 (0.67-2.39)	.468	0.966 (0.51-1.84)	.916
≥2	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
Age at first live birth(year)								
≤23	0.288(0.20-0.41)	<.001	0.209 (0.14-0.30)	<.001	1.512 (0.59-3.89)	.102	1.189 (0.43-3.26)	.890
24-29	0.307 (0.22-0.42)		0.256 (0.18-0.36)		0.956 (0.39-2.38)		1.079 (0.41-2.84)	
≥30	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
Family history of breast cancer								
Yes	1.189 (0.73-1.93)	.482	1.098 (0.65-1.86)	.727	2.515 (1.10-5.78)	.030	0.537 (0.13-2.31)	.403
No	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
Breastfeeding								
No	1.543 (1.02-2.33)	.039	1.493 (0.95-2.35)	.082	1.466 (0.67-3.23)	.342	1.738 (0.72-4.22)	.222
Yes	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
Breastfeeding duration/birth (month)								
≤6	2.804 (1.90-4.15)	<.001	2.690 (1.74-4.16)	<.001	3.779 (1.62-8.80)	.001	2.564 (1.11-5.94)	.022
7-12	1.855 (1.34-2.57)		2.065 (1.45-2.95)		1.329 (0.61-2.90)		1.168 (0.55-2.47)	
13-24	1.831 (1.32-2.54)		1.772 (1.24-2.54)		1.908 (0.89-4.07)		1.869 (0.91-3.84)	
≥25	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
Oral contraceptive use								
Yes	0.820 (0.59-1.14)	.240	0.871 (0.61-1.24)	.446	0.673 (0.30-1.50)	.333	0.667 (0.30-1.49)	.323
No	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
Overweight/obesity								
Yes	1.156 (0.97-1.38)	.111	1.134 (0.93-1.38)	.207	1.279 (0.87-1.88)	.211	1.187 (0.81-1.75)	.384
No	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	

[a]Multivariable logistic regression models were used to estimate OR, 95% CI, and *P*-value. Odds ratios were adjusted for parity.

Table 3. Associations between risk factors and breast cancer subtypes by menopausal status.

