A Case-Control Study of Breast Cancer in Tianjin, China[1]

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Abstract

In a population-based case-control study of breast cancer in Tianjin, China, involving 300 cases and 300 population controls interviewed during 1985–1986, a number of strong risk factors were identified. Although average age at menarche was late by Western standards in this developing country (14.4 years), it was clearly related to risk. Women with their first menstrual period at age 12 years or earlier had 80% greater risk than women who started at age 17 years or later. Age at first full-term pregnancy was also strongly related to risk, with women whose first birth after age 30 years having 3.2 times the risk of women whose first birth was under age 20 years. Other established breast cancer risk factors in Western populations (family history of breast cancer, a history of benign breast disease, and use of oral contraceptives late in reproductive life) were also risk factors in this population.

Parity and duration of lactation were both strongly protective against breast cancer development in univariate analyses. These two variables were highly correlated with each other and with age at first full-term pregnancy. Although the effects of each variable dissipated somewhat in multivariate analysis, our data strongly suggest that both parity and lactation independently contribute to breast cancer risk.

Introduction

In the mid-1980s, we initiated case-control studies of breast cancer in the three largest urban areas of the People's Republic of China. These studies were designed to determine whether the well-established risk factors for breast cancer in Western populations (age at menarche, age at first birth, age at and type of menopause, postmenopausal obesity, benign breast disease history, and a family history of breast cancer) (1) were also associated with breast cancer development in a low-risk developing country. In addition, we were interested in clarifying the relationships between lactation and parity and breast cancer risk in populations which appeared particularly well suited for studying these associations. Finally, we wished to evaluate the relationship between diet, especially dietary fat and certain micronutrients, and breast cancer development in these low-risk populations.

We have previously reported the results of nondietary risk factors from the Shanghai and Beijing studies (2, 3). We report here the results of the nondietary risk factors from Tianjin.

Shanghai and Beijing are both regarded as rather cosmopolitan urban areas by Chinese standards, whereas Tianjin is a large industrial port city, located some 120 km from Beijing. The annual age-standardized incidence rate (to the world population) of breast cancer in Tianjin is about 19/100,000. A comparison between the age incidence of breast cancer in Tianjin and in Los Angeles whites close to the time of the study is shown in Fig. 1. These data were derived from the Los Angeles County Cancer Surveillance Program (4), the population-based cancer registry in Los Angeles which we operate, and from cancer incidence rates reported in *Cancer in Five Continents* (5).

Materials and Methods

Breast cancer cases in this study included all histologically confirmed incident cases aged 20–55 years that were identified by the Tianjin Cancer Registry beginning on January 1, 1985 until 300 cases had been recruited into the study. All cases were diagnosed between November 1984 and November 1986. About two-thirds of all breast cancer cases in Tianjin are diagnosed or treated at the Tianjin Cancer Hospital, and nearly 20% of the remainder are seen at two of the other 17 hospitals in Tianjin equipped to diagnose or treat breast cancer. Since the Tianjin Cancer Registry uses a strategy of passive reporting by hospitals to ascertain cases, we also routinely rescreened these three hospitals on a monthly basis during the entire study period to identify additional cases not routinely reported. Coincidentally, we began this study at the same time that the Tianjin municipality was implementing a mandatory cancer reporting rule, which might have also assisted us in gaining reasonably complete case ascertainment.

Controls in this study were identified from complete residence files maintained in what are, in effect, neighborhood police stations. We followed an algorithm in which we systematically searched these files, beginning with a residence a specified distance from the index case's residence to identify the first two women who were exact age matches (±1 year) to the case. Two potential controls were chosen to allow for the event that the first identified control refused to participate.

