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Associations of reproductive time events and intervals with breast cancer risk: a report from the Shanghai Breast Cancer Study

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Abstract

While there is clear evidence for an association between later age at first live birth and increased breast cancer risk, associations of other reproductive timings are less clear. As breast tissues undergo major structural and cellular changes during pregnancy, we examined associations between reproductive time events and intervals with breast cancer risk among parous women from the population-based Shanghai Breast Cancer Study (SBCS). Unconditional logistic regression was used to evaluate associations with breast cancer risk for 3,269 cases and 3,341 controls. In addition to later age at first live birth, later ages at first pregnancy and last pregnancy were significantly associated with increased breast cancer risk (P -trend=0.002, 0.015, 0.008, respectively); longer intervals from menarche to first or last live birth were also associated with increased risks (P -trend<0.001, = 0.018, respectively). Analyses stratified by menopausal status and estrogen receptor (ER) / progesterone receptor (PR) status revealed that associations for later age at first pregnancy or live birth and longer intervals from menarche to first or last live birth occurred among pre-menopausal women and ER+/PR+ breast cancers, whereas the association for later age at last pregnancy occurred among postmenopausal women and ER+/PR- or ER-/PR+ breast cancers. Due to high correlation with other reproductive variables, models did not include adjustment for age at first live birth; when included, significance of all associations was attenuated. These findings suggest while reproductive time events and intervals play an important role in breast cancer etiology, contributions may differ by menopausal status and hormone receptor status of breast cancers.

Keywords

reproductive; breast cancer risk; case-control study

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Introduction

Breast cancer is the most common cancer among women worldwide ¹. Reproductive events and their timing can affect the differentiation of breast tissue, as well as hormonal and immunological profiles, and may thus influence breast cancer risk ². Epidemiologic studies have clearly demonstrated that many reproductive factors are associated with breast cancer risk; early age at menarche, early age at first birth, increasing number of births, and longer duration of breastfeeding are protective factors for breast cancer ^{3–5}. However, associations of other reproductive time events and intervals with breast cancer risk have not been established and results are controversial. Some studies found that later age at last birth increased the risk of breast cancer ^{6–8}, but this was challenged by other studies which found that age at last birth was no more important than age at any intermediate birth ^{9,10}. Some researchers have postulated that the association between breast cancer risk and age at last birth is in part explained by the association of time since last birth ¹¹. Due to a growth enhancing effect of estrogens during pregnancy on premalignant breast cells ¹², a transient increase in breast cancer risk was found among women within 5 years after delivery ¹³; this may explain why a shorter interval since last birth was related to a higher breast cancer risk ¹⁴. Recently, some investigations have focused on the strong influence on breast cancer risk caused by a short interval from first to second birth ¹⁵. They theorized that two closely occurring pregnancies might increase breast cancer risk due to stimulatory effects of female steroid hormones and either short-term or lack of breastfeeding of the first child which may leave breast cells more susceptible to carcinogenic influences ¹⁶. A long interval from menarche to first live birth was also suggested to be an independent risk factor for breast cancer in a recent study; this was attributed to a high susceptibility to carcinogens during this time period ¹⁷.

The majority of studies conducted to date on reproductive timing and breast cancer risk have included only Caucasian women; few studies have been conducted among Asian women. Therefore, we examined the associations of reproductive time events and intervals with breast cancer risk among Chinese women in a large scale case-control study involving 3,443 cases and 3,474 controls.

Material and Methods

Study population

We analyzed data from the Shanghai Breast Cancer Study (SBCS), a population-based case-control study conducted among women in urban Shanghai, China. Details of the SBCS have been described previously ^{18,19}. Briefly, the SBCS had two phases of recruitment, phase I (August 1996–March 1998) and phase II (April 2002–February 2005). Eligibility criteria for the study participants were as follows: permanent resident of urban Shanghai, no prior history of any cancer, aged 25–65 years for phase I, or aged 25–70 years for phase II. A total of 1,602 and 2,388 cases were identified in phase I and II, respectively, through a rapid case-ascertainment system of the Shanghai Cancer Registry. A total of 1,724 and 2,724 controls were randomly selected in phase I and II, respectively, from permanent female residents of the study area through the Shanghai Resident Registry and frequency matched to cases on age by 5-year intervals. A total of 3,443 (response rate: 86.3%) cases and 3,474 (response

