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ASSOCIATION OF MENSTRUAL AND REPRODUCTIVE FACTORS WITH BREAST CANCER RISK: RESULTS FROM THE SHANGHAI BREAST CANCER STUDY

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The incidence of breast cancer among women in Shanghai, a traditionally low-risk population, has increased substantially over the past 20 years. To evaluate the association of menstrual and reproductive factors with breast cancer risk and the influence of these factors on the temporal trend of breast cancer incidence, we analyzed data from the Shanghai Breast Cancer Study, a population-based case-control study of breast cancer recently completed among Chinese women in urban Shanghai. In-person interviews were completed for 1,459 women newly diagnosed with breast cancer between ages 25 and 64 and for 1,556 controls frequency-matched to cases by age. Unconditional logistic regression was employed to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) related to menstrual and reproductive factors. Earlier menarcheal age, nulliparity, and later age at first live birth were associated with increased risk of breast cancer among both pre- and post-menopausal women, while never having breast-fed and later age at menopause were associated with elevated risk only among post-menopausal women. Among controls, 32% of younger women (≤40 years) and 24% of older women (>40 years) reported starting menarche at age of 13 or younger, and this factor contributed to 44% of cases diagnosed among younger women and 26% to 28% of cases in older women. Older age at first live birth or at menopause explained a considerable portion of cases diagnosed in older, but not younger, women. Our study suggests that the changes in menstrual and reproductive patterns among women in Shanghai have contributed to the recent increase in breast cancer incidence, particularly among younger women. *Int. J. Cancer* 87:295–300, 2000.

Chinese women historically have a lower risk of breast cancer compared to their counterparts in the United States and other Western countries. The age-adjusted breast cancer incidence rate from 1988 to 1992 among women in Shanghai, the largest city on the east coast of China with a population of over 6 million, was 26.5/100,000, about one-third the incidence in U.S. white women (90.7/100,000, SEER population) (Parkin *et al.*, 1997). The incidence of breast cancer among women in urban Shanghai, however, has been increasing at an alarming rate (averaging 2.7% annually) over the last 2 decades, with a total increase of 50.5% from 1972–1974 to 1993–1994 (Jin *et al.*, 1999). The increase was more pronounced among younger women, 87.1% and 85.4% for age groups 35 to 44 and 45 to 54, respectively, for the same time period. Parallel to the marked change in breast cancer incidence, there have been socio-economic advances, including major alterations in various reproductive patterns and menstrual characteristics. During 1996 and 1998, we conducted a population-based case-control study of breast cancer in urban Shanghai to identify factors that may have contributed to the change in breast cancer incidence. We report here associations of breast cancer with menstrual and reproductive factors, as well as breast-feeding practices.

MATERIAL AND METHODS

This population-based case-control study, the Shanghai Breast Cancer Study, was designed to recruit all women newly diagnosed with breast cancer between the ages of 25 and 64 during the period August 1996 to March 1998. All study subjects were permanent residents of urban Shanghai who had no prior history of cancer and were alive at the time of interview. Through a rapid case-ascertainment system, supplemented by the population-based Shanghai Cancer Registry, 1,602 eligible breast cancer cases were identified during the study period, and in-person interviews were completed for 1,459 (91.1%) of them. The major reasons for non-participation were refusal (109 cases, 6.8%), death prior to interview (17 cases, 1.1%), and inability to locate (17 cases, 1.1%). All diagnoses were confirmed by 2 senior pathologists through the review of slides.

Controls were randomly selected from female permanent residents in urban Shanghai and frequency-matched to cases by age (5-year interval). The number of controls in each age-specific stratum was determined in advance according to the age distribution of the incident breast cancer cases reported to the Shanghai Cancer Registry from 1990 to 1993. The Shanghai Resident Registry, which keeps registry cards for all permanent residents in urban Shanghai, was used to randomly select controls. For each age–pre-determined control, a registry card identifying a potential control in the same 5-year age group was randomly selected. Only women who lived at the registered address during the study period were considered to be eligible for the study. In-person interviews were completed for 1,556 (90.3%) of the 1,724 eligible controls. Reasons for non-participation included refusal (166 controls, 9.6%) and death or a prior cancer diagnosis (2 controls, 0.1%).