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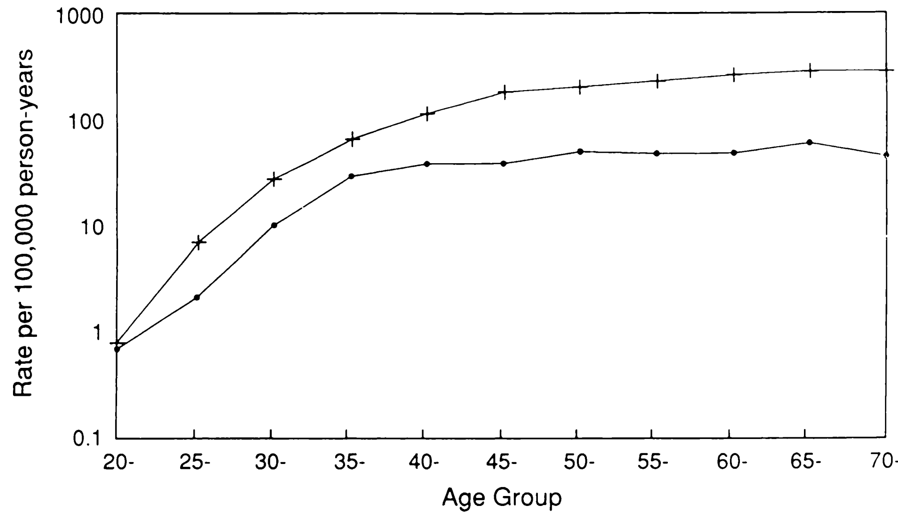

Fig. 1. Age-specific incidence rates of breast cancer in Tianjin Chinese (1981-82) and Los Angeles white (1978-82) women. +, Los Angeles white women (1978-82); ●, Tianjin Chinese women (1981-82).

Interviews were conducted in the residences of the cases and controls by a nurse interviewer using a structured and previously pilot-tested questionnaire. Matched case-control pairs were interviewed by the same nurse in every instance. All interviews were conducted between January 1985 and December 1986. The mean time interval between diagnosis and interview of cases was 2.9 months, and 82% of cases were interviewed within 6 months of diagnosis. The mean time interval between interview of the index case and her matched control was 1.4 months. Seventy-three % (219) of the 300 case-control pairs were interviewed within 2 months of each other.

We used standard matched-pair methods to analyze the interview data of the 300 completed pairs (6). Study variables were examined individually and then simultaneously for confounding and interaction effects. For each study variable, odds ratios (RR[1] estimates) and their corresponding *P* values and 95% CI were calculated. Tests for linear trend were performed on all ordinal and continuous variables. We used exact binomial tests on individual dichotomous variables. The multivariate conditional logistic regression method was used on single variables with more than two possible outcomes, as well as for multivariate analysis. All *P* values quoted are two-sided.

Results

Three hundred cases and 300 individually matched controls participated in this study. The participation rate among qualified cases was 69% (300 of 434). The first qualified control identified by our algorithm participated 99% (297 of 300) of the time. The mean age of cases and controls was 43.3 and 43.4 years, respectively, indicating the high degree of success of our age-matching procedures. As expected, cases were more educated than controls (Table 1). The relative risk for a university education *versus* no formal education was 4.1 (95% CI = 1.7, 10.3). Per capita family income was low by Western standards, although there was a significant trend toward higher income among cases. Most cases (93%) and controls (92%) reported that they were currently married.

A summary of the results evaluating several menstrual and reproductive variables is provided in Table 2. For comparison, we have provided the RR estimates for these variables from our population-based case-control study in Shanghai (2).

There was a strong relationship between age at menarche and breast cancer risk. Women with their first menstrual period at age 12 years or earlier had an approximately 80% higher breast cancer risk than women who started menstruating at age 17 years or later. Risk increased more or less consistently with each decremental age at menarche (*P* for linear trend = 0.04). The mean age at menarche in breast cancer cases in this study was 14.1 years, compared to 14.4 years in controls.

Both age at first FTP and total number of FTPs were strongly associated with risk in univariate analysis. Women who had their first pregnancy at age 30 years or thereafter had 3.2 times the breast cancer risk of women whose first birth was before age 20 years. Nulliparous women had a risk level comparable to that of women whose first birth was between the ages of 25 and 29 years. The effect of parity on breast cancer was profound. Women with five or more term pregnancies had only one-tenth the risk of women with just one term birth. Risk decreased monotonically with incremental increases in term pregnancies (*P* for linear trend < 0.00005).