rate: 78.1%) controls were recruited. Participants were interviewed by trained interviewers using a structured questionnaire that included detailed information on demographic factors, menstrual and reproductive history, hormone use, dietary habits, prior disease history, physical activity, tobacco and alcohol use, weight history, and family history of cancer. Menstrual and reproductive information included age at menarche, timing and outcome of each pregnancy, duration of breastfeeding after each pregnancy, and reasons known if gravidity or lactation were denied. Menopausal status (premenopausal or postmenopausal) was defined by whether participants reported having any menstrual periods in the 12 months prior to completing the baseline questionnaire; bleeding due to use of female hormones was not included as menstrual periods. The information on ER and PR status were obtained by review of medical and pathology records from the participating hospitals or by immunohistochemical staining for those missing ER and PR status (n=299) by the Vanderbilt Molecular Epidemiology Laboratory¹⁹. As all of our cases were diagnosed prior to 2010, cut-offs for ER and PR positivity were 10% and 1%, respectively. This study was approved by the Institutional Review Boards of all relevant institutions; all participants provided written informed consent.

Statistical methods

Unconditional logistic regression was used to derive odds ratio (OR) and 95% confidence intervals (CIs) for associations between breast cancer and selected reproductive factors. Exposures of interest included age at first pregnancy or live birth, age at last pregnancy or live birth, as well as intervals from menarche to first pregnancy or live birth, menarche to last pregnancy or live birth, first to second live birth, first pregnancy or live birth to reference date (diagnosis date for cases or interview date for controls), and last pregnancy or live birth to reference date. Factors evaluated as potential confounders or effect modifiers included age at menarche, number of live births, duration of breastfeeding (months), menopausal status (Y/N), body mass index (BMI), active smoking (Y/N), drinking (Y/N), physical activity in recent 10 years (Y/N), family history of breast cancer among first degree relatives (Y/N), history of fibroadenoma (Y/N), hormone replacement therapy (HRT) use (Y/N), oral contraceptive use (Y/N), age, education, and study phase. Covariates were considered as confounders and included in the final multivariable models if they changed the estimates of association by 10% or more. Stratified analyses were used to examine if associations with breast cancer risk differed by menopausal status or hormone receptor status (ER / PR). A total of 307 women without a live birth were excluded from our analyses in order to reduce confounding by gravidity. For variables related to the last live birth, all uniparous women were excluded. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). Statistical significance was based on a two-sided probability with a significance level of 0.05.

Results

Table 1 shows demographic and selected characteristics of parous SBCS participants by case-control status. As compared with controls, cases were more likely to have higher educational attainment, be premenopausal, have a later age at menopause, have a positive family history of breast cancer, have a positive history of fibroadenoma and hormone

replacement therapy use, and have a greater body mass index (BMI). Cases were less likely than controls to have a later age at menarche, a greater number of pregnancies or live births, longer durations of breastfeeding, and recent physical activity.

Table 2 presents the associations of reproductive ages and intervals with breast cancer risk among all women, and women stratified by menopausal status. Among all women, in addition to later age at first live birth, later age at first pregnancy and later age at last pregnancy were also associated with higher breast cancer risks (P -trend=0.002, 0.015, 0.008, respectively). Compared to women aged less than 25, those with a first live birth, first pregnancy, or last pregnancy after age 35, had approximately 51%, 49%, and 16% greater risks of breast cancer, respectively. No association was observed for age at last live birth. Two reproductive intervals were found to be associated with risk; longer interval from menarche to first or last live birth was associated with an increased breast cancer risk (P -trend< 0.001, = 0.018, respectively). While no other interval had significant trends, a transient association was observed for interval from first to last pregnancy. Compared to women with less than three years between their first and last pregnancy, those with 3 to 5 years had a 17% decreased risk of breast cancer (OR=0.83, 95% CI: 0.72-0.96). No difference were seen in additional analysis that examined whether associations varied by study phase (data not shown). No associations with risk were found to significantly differ by menopausal status, however, several associations were more pronounced among subgroups of women. Among pre-menopausal women, later age at first pregnancy or live birth and longer interval from menarche to first or last live birth were associated with increased breast cancer risks (P -trend=0.044, 0.006, 0.004, 0.006, respectively). Among postmenopausal women, later age at last pregnancy was associated with an increased breast cancer risk (P -trend=0.048).