All study participants were interviewed by trained interviewers at hospitals (cases) or at home (cases and controls). A structured questionnaire was used to elicit 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. Information on menstrual and reproductive history included age at menarche, usual length of menstrual cycle, menopausal status, cause of menopause, age at menopause, pregnancies and their outcomes, causes of infertility, and duration of breast-feeding for each live birth. All participants were also measured for current

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weight, circumferences of the waist and hip, and sitting and standing heights.

Odds ratios (ORs), approximators of relative risk, were used to measure the association of breast cancer risk with menstrual and reproductive characteristics. Unconditional logistic regression models were used to obtain maximum likelihood estimates of the ORs and their 95% confidence intervals (CIs) after adjusting for potential confounders (Breslow and Day, 1980). Age was included as a continuous variable throughout data analyses, and categorical variables were treated as dummy variables in the model. Tests for trend were performed by entering the categorical variables as continuous parameters in the models. Population attributable risk (PAR) was calculated using the method of Mezzetti *et al.* (1996).

RESULTS

Presented in Table I are comparisons of cases and controls on demographic factors and traditional breast cancer risk factors other than menstrual and reproductive ones. Cases were slightly older than controls, with mean ages of 47.9 and 47.3 years, respectively ($P < 0.05$). There were no major case–control differences regarding family income (adjusted for education), alcohol consumption, use of oral contraceptives, or hormone-replacement therapy. Compared with controls, cases were more likely to have had more years of education, a family history of breast cancer among first-degree relatives, a history of breast fibroadenoma, a higher body mass index, and a higher waist-to-hip ratio and less likely to exercise during the past 10 years. All subsequent analyses included these variables and age to control for potential confounding effects.

Age at menarche was inversely associated with risk of breast cancer (P for trend < 0.01) (Table II). Compared to subjects with menarcheal age ≤12, subjects with menarcheal age of ≥17 years had a 30% (95% CI 0.5–0.9) lower risk of breast cancer. The percentage of menopausal women was lower in cases than controls (OR = 0.6, 95% CI 0.5–0.8). Risk of breast cancer was increased with later age at menopause (P for trend = 0.02). Compared with women whose menopause occurred before age 45, those whose menstrual periods continued until age 55 or later had a 2.4-fold (95% CI 1.1–5.2) increased risk of breast cancer. Length and regularity of menstrual cycles, as well as reasons for menopause, were unrelated to risk of breast cancer.

TABLE I – COMPARISON OF CASES AND CONTROLS ON DEMOGRAPHICS AND SELECTED BREAST CANCER RISK FACTORS

	Cases (n = 1,459)		Controls (n = 1,556)		P value
	Number	%	Number	%	
Age (years)					
25–34	42	2.9	82	5.3	
35–44	523	35.9	566	36.4	
45–54	565	38.7	520	33.4	
55–64	329	22.5	388	24.9	<0.01
Education					
No formal educ.	53	3.6	85	5.5	
Elementary	124	8.5	131	8.4	
Middle + high	1,084	74.3	1,174	75.4	
Prof. + college	198	13.6	166	10.7	0.01
Per capita income (last year, yuan)					
<4,000	289	19.8	284	18.2	
4,000–5,999	462	31.7	497	31.9	
6,000–7,999	190	13.0	217	13.9	
8,000–8,999	295	20.2	365	23.5	
≥9,000	222	15.2	193	12.4	0.05
Breast cancer among first-degree relatives					
No	1,405	96.3	1,518	97.6	
Yes	54	3.7	38	2.4	0.05
Ever had breast fibroadenoma					
No	1,318	90.4	1,478	95.0	
Yes	140	9.6	78	5.0	<0.01
Body mass index (by quartile)					
≤20.70	295	20.3	379	24.4	
20.71–22.79	349	24.0	395	25.4	
22.80–25.10	390	26.8	394	25.3	
>25.10	421	28.9	387	24.9	0.01
Waist-to-hip ratio (by quartile)					
≤0.764	284	19.5	388	25.0	
0.765–0.800	368	25.3	416	26.8	
0.801–0.835	364	25.0	357	23.0	
>0.835	440	30.2	394	25.3	<0.01
Alcohol consumption					
Never	1,398	96.0	1,489	95.9	
Ever	59	4.0	63	4.1	0.99
Oral-contraceptive use					
Never	1,140	78.1	1,231	79.1	
Ever	319	21.9	325	20.9	0.51
Hormone-replacement therapy					
Never	1,415	97.1	1,514	97.3	
Ever	42	2.9	42	2.7	0.76
Physical activity during past 10 years					
Never	1,185	81.3	1,163	74.8	
Ever	273	18.7	392	25.2	<0.01

Subjects with missing values were excluded from the analysis.