The median total duration of nursing among parous control women in this study was 36 months. Women who had accumulated at least 9 years of lactation had about one-sixth the risk of women who had never nursed. The trend of decreasing risk with increasing months of nursing was highly significant (*P* for linear trend = 0.0003). The quantitative effect of each of these menstrual and reproductive risk factors was highly com-

[1] The abbreviations used are: RR, relative risk; CI, confidence interval; FTP, full-term pregnancy; OC, oral contraceptives.

Table 1 Sociodemographic factors	No. of cases	No. of controls	RR	95% CI
Level of education				
No formal education	34	47	1.0	
Primary school	68	82	1.6	(0.8, 3.3)
Secondary school	163	151	2.5	(1.2, 5.4)
University	35	20	4.1[a]	(1.7, 10.3)
Marital status				
Currently married	280	275	1.0	
Never married	12	14	0.8	(0.3, 2.0)
Other	8	11	0.7	(0.3, 1.8)
Per capita family income (yuan/month)				
0-29	47	74	1.0	
30-39	97	88	1.8	(1.1, 2.9)
40-49	66	71	1.6	(0.9, 2.6)
50+	90	67	2.3[a]	(1.4, 3.8)

[a] Two-sided P value (linear trend) <0.05.

parable to the effect observed in our previous population-based case-control study in Shanghai (2) (Table 2).

Age at first full-term pregnancy, total number of term pregnancies, and total months of lactation were highly correlated with one another. Using multivariate statistical methodology, we attempted to establish the independence of the latter two factors on breast cancer risk. Table 3 shows RR estimates for number of full-term pregnancies adjusted for age at first full-term pregnancy and duration of nursing, and estimates of RR for duration of nursing adjusted for age at first full-term pregnancy and number of full-term pregnancies. We include in the table, for comparison, the corresponding RR estimates from our Shanghai case-control study (2). The multivariate analysis suggests that both number of full-term pregnancies and duration of nursing have independent effects on risk, although only the result for total term pregnancies achieved statistical significance (P for linear trend = 0.02). Women with five or more FTPs experienced a risk of breast cancer only 0.3 of that in primiparous women, and relative to women whose total nursing time was 3 years or less, those who nursed for more than 9 years had one-half the risk of breast cancer. The magnitude of these adjusted RRs are closely comparable to those previously observed in Shanghai.

About one-third of control women in Tianjin reported a positive history of oral contraceptive use. There was little evidence that past use of oral contraceptives overall was associated with an increased risk of breast cancer (Table 4). However, women who began use relatively late in reproductive life exhibited a significant increase in breast cancer risk. Although based on relatively small numbers of cases and controls, breast cancer risk was 2.6-fold (95% CI = 1.2, 5.8) higher among short-term users (up to 24 months) and 4.0-fold (95% CI = 1.1, 15.1) higher among long-term users who began use after age 35 years. Of the 33 cases and 12 controls who started use of oral contraceptives after age 35 years, 26 cases and 5 controls provided information on specific oral contraceptives used. All were combination-type oral contraceptives, except for one case who used a progestagen only pill. There were no detectable differences in risk by the four brands of combination oral contraceptives used by the remaining 25 cases and 5 controls.

Table 2 Menstrual and reproductive factors

	No. of cases	No. of controls	RR	95% CI	RR from Shanghai study (2)
Age at menarche (yr)					
17+	27	36	1.0		1.0
16	41	49	1.2	(0.6, 2.3)	1.3
15	61	60	1.4	(0.7, 2.6)	1.6
14	63	59	1.5	(0.8, 2.7)	1.4
13	53	53	1.4	(0.7, 2.7)	1.7
12 or under	55	43	1.8[a]	(0.9, 3.4)	1.9
Age at first FTP (yr)					
≤19	23	33	1.0		1.0
20-24	83	113	1.2	(0.6, 2.3)	1.1
25-29	123	104	2.3	(1.1, 4.5)	1.7
30+	37	23	3.2	(1.4, 7.5)	2.7
Nulliparous	34	27	2.4	(1.1, 5.6)	2.1
No. of FTP (parous pairs only)[b]					
1	56	46	1.0		1.0
2	108	87	0.9	(0.5, 1.8)	0.6
3	55	50	0.6	(0.3, 1.2)	0.5
4	17	38	0.2	(0.1, 0.5)	0.3
5+	10	25	0.1[a]	(0.04, 0.4)	0.2
Duration of nursing by months (parous pairs only)[b]					
Never	18	12	1.2	(0.6, 2.6)	1.1
1-36	134	117	1.0		1.0
37-72	73	74	0.7	(0.4, 1.1)	0.6
73-108	16	30	0.3	(0.1, 0.7)	0.2
109+	5	13	0.2[a]	(0.1, 0.6)	0.2