Associations with reproductive intervals could not be uniformly adjusted for age at first live birth, because this age was involved in the calculation of many intervals, including menarche to first live birth, interval from first to second live birth and interval from first to last live birth. Further, age at first live birth was also highly correlated with other variables, such as age at first pregnancy (correlation coefficient=0.98) and interval from menarche to first live birth (correlation coefficient=0.92). When either age or interval models included adjustment for age at first live birth, significance of all associations was attenuated. Similarly, when regression models for intervals included adjustment for either beginning or ending variables, significance of findings was also attenuated. We also analyzed intervals from first pregnancy or live birth to diagnosis and interval from last pregnancy or live birth to diagnosis; no association with breast cancer risk was observed (results not shown).

To examine if associations of reproductive ages and intervals with breast cancer risk differed by hormone receptor status, we also stratified analyses by ER/PR status (Table 3). Later age at first pregnancy or live birth was associated with ER+/PR+ breast cancers (P -trend=0.035, 0.009, respectively). The association of later age at last pregnancy with breast cancer risk was associated with ER+/PR- or ER-/PR+ breast cancers (P -trend=0.049). Longer interval from menarche to first live birth increased the risk of both ER+/PR+ and ER+/PR- or ER-/PR+ breast cancers (P -trend=0.008, 0.035, respectively), while longer interval from menarche to last live birth was associated with only increased risk of ER+/PR+ breast

cancers (P -trend=0.018). Finally, a shorter interval between first and second live birth was associated only with ER+/PR+ breast cancers (P -trend=0.013); this was the only risk factor with a significant degree of heterogeneity across strata (P -homogeneity= 0.002).

Discussion

We found that later age at first pregnancy, first live birth and last pregnancy, as well as longer interval from menarche to first or last live birth were significantly associated with increased risks of breast cancer among parous women from the SBCS. Shorter interval between first and second live birth was associated with breast cancer risk only among women with ER+/PR+ breast cancers. No association was found for later age at last live birth, longer interval from first to last pregnancy or live birth, or intervals from any reproductive events to diagnosis. Adjustment for age at first live birth attenuated the significance of all associations found, likely due to its high correlation with other reproductive variables. Given this caveat, our findings must be interpreted with caution.

The inverse association between early age at first live birth and breast cancer risk found in our study is consistent with the results of many other studies that were conducted predominantly among Caucasian women^{20–23}. This association most evident among premenopausal women and among women with ER+/PR+ breast cancers. Age at first pregnancy was also associated with breast cancer risk in our study. Very little was found in the literature on the association of age at first pregnancy, which can end in not only a live birth but also in an incomplete pregnancy, such as an abortion or miscarriage. Pregnancy has many direct effects on the breast, such as stopping monthly menstrual cycles, changing endogenous hormones, and inducing the differentiation of breast tissue, all of which may result in a long-term reduction in breast cancer risk^{24,25}. However, induced abortion, which is a kind of incomplete pregnancy, shows no association with breast cancer risk²⁶. This was also demonstrated in a previous analysis of the SBCS²⁷. Different trimesters of pregnancy have different effects on breast cells, including proliferation and differentiation²⁸; the effect of an interruption of pregnancy during different trimesters on breast cancer risk is not clear²⁹. The association of age at first pregnancy may largely be influenced by the high percent (85.31%) of women for whom their first pregnancy ended in a live birth, and the high correlation between age at first pregnancy and age at first live birth in our study (correlation coefficient=0.98). Prior studies also suspected that because of the seriousness of malignant disease, reporting of incomplete pregnancy was more accurate among breast cancer cases, while underreporting may occur among healthy controls, who may be more reluctant to report on a controversial, emotionally charged subject such as induced abortion^{30,31}. This may result in an elevated association between age at first pregnancy and breast cancer risk; as a case-control study, this possibility cannot be excluded as a possible contributing factor to our results. However, unlike western countries such as the US, in which induced abortion was legalized only after 1970 and has not reached full social acceptance, induced abortion is an acceptable practice in China, and does not carry the same social stigma as in the US. Thus, underreporting of incomplete pregnancy would not likely be a remarkable source for bias in studies among Chinese women³².