TABLE II – OR AND 95% CI FOR BREAST CANCER RISK ASSOCIATED WITH MENSTRUAL CHARACTERISTICS

	Case	Control	OR[1] (95% CI)	OR[2] (95% CI)
Age at menarche (years)				
≤12	139	133	1.0 (reference)	1.0 (reference)[3]
13	323	281	1.1 (0.8–1.5)	1.2 (0.9–1.6)
14	309	337	0.9 (0.7–1.2)	0.9 (0.7–1.2)
15	304	305	0.9 (0.7–1.3)	1.0 (0.7–1.3)
16	231	276	0.8 (0.6–1.1)	0.8 (0.6–1.1)
≥17	153	224	0.6 (0.5–0.9)	0.7 (0.5–0.9)
Trend test			$P < 0.01$	$P < 0.01$
Menopause				
No	952	990	1.0 (reference)	1.0 (reference)[4]
Yes	501	562	0.6 (0.5–0.8)	0.6 (0.5–0.8)
Reasons for menopause (menopausal women)				
Natural	433	489	1.0 (reference)	1.0 (reference)[4]
Surgery	63	65	1.1 (0.7–1.6)	1.1 (0.8–1.7)
Other	3	3	1.1 (0.2–5.6)	1.5 (0.3–7.7)
Age at menopause (women with natural menopause)				
<45	45	75	1.0 (reference)	1.0 (reference)[4]
45–49	192	213	1.4 (0.9–2.1)	1.4 (0.9–2.2)
50–54	172	183	1.5 (1.0–2.3)	1.5 (0.9–2.3)
≥55	24	18	2.1 (1.0–4.3)	2.4 (1.1–5.2)
Trend test			$P < 0.01$	$P = 0.02$
Length of menstrual cycle				
26–30 days	894	931	1.0 (reference)	1.0 (reference)[5]
<26 days	296	345	0.9 (0.8–1.1)	0.9 (0.7–1.1)
>30 days	268	278	1.0 (0.8–1.2)	1.0 (0.9–1.3)
Regularity of menstrual cycle				
Always regular	1,384	1,479	1.0 (reference)	1.0 (reference)[5]
Always irregular	46	42	1.2 (0.8–1.8)	1.2 (0.7–1.8)
Sometimes irregular	28	33	0.9 (0.6–1.6)	1.0 (0.6–1.7)

[1]Adjusted for age.–[2]Adjusted for age, education, breast cancer history among first-degree relatives, history of breast fibroadenoma, waist-to-hip ratio, ever having had a live birth, age at first live birth, and physical activity.–[3]Additionally adjusted for menopausal status and menopausal age.–[4]Additionally adjusted for menarcheal age, among women who had natural menopause.–[5]Additionally adjusted for menopausal status, menopausal age, and menarcheal age.

Breast cancer cases were more likely than controls to have never been pregnant, to have had few pregnancies and live births, and to have had later ages at first live birth (Table III). Adjusted ORs, however, were statistically significant only for never having had a live birth (OR = 3.6, 95% CI 1.8–7.0) and later age at first live birth (trend test, $P < 0.01$). Numbers of pregnancies and of live births were no longer associated with breast cancer risk after adjustment for age at first live birth. Women who had their first live birth at age 30 or older had a similar or higher risk of breast cancer compared with nulliparous women. Cases and controls were similar regarding the history and number of spontaneous miscarriages, induced abortions, and stillbirths.

Among parous women, a lower proportion of cases than controls had breast-fed for more than 24 months (OR = 0.6, 95% CI 0.5–0.9) compared with women who had never breast-fed (Table IV). The difference, however, was diminished after adjustment for other breast cancer risk factors (OR = 0.9, 95% CI 0.7–1.4).