[a] Two-sided P value (linear trend) <0.05.
[b] There were 246 case-control pairs of parous women.

Table 3 Number of full-term pregnancies and duration of nursing
Pairs in which either the case or the control was nulliparous were excluded from the analysis. There were 246 pairs of parous women

	RR (95% CI)	Adjusted RR (95% CI)	Adjusted RR from Shanghai study (2)
Number of FTPs			
1	1.0	1.0[a]	1.0
2	0.9 (0.5, 1.8)	1.3 (0.7, 2.6)	0.7
3	0.6 (0.3, 1.2)	1.0 (0.4, 2.4)	0.7
4	0.2 (0.1, 0.5)	0.5 (0.1, 1.4)	0.6
5+	0.1[b] (0.0, 0.4)	0.3[b] (0.1, 1.2)	0.4
Duration of Nursing (months)			
1–36	1.2 (0.6, 2.6)	0.9 (0.4, 2.0)	1.1
37–72	1.0	1.0[c]	1.0
73–108	0.7 (0.4, 1.1)	0.9 (0.6, 1.6)	0.8
109+	0.3 (0.1, 0.7)	0.7 (0.3, 1.7)	0.3
	0.2[b] (0.0, 0.6)	0.5 (0.1, 1.8)	0.4

[a] RR adjusted for age at first FTP and duration of nursing.
[b] Two-sided *P* value (linear trend) <0.05.
[c] RR adjusted for age at first FTP and number of FTPs.

Two other well-established risk factors for breast cancer in Western populations (a personal history of surgically confirmed benign breast disease and a family history of breast cancer) were both statistically significant risk factors for breast cancer in Tianjin (Table 4). The reported prevalence of first-degree relatives with breast cancer in this young, low-risk population was very low.

We observed no strong or consistent relationship between weight (as estimated at 2 years prior to the index case's cancer diagnosis) and breast cancer risk (Table 5). Within the limited age range of cases in this study, we looked for an age-related effect of weight on risk. For matched pairs in which the breast cancer patient was over age 50 years at diagnosis, there was some evidence that risk increased with increasing weight, but this effect was not statistically significant ($P = 0.51$). There was no evidence of any relationship between weight and breast cancer risk among younger patients ($P = 0.95$).

The conditional logistic regression method was used to examine the simultaneous effect of all of the significant risk factors from these univariate analyses (the factors were family history of breast cancer, age at menarche, age at FTP, parity, duration of nursing, use of OC late in reproductive life, and history of benign breast disease) while adjusting for level of education. Adjusted and nonadjusted regression coefficients were similar for all factors except the three highly correlated reproductive factors: age at first FTP, number of FTPs, and duration of nursing. As shown in Table 3, inclusion of these three correlated variables in a regression model weakened somewhat the association of each of these variables with breast cancer. Dietary factors evaluated in this study explained none of these observed relationships.