The most interesting finding in the current study was that a long interval from menarche to first live birth also increased breast cancer risk. Breast tissue is largely undifferentiated and exposed to mitogenic effects of ER and PR during this period, thus particularly susceptible to carcinogens³³. The interval between menarche to first live birth has been described as a “window of high susceptibility”³⁴. A shorter interval from menarche to first live birth is linked to higher endogenous hormone levels². A French prospective cohort study reported that the risk of breast cancer for women in the highest quartile of cumulative number of menstrual cycles before their first birth was 1.42-fold higher³⁵. A combined analysis of seven case-control studies had similar results^{36,37}. The association of this interval with breast cancer risk was evident among premenopausal women and those with ER+/PR+ breast cancers. Our findings are consistent with a prior study conducted among women in the US, which showed that this interval was associated with the risk of ER+/PR+ breast cancers, particularly among premenopausal White women, but was absent among premenopausal African-American women, possible due to a sample size limitation (731 cases and 658 controls)¹⁷. However, the number of premenopausal women in our study was larger (1,970 cases and 1,890 controls), and so a sample size limitation is not a concern in the current study. While few studies on this potential risk factor had been reported in the literature, it is unclear whether the association of interval from menarche to first live birth with breast cancer risk differs by race; further research among additional study populations is therefore needed.

In agreement with many other studies^{9,10,22}, no association with breast cancer risk was found for age at last live birth or time since last live birth in the current study. The association between last live birth and breast cancer risk found in some studies may be due to the short-term increase in breast cancer risk that occurs after a live birth¹⁰. Maternal breast cancer risk reaches its highest level around 5 years after giving birth, and it takes 15 years to lower the risk¹³. The participants in our study had a long interval from time of last live birth to diagnosis or reference date (mean=29.87, standard deviation=7.78), and only 658 women had another pregnancy within 5 years of their last live birth; this prohibited us from further investigating the transient risk after pregnancy that has been seen in other studies.

In summary, this large population-based case-control study is the first to comprehensively examine associations of reproductive time events and intervals with breast cancer risk among Chinese women. Strengths of the study include a large population of parous women, and detailed data on reproductive events and timings and tumor characteristics. A potential limitation is recall bias, as data collection occurred after diagnosis for breast cancer cases. While this possibility cannot be alleviated, many of our results are in agreement with those from prospective analyses^{8,35}, so this is unlikely to be a major concern. In this study, later age at first pregnancy, first live birth, and longer interval from menarche to first or last live birth were associated with increased breast cancer risk; these associations were more apparent for pre-menopausal women and ER+/PR+ breast cancers. Later age at last pregnancy was also associated with breast cancer risk, but this was more apparent among postmenopausal women or women with ER+/PR- or ER-/PR+ breast cancers. Thus, reproductive time events and intervals play an important role in breast cancer etiology

among Chinese women, and their effects may differ by menopausal status or tumor characteristics.

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Abbreviations

BMI	Body mass index
CI	Confidence interval
ER	Estrogen receptor
HRT	Hormone replacement therapy
OR	Odds ratio
PR	Progesterone receptor
SBCS	Shanghai Breast Cancer Study
sd	Standard deviation

What's new?

Early age at menarche and first live birth have been widely reported to be associated with decreased breast cancer risks; however, associations of other reproductive timings is less clear, especially among Asian women. This large population-based case-control study is the first to comprehensively examine associations of reproductive time events and intervals with breast cancer risk among parous women, and one of a few such studies among Chinese women. Findings include that in addition to later age at first live birth, later age at first pregnancy, later age at last pregnancy, and longer intervals from menarche to either first live birth or last live birth were associated with increased breast cancer risk. Further, these associations were found to vary by menopausal status and hormone-receptor status. Notably, significance of all associations was attenuated when adjusted included age at first birth, possibly due to its high correlation with other reproductive events and intervals.