Characteristic	Premenopausal						P^a	Postmenopausal						P^a
	HR-positive (*n* = 584)		HER2-enriched (*n* = 85)		TNBC (*n* = 82)			HR positive (*n* = 318)		HER2-enriched (*n* = 47)		TNBC (*n* = 54)		
	OR (95% CI)	*P*	OR	*P*	OR	*P*		OR	*P*	OR	*P*	OR	*P*	
Age (year)														
≤40	3.334 (0.62-17.85)	.192	0.919 (0.10-8.21)	.990	1.027 (0.12-8.93)	.981	0.129	0.385 (0.07-2.20)	.283	—		—		.756
41-50	3.705 (0.70-19.68)		0.931 (0.11-8.04)		0.760 (0.09-6.47)			0.519 (0.31-0.88)		0.645 (0.22-1.91)	.428	1.812(0.56-5.85)	.320	
51-60	3.705 (0.48-14.35)		1.052 (0.11-9.87)		1.605 (0.18-14.41)			0.855 (0.59-1.24)		0.870 (0.41-1.86)		2.644(1.09-6.40)		
≥61	1.0 (ref)		1.0 (ref)		1.0 (ref)			1.0 (ref)		1.0 (ref)		1.0 (ref)		
Age at menarche (year)														
≤13	0.932 (0.51-1.72)	0.468	0.554 (0.21-1.46)	0.113	0.863 (0.26-2.83)	0.808	0.559	-		-		-		
14-17	0.802 (0.45-1.44)		0.407 (0.16-1.01)		0.918 (0.30-2.80)			-		-		-		
≥18	1.0 (ref)		1.0 (ref)		1.0 (ref)			-		-		-		
Parity														
≤1	**2.212 (1.23-3.99)**	**.008**	1.499 (0.63-3.55)	0.358	1.979 (0.66-5.95)	0.224	**.008**	1.294 (0.77-2.18)	.333	0.789 (0.28-2.16)	.645	0.596(0.25-1.42)	.243	**.037**
≥2	1.0 (ref)		1.0 (ref)		1.0 (ref)			1.0 (ref)		1.0 (ref)		1.0 (ref)		
Age at first live birth (year)[b]														
≤23	**0.104 (0.06-0.17)**	**<.001**	0.639 (0.23-1.80)	.396	1.171 (0.32-4.30)	0.812	**<.001**	**0.534 (0.29-0.99)**	**.045**	0.998 (0.52-6.43)	—	1.033 (0.20-5.35)	.969	**.033**
24-29	**0.178 (0.11-0.28)**		0.368 (0.14-0.999)		0.982 (0.28-3.49)			**0.404 (0.23-0.70)**		—		1.215 (0.26-5.70)		
≥30	1.0 (ref)		1.0(ref)		1.0 (ref)			1.0 (ref)		1.0 (ref)		1.0 (ref)		
Family history of breast cancer														
Yes	1.086 (0.55-2.13)	.810	0.917 (0.20-4.32)	.913	0.907 (0.20-4.09)	0.899	.640	1.053(0.44-2.51)	.907	**5.745 (1.85-17.80)**	**.002**	—	—	**.009**
No	1.0 (ref)		1.0 (ref)		1.0 (ref)			1.0 (ref)		1.0 (ref)		1.0 (ref)		
Breastfeeding														
No	**2.271 (1.20-4.29)**	**.012**	**3.533 (1.17-10.71)**	**.026**	1.932 (0.58-6.39)	0.281	.732	0.700 (0.35-1.39)	.309	0.397 (0.11-1.41)	.153	1.885 (0.46-7.81)	.392	.660
Yes	1.0 (ref)		1.0 (ref)		1.0 (ref)			1.0 (ref)		1.0 (ref)		1.0 (ref)		
Breastfeeding duration/birth (month) [b]														
≤6	**5.053 (2.87-9.03)**	**<.001**	**7.737 (2.76-21.66)**	**<.001**	2.816 (0.97-8.14)	0.056	**.012**	0.685 (0.33-1.41)	.305	0.972 (0.21-4.47)	.971	3.185 (0.619-16.40)	.166	0.150
7-12	**3.310 (2.07-5.30)**		1.908 (0.73-5.01)		1.228 (0.51-2.94)			0.795 (0.43-1.46)		0.731 (0.18-2.91)		1.259 (0.26-6.10)		
13-24	**2.719 (1.69-5.30)**		2.403 (0.94-6.15)		1.779 (0.77-4.09)			0.694 (0.37-1.29)		1.260 (0.33-4.74)		2.613 (0.56-12.21)		
≥25	1.0 (ref)		1.0 (ref)		1.0 (ref)			1.0 (ref)		1.0 (ref)		1.0 (ref)		
Oral contraceptive use														
Yes	0.878 (0.54-1.42)	.596	0.614 (0.21-1.79)	.371	1.148 (0.47-2.83)	.764	0.774	0.838 (0.48-1.46)	.534	0.672 (0.19-2.37)	.536	0.185 (0.02-1.42)	.105	.194
No	1.0 (ref)		1.0 (ref)		1.0 (ref)			1.0 (ref)		1.0 (ref)		1.0 (ref)		
Overweight/obesity														
Yes	1.209 (0.94-1.56)	.148	1.178 (0.71-1.95)	.523	1.469 (0.90-2.41)	0.128	.320	1.150 (0.84-1.58)	.391	1.737 (0.90-3.34)	.097	0.804 (0.43-1.52)	.503	.156
No	1.0 (ref)		1.0 (ref)		1.0 (ref)			1.0 (ref)		1.0 (ref)		1.0 (ref)		
Menstrual period (year)[b]														
≤30								**0.397 (0.22-0.71)**	**.002**	0.439 (0.13-1.48)	.185	4.162 (0.53-32.63)	.175	**<.001**
31-39								1.016 (0.57-1.81)		0.650 (0.19-2.17)		1.734 (0.21-14.47)		
≥40								1.0 (ref)		1.0 (ref)		1.0 (ref)		

Odds ratios were adjusted for parity.
[a]*P*-value for trends between different subtypes was calculated by trend chi-square.
[b]Among parous women.

OR 2.564; 95% CI, 1.107-5.938, P = .022) (Table 2). while stratified analyses by menopause status indicated that the effect was still significant only in premenopausal HR positive (OR 5.053; 95% CI 2.826-9.032) and HER2-enriched (OR 7.737; 95% CI 2.763-21.664) subtypes (Table 3).

For postmenopausal patients, shorter period of lifetime menstrual cycles (≤30 years) had an obviously decreased risk in HR positive cases (OR 0.397; 95%CI 0.222-0.712), while there was no similar appearance in other molecular subtypes (Table 3).

The effect of family history increasing the risk of breast cancer was only observed in HER2-enriched subtype (OR 2.515; 95%CI 1.095-5.776, P = .030). In stratified analyses, this effect was significant only in postmenopausal subgroup (Table 3). Overweight/obesity were no longer a significant risk factor for any subtype of breast cancer in multiple-factor analysis.

Discussion

Aside from age and family history, risk of developing breast cancer is largely related to reproductive factors. Previous studies have shown that risk of developing breast cancer may be increased by early menarche, late menopause, late age at first pregnancy, use of hormone replacement therapy, while risk is reduced by higher parity and lactation.[21-24]

Estrogen receptor (ER)-positive tumors are more likely affected by exposure to estrogens, while parity can reduce the risk through reducing in lifetime exposure to circulating estrogens.[21] In the past several years, a number of studies have evaluated reproductive risk factors in relation to breast cancer according to molecular subtypes.[25-27] A meta-analysis on reproductive behaviors and risk of developing breast cancer according to tumor subtype factors indicated that parity was associated with a 25% reduced risk of developing HR-positive subtype (OR 0.75; 95% CI, 0.70–0.81; P < .0001). While there was no difference in the risk of developing HER2-enriched and triple negative breast cancer subtype.[26] Recently, a study from North China found that parity reduced the risk of luminal A and luminal B tumor subtypes in both young and older women.[28] Our results showed that having ≤1 child increased risk of HR-positive breast cancer, especially in premenopausal group, which was similar to previous studies.