Discussion

This study completes our series of reports on the relationship between reproductive and menstrual factors and breast cancer risk among the large urbanized populations of China. In addition to providing strong evidence that

Table 4 Other nondietary factors

	No. of cases	No. of controls	RR	95% CI	RR from Shanghai study (2)
Ever used OC					
No	196	202	1.0		1.0
Yes	104	98	1.1	(0.8, 1.6)	1.1
OC use: duration (months) by age (yr) began					
–24 months					
34 yrs or under	48	53	0.9	(0.6, 1.4)	1.0
35+ yrs	22	9	2.6	(1.2, 5.8)	2.9
25+ months					
34 yrs or under	23	33	0.8	(0.4, 1.4)	0.9
35+ yrs	11	3	4.0	(1.1, 15.1)	2.0
Had benign breast disease					
No	249	276	1.0	(1.4, 4.0)	1.0
Yes	51	24	2.4		4.6
Female first-degree relative had breast cancer					
No	292	299	1.0		1.0
Yes	8	1	8.0	(1.3, 175.0)	2.8

Table 5 Weights overall and by age

	No. of cases	No. of controls	RR	95% CI
Weight (kg)[a]				
≤50	54	57	1.0	
51-55	78	69	1.2	(0.7, 2.0)
56-60	55	64	0.9	(0.5, 1.6)
61-65	42	48	0.9	(0.5, 1.7)
66+	71	62	1.2	(0.7, 2.1)
Case's age 49 yrs or under				
≤50	43	43	1.0	
51-55	65	54	1.2	(0.7, 2.1)
56-60	38	50	0.7	(0.4, 1.4)
61-65	29	36	0.8	(0.4, 1.6)
66+	51	43	1.2	(0.6, 2.2)
Case's age 50+ yrs				
≤50	11	14	1.0	
51-55	13	15	1.2	(0.3, 3.9)
56-60	17	14	1.6	(0.5, 5.2)
61-65	13	12	1.5	(0.5, 4.7)
66+	20	19	1.4	(0.5, 4.2)

[a] At 2 years prior to the cancer diagnosis of the index case.

the standard risk factors for breast cancer identified in Western populations (age at menarche, age at first full-term pregnancy, history of benign breast disease, family history of breast cancer, and postmenopausal weight) are also risk factors in Chinese urban populations, these studies show rather conclusively that parity and lactation have important independent influences on breast cancer development (2, 3). An effect of age at menopause on breast cancer risk has been observed in our Beijing study and an earlier study in Tianjin (3, 7). In the young population studied here, no strong effect would be expected. This study also supports the growing body of evidence that long-term use of oral contraceptives, especially during certain parts of reproductive life, is associated with a modest increase in breast cancer risk (8). The effects of parity and lactation on breast cancer risk in each of the three Chinese populations which we studied were quite substantial and generally quite comparable. In the study reported here, after adjusting for other breast cancer risk factors, breast cancer risk decreased 22% with each term pregnancy and 11% for each year of lactation experience. Comparable figures based on our Shanghai study were 15% and 8%, respectively (2).

One intriguing aspect of breast cancer epidemiology is the substantial international variation in risk, particularly the low risk in Asian populations compared to U.S. whites (5). There is roughly a 6-fold difference in overall risk between Japanese and Chinese women in those countries and Caucasian women in the United States. We have previously calculated that much of this difference is probably explicable on the basis of differences between populations in two established breast cancer risk factors: postmenopausal obesity, which is less common in Asian populations, and age at menarche, which historically has occurred substantially later in these Asian populations (2, 3, 7). The average age at menarche among the healthy control women in this study, for example, was 14.4 years, some 2 to 3 years later than is typical for U.S. white girls. It is possible that the residual difference is explicable, in part, by differences in average cycle length between Asian and U.S. white women (9) and, in China at least, by the higher parity and much longer average cumulative lactation experience. We have reported previously that both healthy pre- and postmenopausal Asian women have lower circulating estrogen levels than comparably aged healthy U.S. white women (10, 11). The reason for these differences has not been established. In postmenopausal women, we have demonstrated that differences in body weight explain only a small part of these large differences in circulating estrogen levels. We have speculated that the residual difference is most likely due to differences in diet (possibly fat intake) or perhaps in genetically determined or environmentally induced differences in estrogen metabolism. Based on the results of the current study, it would be useful to establish whether the substantial differences in circulating estrogen levels in premenopausal women could be explained in part by the long-term effects of high parity and/or long duration of lactation on serum estrogen levels.

Acknowledgments

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