Table 1
Demographic and selected breast cancer risk factors among parous participants; the Shanghai Breast Cancer Study

Characteristic	Cases (n=3443)		Controls (n=3474)		P
	n	mean <i>I</i> / sd <i>2</i>	n	mean <i>I</i> / sd <i>2</i>	
Study Phase					
I	1381	42.25	1495	44.75	
II	1888	57.75	1846	55.25	0.040
Age (years) ³	49.89	8.13	50.28	8.68	0.059
Education					
Elementary School or less	280	8.57	420	12.57	
Junior High School	1300	39.77	1389	41.57	
Senior High School	1224	37.44	1174	35.14	
College or more	465	14.22	358	10.72	<.001
Age at Menarche	14.42	1.63	14.68	1.74	<.001
Menopausal Status					
Premenopausal	1970	60.26	1890	56.59	
Postmenopausal	1299	39.74	1450	43.41	0.002
Age at Menopause ^a	49.91	3.40	49.33	3.75	<.001
Number of Pregnancies					
1	693	21.20	648	19.40	
2	1154	35.30	1131	33.85	
3	775	23.71	839	25.11	
4	647	19.79	723	21.64	0.052
Number of Live Births					
1	2376	72.68	2285	68.39	
2	629	19.24	698	20.89	
3	184	5.63	239	7.15	
4	80	2.45	119	3.56	<.001
Abortion					
Never	1168	35.73	1156	34.60	
Ever	2101	64.27	2185	65.40	0.336

Characteristic	Cases (n=3443)			Controls (n=3474)			P
	n	mean	% / sd	n	mean	% / sd	
Breastfeeding							
Never	750		22.94	689		20.62	
Ever	2519		77.06	2652		79.38	0.022
Lifetime Duration of Breastfeeding (months) ^b	13.2		11.48	14.85		12.97	<.001
Breast Cancer among First Degree Relatives							
Never	3118		95.38	3249		97.25	
Ever	151		4.62	92		2.75	<.001
Ever had Breast Fibroadenoma							
Never	2942		90.25	3158		94.58	
Ever	318		9.75	181		5.42	<.001
Oral Contraceptive Use							
Never	2612		79.90	2647		79.23	
Ever	657		20.10	694		20.77	0.497
Hormone Replacement Therapy							
Never	3140		96.11	3243		97.07	
Ever	127		3.89	98		2.93	0.033
Body Mass Index (BMI)	23.69		3.30	23.35		3.29	<.001
Ever Smoking							
Never	3180		97.28	3245		97.13	
Ever	89		2.72	96		2.87	0.710
Ever Drinking							
Never	3120		95.47	3152		94.43	
Ever	148		4.53	186		5.57	0.053
Physical Activities in recent 10 years							
Never	2467		75.47	2330		69.74	
Ever	802		24.53	1011		30.26	<.001

¹ n for categorical variables or mean for continuous variables

² % for categorical variables or standard deviation(sd) for continuous variables

³ Age at diagnosis for cases or age at interview for controls

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Among women with natural menopause
Among women who ever breastfed

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Association of reproductive ages and intervals with breast cancer risk, by menopausal status; the Shanghai Breast Cancer Study

Table 2

Risk Factors	All Women				Prenopausal Women				Postmenopausal Women				$P_{\text{interaction}}^c$
	Cases / Controls(3269 / 3341)	OR	$I.2$	P	Cases / Controls(1970 / 1890)	OR	$I.2$	P	Cases / Controls(1299 / 1450)	OR	$I.2$	P	
Ages at:													
First Pregnancy (years) ^a													
<25	1067/1246	1 (reference)	I	-	441/473	1 (reference)	I	-	626/773	1 (reference)	I	-	
25-29	1732/1721	1.04 (0.92-1.17)	0.583		1229/1180	1.06 (0.90-1.25)	0.458		503/541	0.96 (0.79-1.16)	0.673		
30-34	400/326	1.22 (1.01-1.47)	0.035		256/208	1.21 (0.95-1.53)	0.129		144/117	1.22 (0.91-1.65)	0.182		
>=35	70/48	1.49 (1.00-2.20)	0.048		44/29	1.60 (0.96-2.64)	0.070		26/19	1.35 (0.72-2.52)	0.355		
P trend			0.015				0.044				0.248		0.889
First Live Birth (years) ^a													
<25	759/914	1 (reference)	I	-	252/260	1 (reference)	I	-	507/654	1 (reference)	I	-	
25-29	1819/1878	1.01 (0.87-1.16)	0.936		1254/1281	0.96 (0.78-1.18)	0.666		565/597	1.03 (0.84-1.26)	0.768		
30-34	571/467	1.22 (1.02-1.46)	0.034		385/297	1.21 (0.94-1.56)	0.133		186/169	1.13 (0.85-1.50)	0.395		
>=35	120/82	1.51 (1.10-2.07)	0.011		79/52	1.51 (1.00-2.28)	0.048		41/30	1.43 (0.85-2.40)	0.173		
P trend			0.002				0.006				0.192		0.485
Last Pregnancy (years) ^a													
<30	1078/1267	1 (reference)	I	-	599/641	1 (reference)	I	-	479/626	1 (reference)	I	-	
30-34	935/918	1.09 (0.97-1.23)	0.133		521/499	1.01 (0.87-1.18)	0.885		414/418	1.20 (1.01-1.43)	0.043		
>=35	560/507	1.16 (1.01-1.33)	0.040		310/268	1.10 (0.91-1.33)	0.320		250/239	1.22 (0.99-1.51)	0.067		
P trend			0.008				0.113				0.048		0.245
Last Live Birth (years) ^b													
<30	579/722	1 (reference)	I	-	88/107	1 (reference)	I	-	491/615	1 (reference)	I	-	
30-34	253/269	1.04 (0.85-1.27)	0.703		46/40	1.26 (0.76-2.09)	0.379		207/229	0.98 (0.79-1.23)	0.882		
>=35	61/64	1.00 (0.69-1.45)	0.994		17/16	1.08 (0.51-2.28)	0.846		44/48	0.98 (0.63-1.53)	0.935		
P trend			0.602				0.077				0.949		0.935