Further analyses were conducted, stratified by both age and menopausal status: age ≤40 and pre-menopause, age >40 and pre-menopause [mean (range) ages were 45.8 (41–59) and 45.5 (41–58) for cases and controls, respectively], and age >40 and post-menopause [mean (range) ages were 56.5 (41–64) and 56.6 (41–64) for cases and controls, respectively] (Table IV). Associations of breast cancer with age at menarche, nulliparity, and age at first live birth were observed in all strata defined by age and menopausal status. Breast-feeding, however, was associated with reduced risk only among post-menopausal women.

Finally, we calculated the PAR of breast cancer associated with menstrual and reproductive factors, separately for pre-menopausal women ≤40 years of age, pre-menopausal women >40, and post-menopausal women >40 years (Table VI). Among younger pre-menopausal women, early menarcheal age was the major contributor to breast cancer risk (PAR = 44.1%). For cancer occurring in older pre-menopausal women, early age at menarche (PAR = 26.1%) and later age at first live birth (PAR = 19.4%) played a major role. Early age at menarche (PAR = 27.5%), late age at first live birth (PAR = 7.1%), late age at menopause (PAR = 26.9%), and never having breast-fed (PAR = 9.4%) explained about 50% of post-menopausal breast cancer risk. The CIs of these stratum-specific PARs, however, overlap each other.

DISCUSSION

This population-based case-control study, conducted in a low-risk population, found that early age at menarche, late age at menopause, and nulliparity were related to increased risk of breast cancer, similar to that found in most epidemiological studies conducted in Western and Asian countries (Brinton *et al.*, 1995; Yuan *et al.*, 1988; Nagata *et al.*, 1995; MacMahon *et al.*, 1970; Magnussen *et al.*, 1999; Yang *et al.*, 1997; Enger *et al.*, 1997). We, however, did not find that numbers of live births, abortions, and miscarriages were associated with risk after adjusting effects of age at first live birth, consistent with some (Adami et al., 1990), but contrary to other (Brind *et al.*, 1996; Pike *et al.*, 1981) studies. Our data show that, compared to nulliparous women, women whose age at first live birth was <30 years had a lower risk of breast cancer. Women who had their first live birth at age ≥30 years had a similar or higher risk of breast cancer compared with nulliparous women. This observation supports the hypothesis that pregnancy at a younger age is associated with a favorable estrogen profile, which drastically reduces the presence of undifferentiated/vulnerable breast cells (Krieger, 1989), differentiates terminal end buds to lobules (Russo and Russo, 1993), and/or reduces the pool of estrogen receptor-positive cells. Some women who did not have a full-term pregnancy until age 30 may already have had cells that had undergone early stages of malignant transformation, and pregnancy could have stimulated the growth of these mutated cells.

Earlier studies on the effect of breast-feeding have generated inconsistent results. A re-analysis of the data from the original study by MacMahon and colleagues (1970) showed no significant

TABLE III – OR AND 95% CI OF BREAST CANCER ASSOCIATED WITH REPRODUCTIVE CHARACTERISTICS AND BREAST-FEEDING

	Case	Control	OR[1] (95% CI)	OR[2] (95% CI)
Pregnancy				
Ever	1396	1511	1.0 (reference)	1.0 (reference)[3]
Never	63	45	1.5 (1.0–2.3)	1.8 (0.7–4.3)
Number of pregnancies (gravid women)				
1	262	268	1.0 (reference)	1.0 (reference)[3]
2	484	493	1.0 (0.8–1.2)	1.0 (0.8–1.3)
3	313	401	0.7 (0.6–0.9)	0.8 (0.7–1.1)
4	217	225	0.9 (0.7–1.1)	1.0 (0.8–1.3)
≥5	120	124	0.8 (0.6–1.1)	1.1 (0.8–1.6)
P trend			$P = 0.06$	$P = 0.96$
Abortion (gravid women)				
Never	405	429	1.0 (reference)	1.0 (reference)[3]
Ever	991	1,082	1.0 (0.8–1.1)	1.0 (0.8–1.2)
Induced only	832	905	1.0 (0.8–1.2)	1.0 (0.8–1.2)
Miscarriage only	76	83	1.0 (0.7–1.3)	0.9 (0.7–1.3)
Both induced and miscarriage	83	94	0.9 (0.7–1.3)	0.9 (0.7–1.3)
Stillbirth (gravid women)				
Never	1,368	1,485	1.0 (reference)	1.0 (reference)[3]
Ever	28	26	1.2 (0.7–2.0)	1.1 (0.6–1.9)
Live birth				
Ever	1,385	1,495	1.0 (reference)	1.0 (reference)[4]
Never	74	61	1.3 (0.9–1.9)	3.6 (1.8–7.0)
Number of live births (parous women)				
1	912	975	1.0 (reference)	1.0 (reference)[4]
2	317	333	0.8 (0.6–1.0)	1.0 (0.8–1.3)
3	104	121	0.6 (0.4–0.9)	1.1 (0.7–1.6)
≥4	52	66	0.5 (0.3–0.8)	1.1 (0.6–1.8)
P trend			$P < 0.01$	$P = 0.70$
Age at first live birth (years)				
<20	62	73	1.0 (reference)	1.0 (reference)[5]
20–24	303	360	1.1 (0.7–1.6)	0.9 (0.6–1.4)
25–29	712	816	1.3 (0.9–1.8)	1.0 (0.6–1.5)
30–34	248	206	1.7 (1.1–2.6)	1.3 (0.8–2.0)
≥35	60	40	2.1 (1.2–3.6)	1.6 (0.9–2.8)
P trend			$P < 0.01$	$P < 0.01$
Nulliparity	74	61	1.8 (1.1–2.9)	1.4 (0.8–2.4)