Later age at first pregnancy, early age at menarche, and late age at menopause were positively associated with HR+ breast cancers in a majority of studies, which may be associated with longer duration of exposure to estrogen.[6,14,15,29,30] The results of this study suggest that later age at first birth was associated with a reduced risk of HR-positive breast cancer. A meta-analysis showed that advanced age at first birth (OR 1.15; 95% CI 1.00–1.32; P = .05) was associated with a reduced risk of developing HR-positive tumor.[26] A prospective study of Norwegian women on reproductive history and the risk of molecular breast cancer subtypes also showed that higher age at first birth was associated with increased risk (HR 1.15, 95 % CI 1.05–1.26, for each 5-year increase in age) in HR-positive subtype.[31] While a study focus on women 20-44 years of age indicated that age at first live birth were inversely associated with risk of triple-negative breast cancer but were not associated with risk of ER-positive cancers.[27] Age distribution and the proportion of later ages at first birth may be the main reason of the contrary results. All the women in the meta-analysis were 20-44 years old, the rates of first birth after 30 years old was about 40%. while in our study, the proportion of women aged 20-44 was about 60%, the rate of first birth after 30 years was about 90%. Most of the studies with the comparable demographic characteristics had similar results with ours.[13,15,29-32]

The results above are concordant with studies in mice and rats,[33,34] in which mammary tumorigenesis was prevented in parous animals. However, the etiology mechanisms behind the parity-induced breast cancer protective effect remain to be revealed. One hypothesis is pregnancy induces functional and long-lived memory and effector T cells that react against multiple tumor-associated antigens.[35] Another study has shown that expression levels of proteins which are critical for regulating apoptosis and DNA damage repairing, such as RAD51 and p53, decrease in the late or nulliparous women in comparison to the early parous ones.[36-38] The result from a study in BALB/c mice also showed that mammary tumorigenesis was prevented in estrogen and progesterone pretreated mice, while oncogenic transformation was not resisted in p53-null mammary epithelium.[39]

Breastfeeding is another important risk factor for breast cancer. Breastfeeding may increase the protective effect of pregnancy by inducing terminal differentiation, removal of initiated breast epithelial cells, excretion of carcinogenic agents, and delay in ovulation.[39] Several case-control and cohort studies have examined the association between breastfeeding and conclusions were controversial.[26,40-42] Previous studies in China showed that breastfeeding for 6 months or longer correlated with a decrease in the risk of TNBC than never breastfeeding in young parous women, (OR = 0:18 and 0.45, respectively).[43] The result of our study showed that shorter period of breastfeeding (≤6 months)/birth decreased the risk of all type of breast cancer. This accords with some meta-analysis,[26,43,44] which demonstrated that lack of breastfeeding increased the risk of all breast cancer subtypes. Breastfeeding is associated with a permanent alteration in the molecular histology of the breast, characterized by involution of terminal duct lobular units: this is a process known to be associated with a reduced breast cancer risk.[45] On the other hand, Chinese women seems to have a long period of breastfeeding time. The proportion of over 25 months feeding time is about 10%, which was not negligible. Using ≥25 months breastfeeding time/birth as the reference may be the other explanation of shorter period of breastfeeding had effects in all molecular types of tumor.

According to our findings, reproductive factors such as parity, breast feeding duration, and period of lifetime menstrual may be more likely to predict the risk of HR-positive disease but not all types of breast cancer. This study had some limitations. Firstly, the potential selection and recall bias since the study was based on a hospital-based investigation. Secondly, the study involved a lot of premenopausal women (63.5%). Thirdly, there was a strict reproductive control policy in China during 1980s-2000s, hence most of the women (87.6%) had just one child. These may restrict the levels of categorization for some variables, and hence, the heterogeneity of the index as there was not enough data for finer stratification.

Conclusion

In conclusion, parity factors were related to the risk of breast cancer. Reproductive behaviors affected risk of breast cancer

differently according to the major molecular subtypes of breast cancer.

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Conflict of Interest

The authors indicated no conflict of interest.

Author Contributions

Conception/design: Z.Y., S.W. **Provision of study material or patients:** F.X., L.L., H.Y., M.L., S.W., J.G., L.Y., F.Z., F.W., Y.X. **Collection and/or assembly of data:** H.Y., M.L., S.W., J.G., L.Y., F.Z., F.W., Y.X., Z.Y., S.W. **Data analysis and interpretation:** F.X., L.L. **Manuscript writing:** F.X., L.L. **Final approval of manuscript:** All authors.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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