Risk Factors	All Women			Premenopausal Women			Postmenopausal Women			$P_{\text{interaction}}^c$
	Cases / Controls(3269 / 3341)	OR 1,2	P	Cases / Controls(1970 / 1890)	OR 1,2	P	Cases / Controls(1299 / 1450)	OR 1,2	P	
Menarche to First live birth (years) ^a										
<10	747/953	1 (reference) ²	-	261/291	1 (reference) ²	-	486/662	1 (reference) ²	-	
10-14	1565/1612	1.07 (0.93-1.23)	0.321	1057/1083	1.04 (0.85-1.27)	0.690	508/529	1.08 (0.89-1.32)	0.441	
>=15	952/775	1.31 (1.11-1.53)	0.001	650/515	1.31 (1.05-1.63)	0.018	302/259	1.25 (0.98-1.60)	0.076	
P trend			<.001			0.004			0.074	0.366
Menarche to Last live birth (years) ^b										
<10	132/223	1 (reference) ²	-	12/27	1 (reference) ²	-	120/196	1 (reference) ²	-	
10-14	402/485	1.06 (0.87-1.30)	0.582	71/79	1.17(0.63-2.19)	0.626	331/406	1.08 (0.86-1.36)	0.514	
>=15	358/347	1.16 (0.94-1.42)	0.179	68/57	1.48 (0.78-2.82)	0.230	290/290	1.12 (0.88-1.42)	0.371	
P trend			0.018			0.006			0.107	0.952
First to Second Live Birth (years) ^b										
<1.5	112/112	1 (reference) ¹	-	18/18	1 (reference) ¹	-	94/94	1 (reference) ¹	-	
1.5-2.99	412/517	0.90 (0.73-1.12)	0.357	45/51	0.73 (0.37-1.43)	0.354	367/466	0.94 (0.74-1.20)	0.636	
>=3	366/422	0.88 (0.73-1.07)	0.193	87/92	0.74 (0.42-1.30)	0.300	279/330	0.89 (0.71-1.11)	0.291	
P trend			0.391			0.997			0.360	0.921
First to Last Pregnancy (years) ^a										
<3	912/877	1 (reference) ¹	-	650/630	1 (reference) ¹	-	262/246	1 (reference) ¹	-	
3-4.99	480/573	0.83 (0.72-0.96)	0.011	271/286	0.87 (0.72-1.05)	0.151	209/287	0.79 (0.62-1.00)	0.050	
5-9.99	785/826	0.99 (0.86-1.13)	0.853	324/338	0.89 (0.74-1.07)	0.206	461/488	1.10 (0.89-1.36)	0.403	
>=10	384/410	1.00 (0.84-1.18)	0.976	176/149	1.07 (0.84-1.36)	0.582	208/261	0.97 (0.75-1.25)	0.786	
P trend			0.787			0.869			0.791	0.085
First to Last Live Birth (years) ^b										
<3	308/344	1 (reference) ¹	-	54/64	1 (reference) ¹	-	254/280	1 (reference) ¹	-	
3-4.99	239/298	0.88 (0.71-1.10)	0.265	38/51	0.75 (0.43-1.30)	0.305	201/247	0.89 (0.69-1.14)	0.339	