[1]Adjusted for age.–[2]Adjusted for age, education, breast cancer history among first-degree relatives, history of breast fibroadenoma, waist-to-hip ratio, menarcheal age, menopausal status, menopausal age, and physical activity.–[3]Additionally adjusted for ever having had a live birth and age at first live birth.–[4]Additionally adjusted for age at first live birth.–[5]Additionally adjusted for number of live births.

TABLE IV – OR AND 95% CI OF BREAST CANCER ASSOCIATED WITH BREAST-FEEDING AMONG PAROUS WOMEN

	Case	Control	OR[1] (95% CI)	OR[2] (95% CI)
Breast-feeding				
Never	302	300	1.0 (reference)	1.0 (reference)
Ever	1,083	1,195	0.9 (0.7–1.0)	0.9 (0.7–1.1)
Cumulative duration of breast feeding (months)				
None	302	300	1.0 (reference)	1.0 (reference)
<12	593	638	0.9 (0.8–1.1)	0.9 (0.8–1.1)
12–23	275	307	0.8 (0.6–1.0)	0.9 (0.7–1.1)
≥24	215	250	0.6 (0.5–0.9)	1.0 (0.7–1.4)
P trend			$P < 0.01$	$P = 0.69$

[1]Adjusted for age.–[2]Adjusted for age, education, breast cancer history among first-degree relatives, history of breast fibroadenoma, waist-to-hip ratio, menarcheal age, menopausal status, menopausal age, age at first live birth, number of live births, and physical activity.

association between lactation and pre- or post-menopausal breast cancer risk after adjusting for additional breast cancer risk factors identified since the original analysis (Stuver *et al.,* 1997). Moreover, examination of cumulative duration of lactation did not support an inverse association between breast cancer risk and length of total breast-feeding. Several studies, including a large prospective study and a multinational hospital-based case-control study, have also found no evidence for a protective effect of lactation (Magnussen *et al.,* 1999; Michels *et al.,* 1996; Negri *et al.,* 1996). Several other studies, however, have reported an inverse association between lactation and breast cancer risk (Yang *et al.,* 1997; Enger *et al.,* 1997, 1998; Katsouyanni *et al.*, 1996; Romieu *et al.,* 1996; Newcomb *et al.,* 1994). The inverse association was confined to pre-menopausal women in some studies (Enger *et al.,* 1997; Katsouyanni *et al.,* 1996; Newcomb *et al.,* 1994), while in others the effect was predominant among post-menopausal women (Enger *et al.,* 1998). Effects of age at first breast-feeding have also been examined, with one study showing the reduction in breast cancer risk to be confined primarily to women who breast-fed at younger ages (Enger *et al.,* 1998). In our study population, the vast majority of post-menopausal women had breast-fed (85% of cases *vs.* 92% of controls) and started breast-feeding at a young age (mean ages 24.2 years for cases and 24.1 for controls). Among pre-menopausal women, the breast-feeding rate was much lower

TABLE V – OR AND 95% CI OF BREAST CANCER ASSOCIATED WITH MENSTRUAL/REPRODUCTIVE FACTORS AND LACTATION, BY AGE AT DIAGNOSIS AND MENOPAUSAL STATUS[1]

	Age ≤40 pre-menopause		Age >40 pre-menopause[2]		Age >40 post-menopause[3]	
	Ca/Ctrl	OR (95% CI)	Ca/Ctrl	OR (95% CI)	Ca/Ctrl	OR (95% CI)
Age at menarche (years)[4]						
≤12	32/45	1.0 (ref)	48/42	1.0 (ref)	57/44	1.0 (ref)
13	63/84	1.1 (0.6–1.9)	160/107	1.4 (0.9–2.3)	98/88	1.0 (0.6–1.6)
14	59/89	0.9 (0.5–1.6)	153/131	1.2 (0.7–1.9)	91/116	0.7 (0.4–1.1)
15	54/79	0.9 (0.5–1.7)	140/122	1.1 (0.7–1.8)	110/102	0.9 (0.5–1.5)
16	39/64	0.8 (0.5–1.6)	120/114	1.0 (0.6–1.7)	70/109	0.6 (0.4–1.0)
≥17	14/34	0.5 (0.2–1.1)	69/79	0.8 (0.5–1.4)	69/110	0.5 (0.3–0.9)
P trend		P = 0.10		P = 0.04		P < 0.01
Live birth[5]						
Ever	243/374	1.0 (ref)	660/575	1.0 (ref)	474/539	1.0 (ref)
Never	18/22	4.1 (0.7–24.5)	31/19	3.3 (1.1–10.0)	23/18	3.0 (1.1–8.3)
Number of live births (parous women)[5]						
1	236/365	1.0 (ref)	546/478	1.0 (ref)	124/126	1.0 (ref)
2	6/9 } 7/9	1.1 (0.4–3.1)	107/93	1.1 (0.8–1.6)	203/231	1.1 (0.8–1.6)
≥3	1/0 }		7/4	1.9 (0.5–6.8)	147/182	1.2 (0.7–2.1)
P trend		P = 0.64		P = 0.32		P = 0.57
Age at first live birth[5]						
<25	31/54	1.0 (ref)	89/87	1.0 (ref)	242/289	1.0 (ref)
25–29	174/269	0.9 (0.6–1.6)	380/345	1.1 (0.8–1.6)	154/200	0.9 (0.7–1.3)
30–34	29/44	0.9 (0.5–1.8)	157/119	1.3 (0.9–2.0)	61/41	1.6 (1.0–2.6)
≥35	9/7	1.8 (0.6–5.5)	34/24	1.5 (0.8–2.8)	17/9	2.2 (0.9–5.2)
P trend		P = 0.22		P = 0.03		P = 0.06
Nulliparity	18/22	1.8 (0.8–4.2)	31/19	1.6 (0.8–3.1)	23/18	1.5 (0.8–3.0)
Lactation[6]						
Never	82/125	1.0 (ref)	146/132	1.0 (ref)	71/43	1.0 (ref)
Ever	161/249	0.9 (0.6–1.3)	514/443	1.1 (0.8–1.5)	403/496	0.6 (0.4–0.9)
Cumulative duration of lactation (months)[6]						
None	82/125	1.0 (ref)	146/132	1.0 (ref)	71/43	1.0 (ref)
<12	140/225	0.9 (0.6–1.3)	360/291	1.2 (0.9–1.6)	89/117	0.5 (0.3–0.8)
12–23	21/23 } 21/24	1.2 (0.6–2.3)	117/124	0.9 (0.6–1.3)	137/159	0.6 (0.4–1.0)
≥24	0/1 }		37/28	1.1 (0.6–2.2)	177/220	0.7 (0.4–1.1)
P trend		P = 0.78		P = 0.91		P = 0.59

[1]Adjusted for age, education, breast cancer history among first-degree relatives, history of breast fibroadenoma, and waist-to-hip ratio.–[2]Mean (range) of age was 45.8 (41–59) and 45.5 (41–58) for cases and controls, respectively.–[3]Mean (range) of age was 56.5 (41–64) and 56.6 (41–64) for cases and controls, respectively.–[4]Additionally adjusted for ever having had a live birth and age at first live birth.–[5]Additionally adjusted for age at menarche.–[6]Additionally adjusted for ever having had a live birth, age first live birth, age at menarche, and physical activity.