Risk Factors	All Women			Premenopausal Women			Postmenopausal Women			<i>P</i> _{interaction^c}
	Cases / Controls(3269 / 3341)	OR 1, 2	<i>P</i>	Cases / Controls(1970 / 1890)	OR 1, 2	<i>P</i>	Cases / Controls(1299 / 1450)	OR 1, 2	<i>P</i>	
5-9,99	295/348	1.01 (0.79-1.29)	0.941	49/36	1.41 (0.79-2.51)	0.240	246/312	0.93 (0.71-1.23)	0.626	
>=10	49/63	0.95 (0.60-1.48)	0.804	9/10	0.89 (0.33-2.38)	0.817	40/53	0.89 (0.53-1.48)	0.646	
<i>P</i> trend			0.900			0.155			0.737	0.221

^a Among parous women

^b Among multiparous women

^c Test for interaction of *P*-trend values between premenopausal and postmenopausal women, calculated using multivariable logistic regression

¹ Adjusted for study phase, age, education, age at menarche, menopausal status, number of live births, duration of breastfeeding, body mass index (BMI), physical activities in recent 10 years (Y/N), family history of breast cancer in first degree relative (Y/N), history of fibroadenoma (Y/N) and hormone replacement therapy (HRT) use (Y/N)

² Adjusted for above except variable which is beginning or ending of the intervals

Table 3
Reproductive ages and intervals and breast cancer risk, by ER/PR status; the Shanghai Breast Cancer Study

Risk Factors	Controls(n=3341)	ER / PR Status										$P_{\text{homogeneity}}^c$	
		ER + / PR +				ER + / PR- Or ER - / PR +							
		Cases(n=1412)	OR	I, 2	P	Cases(n=544)	OR	I, 2	P	Cases(n=748)	OR		I, 2
Ages at:													
First Pregnancy (years)													
a													
<25	1246	425	1 (reference)	I	-	165	1 (reference)	I	-	270	1 (reference)	I	-
25-29	1721	777	1.07 (0.91-1.26)		0.407	311	1.15 (0.91-1.45)		0.236	372	0.84 (0.69-1.02)		0.075
30-34	326	182	1.25 (0.99-1.59)		0.060	59	1.12 (0.79-1.59)		0.535	89	1.00 (0.74-1.34)		0.995
>=35	48	28	1.46 (0.88-2.40)		0.141	9	1.19 (0.56-2.54)		0.648	17	1.31 (0.73-2.37)		0.365
P trend					0.035				0.379				0.132
First Live Birth (years)													
a													
<25	914	292	1 (reference)	I	-	113	1 (reference)	I	-	185	1 (reference)	I	-
25-29	1878	811	1.06 (0.88-1.28)		0.536	318	1.14 (0.86-1.51)		0.352	414	0.91 (0.72-1.14)		0.395
30-34	467	260	1.27 (1.00-1.61)		0.050	95	1.31 (0.93-1.85)		0.124	122	1.01 (0.75-1.36)		0.962
>=35	82	49	1.53 (1.02-2.29)		0.042	18	1.46 (0.81-2.63)		0.207	27	1.32 (0.80-2.16)		0.279
P trend					0.009				0.080				0.206
Last Pregnancy (years)													
a													
<30	1267	461	1 (reference)	I	-	167	1 (reference)	I	-	262	1 (reference)	I	-
30-34	918	398	1.05 (0.91-1.22)		0.514	172	1.27 (1.03-1.57)		0.026	199	0.99 (0.82-1.20)		0.918
>=35	507	236	1.09 (0.91-1.30)		0.370	92	1.20 (0.93-1.56)		0.167	135	1.20 (0.96-1.50)		0.115
P trend					0.183				0.049				0.704
Last Live Birth (years)													
b													
<30	722	223	1 (reference)	I	-	90	1 (reference)	I	-	135	1 (reference)	I	-
30-34	269	93	0.95 (0.72-1.25)		0.728	46	1.18 (0.81-1.71)		0.389	56	1.01 (0.73-1.41)		0.933
>=35	64	24	0.86 (0.52-1.42)		0.556	8	0.73 (0.33-1.57)		0.417	17	1.22 (0.69-2.15)		0.496