TABLE VI – PAR OF BREAST CANCER ASSOCIATED WITH MENSTRUAL AND REPRODUCTIVE CHARACTERISTICS AMONG WOMEN IN SHANGHAI[1]

	Age ≤40, pre-menopause		Age >40, pre-menopause[2]		Age >40, post-menopause[3]	
	PAR (%)	95% CI	PAR (%)	95% CI	PAR (%)	95% CI
Younger age at menarche (compared with 17 years old)	44.1	(10.5–77.7)	26.1	(3.5–48.6)	27.5	(7.3–47.7)
Older age at menopause (compared with <45 years old)	N/A		N/A		26.9	(6.4–47.3)
Never had live birth	5.2	(0.1–9.2)	3.1	(1.0–5.3)	3.1	(0.1–5.5)
Older age at first live birth (compared with <25 years old)	0.0	(−46.6–45.7)	19.4	(−7.3–46.1)	7.1	(−7.2–21.4)
Never had breast feeding	3.0	(−9.8–15.9)	−2.3	(−9.8–5.3)	9.4	(3.9–14.8)
All above risk factors	48.3	(8.6–87.9)	38.8	(10.1–63.5)	51.0	(30.4–71.6)

[1]Adjusted for age, education, breast cancer history among first-degree relatives, history of breast fibroadenoma, waist-to-hip ratio, age at menarche, ever having had a live birth, age at first live birth, and physical activity.–[2]Mean (range) of age was 45.8 (41–59) and 45.5 (41–58) for cases and controls, respectively.–[3]Mean (range) of age was 56.5 (41–64) and 56.6 (41–64) for cases and controls, respectively.

(75% of cases *vs.* 73% of controls) and the mean age of starting breast-feeding was higher (27.5 for cases and 27.1 for controls). The difference in the pattern of breast-feeding (*e.g.,* age at first breast-feeding) between pre- and post-menopausal women may, in part, explain the discrepancy in the association of breast-feeding with cancer risk found among pre- and post-menopausal women in our study. We could not disentangle the effect of age at first breast-feeding and age at first live birth because these 2 variables were highly correlated (correlation coefficient = 0.98). It is possible that the protective effect of breast-feeding was counteracted by the adverse effect of late age at first live birth among pre-menopausal women.

The rapid socio-economic development over the past 2 decades in Shanghai, the largest industrial city in China, has been associated with pronounced changes in cancer incidence. Breast cancer incidence has increased approximately 50% among women in Shanghai, especially among younger women (85% to 87%) (Jin *et al.,* 1999). As a result, breast cancer has become the most common malignancy among women in urban Shanghai (Jin *et al.,* 1999). Changes in lifestyle and behavior related to socio-economic development, such as birth-control practices and dietary patterns, may have resulted in earlier ages at menarche, later ages at menopause, later ages at first live birth, fewer children, less breast-feeding, and more abortions. These changes are reflected in our study by substantial differences in menstrual and reproductive factors between younger and older women. For example, the proportions of women starting menarche at 13 years or younger were 22.4% and 32.7%, respectively, for women 45 or older and 40 or younger. Mean age at first live birth was considerably older in younger than in older women. Accordingly, the PAR related to menstrual and reproductive characteristics differed substantially between younger and older women. Early age at menarche was the single most important contributor, with a PAR of 44%, to breast cancer incidence among women younger than 40 years. Among women older than 40 years, however, earlier age at menarche accounted for about one-fourth of breast cancer cases. While age at first live birth contributed to 19% of pre-menstrual breast cancer cases among women older than 40, it played a relatively smaller role among post-menopausal women. Despite the large sample size of this study, the estimates of some stratum-specific PARs were still not very stable. The point estimates of these PARs, therefore, should be interpreted with caution.

In summary, our study suggests that changes in menstrual patterns among women in Shanghai, particularly younger age at menarche, may have resulted in an increase of breast cancer incidence; this emphasizes that prevention of breast cancer should be initiated as early as childhood. Reproductive pattern changes, however, did not appear to play a major role in the increase of breast cancer incidence among women in Shanghai, except for pre-menopausal breast cancers that occurred after age 40. Overall, menstrual and reproductive factors explained only about 40% to 50% of breast cancer risk among women in Shanghai. Studies searching for other contributors, such as dietary and genetic susceptibility factors, are currently on-going.

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