Risk Factors	Controls(n=3341)	ER / PR Status								$P_{\text{homogeneity}}^c$
		ER + / PR +		ER + / PR- Or ER - / PR +		ER - / PR-		P		
		Cases(n=1412)	OR $I, 2$	Cases(n=544)	OR $I, 2$	Cases(n=748)	OR $I, 2$			
P trend				0.920			0.744		0.540	0.937
Intervals from:										
Menarche to First live birth (years) ^a										
<10	953	291	1 (reference) ²	-	115	1 (reference) ²	-	187	1 (reference) ²	-
10-14	1612	697	1.12 (0.93-1.34)	0.254	266	1.11 (0.84-1.45)	0.464	350	0.93 (0.74-1.16)	0.503
>=15	775	423	1.31(1.06-1.62)	0.012	162	1.35 (0.99-1.83)	0.055	211	1.11 (0.86-1.44)	0.435
P trend				0.008			0.035		0.31	0.151
Menarche to Last live birth (years) ^b										
<10	223	40	1 (reference) ²	-	19	1 (reference) ²	-	32	1 (reference) ²	-
10-14	485	162	1.17 (0.89-1.54)	0.268	58	1.06 (0.70-1.59)	0.796	100	1.23 (0.88-1.72)	0.217
>=15	347	138	1.12 (0.84-1.49)	0.432	67	1.39 (0.94-2.06)	0.102	76	1.11 (0.78-1.57)	0.567
P trend				0.018			0.066		0.426	0.238
First to Second Live Birth (years) ^b										
<1.5	112	54	1 (reference) ^I	-	11	1 (reference) ^I	-	18	1 (reference) ^I	-
1.5-2.99	517	162	0.83 (0.62-1.11)	0.201	69	1.33 (0.85-2.07)	0.211	90	1.02 (0.70-1.48)	0.934
>=3	422	123	0.67 (0.51-0.88)	0.004	64	1.14 (0.78-1.68)	0.499	100	1.20 (0.88-1.65)	0.254
P trend				0.013			0.679		0.104	0.002
First to Last Pregnancy (years) ^a										
<3	877	418	1 (reference) ^I	-	137	1 (reference) ^I	-	212	1 (reference) ^I	-
3-4.99	573	195	0.75 (0.62-0.92)	0.004	87	1.00(0.76-1.31)	0.991	106	0.80(0.63-1.03)	0.082
5-9.99	826	326	0.95 (0.80-1.13)	0.587	138	1.25 (0.97-1.60)	0.083	180	1.03 (0.82-1.28)	0.814
>=10	410	151	0.89 (0.71-1.11)	0.304	67	1.23 (0.90-1.68)	0.199	94	1.10 (0.83-1.44)	0.509
P trend				0.474			0.053		0.485	0.112
First to Last Live Birth (years) ^b										

Risk Factors	Controls(n=3341)	ER / PR Status										$P_{\text{homogeneity}}^c$	
		ER + / PR +		ER + / PR- Or ER - / PR +		ER - / PR-							
		Cases(n=1412)	OR $I, 2$	P	Cases(n=544)	OR $I, 2$	P	Cases(n=748)	OR $I, 2$	P			
<3	344	130	1 (reference)	I	-	46	1 (reference)	I	-	66	1 (reference)	I	-
3-4.99	298	86	0.72 (0.53-0.99)	0.043		38	1.00 (0.64-1.55)	0.983		53	1.02 (0.70-1.48)	0.938	
5-9.99	348	103	0.85 (0.60-1.19)	0.334		54	1.44 (0.91-2.29)	0.118		75	1.39 (0.94-2.07)	0.099	
>=10	63	20	0.89 (0.49-1.61)	0.690		6	0.89 (0.35-2.27)	0.800		14	1.57 (0.79-3.13)	0.199	
P trend				0.556				0.364				0.071	0.212

^a Among Parous Women

^b Among Multiparous Women

^c Test for homogeneity of P -trend values among the hormone receptor groups, calculated using multivariable logistic regression

¹ Adjusted for study phase, age, education, age at menarche, menopausal status, number of live birth, duration of breastfeeding, body mass index (BMI), physical activities in recent 10 years (Y/N), family history of breast cancer in first degree relative (Y/N), history of fibroadenoma (Y/N) and hormone replacement therapy (HRT) use (Y/N).

² Adjusted for above except variable which is beginning or ending of the intervals