RESEARCH COMMUNICATION

Passive Smoking and Other Factors at Different Periods of Life and Breast Cancer Risk in Chinese Women who have Never Smoked - A Case-control Study in Chongqing, People's Republic of China

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Abstract

A case-control study of breast cancer (BC) was conducted from 1994 to 1996 in Chongqing, People's Republic of China, in order to explore the etiological role of passive smoking (PS, so-called second hand smoking) as well as other early life factors (weight, height, socioeconomic status and history of suffering from a disease resulting in hospitalization). These factors were reviewed both in childhood (age less than 10 years) and in the teenage years (youth: 10 to 16 years). One hundred and eighty six cases of newly diagnosed and histologically confirmed BC, aged 24 to 55 years, were individually matched by day (within six months) and age (within 2 years) at diagnosis as well as marital status to 186 controls selected from outpatients not suffering from cancer. All subjects, cases and controls were never-smokers. A standardized questionnaire was used for interview in a face-to-face situation. After adjustment for a wide range of covariates using multiple logistic regression analysis, PS was found to be a statistically significant risk factor for BC. This was found for exposure to PS in childhood [odds ratio (OR) and 95% confidence interval (95%CI): 1.24 (1.07-1.43)], in youth [1.15 (0.90-1.47)] and in adulthood for either exposure at home [4.07 (2.21-7.50)] or at work [1.27 (1.04-1.55)]. For exposure to PS in childhood, a significant dose-response effect was evident (test for trend, $p<0.05$) with the number of smokers in the home, as well as the perceived level of exposure to PS, and in adulthood with the number of smokers at work. Our study also found an increased risk of BC in those with a past history of suffering from a disease requiring hospitalization [2.41 (1.21-4.81)]. Subjects with a low body weight in childhood and with a poor economic status in youth were associated with increased risk of BC in their adulthood [1.54 (1.09-2.18) and 1.03 (1.00-1.06)]. Being overweight as an adult, however, was associated with a high risk of BC [1.76 (1.02-3.04)]. Age at menarche [0.83 (0.72-0.95)] was associated negatively with risk of BC. A history of benign breast disease [2.05 (1.01-4.16)] or a history of life stress [2.32 (1.54-3.48)] were both associated with increased risk of BC. Our results therefore indicate a small but definite effect associated with PS, the credibility of which is enhanced by a dose-response relationship to BC risk. The other early life factors, such as age at menarche, history of suffering from a disease requiring hospitalization, history of benign breast disease, being overweight as an adult and life stress are similar to those consistently found in other countries. The associations involving low body weight, low socioeconomic status in early life and subsequent high risk of BC require further study.

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Key words: Passive smoking, early life risk factor, breast cancer, Chinese.

Introduction

Several epidemiological studies have suggested that passive smoking (PS) and other factors in early life may be important factors in the etiology of breast cancer (BC) (Chen et al., 1995; Colditz et al., 1995; Hamajima et al., 1995; Hilakivi et al., 1994; Hsieh et al., 1990; Le-Marchand et al., 1988; Liu et al., 1995; Micozzi et al., 1987; Peters et al., 1996; Sandler et al., 1985a,b; Ursin et al., 1995; Vatten et al., 1990; Yuan et al., 1988). However, few studies have been carried

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out in Chinese women, who have much lower incidence and mortality from BC than is found in the West. In the past twenty years, however, BC incidence appears to be increasing in Chinese women (Department of Health, China 1994) and Chinese people have experienced rapid socioeconomic changes, especially in large cities. To explore the relationships between PS and other early life experience risk factors for BC, a case-control study was conducted in Chongqing city, the largest city in the upper reaches of Yangtze River, People's Republic of China.

Materials and Methods

Study subjects

The cases (N=186) were histologically confirmed BC in women aged 24 to 55 years, diagnosed in the Teaching Hospital of Chongqing University of Medical Sciences. The age of each case was as on the day of the diagnosis. Three cases who had been smoking were excluded from this analysis, because very few Chinese women smoke, and the present study was focused on risk of PS. One hundred and eighty six controls were selected randomly from women who visited the Departments of Women's Health Care and Breast Surgery over the same time period, but who were proved histologically to be free of cancer. Controls were individually matched to cases based on the date of diagnosis (within six months), age at diagnosis (within two years), marital status and never smoking. Only subjects aged 55 or less were studied both in order to minimize recall bias, and because older women may also have other co-diseases. A standardized questionnaire was used for individual face-to-face interviews.

Assessment of early life experience

Two early life periods were defined in the study. The first period termed as "childhood" was defined as age less than 10. The second period defined as "youth" was age 10-16 years old. The main study variables were five: (1) Passive smoking. (2) Body weight. (3) Height. (4) History of diseases leading to hospitalization. (5) Family economic situation. These variables were reviewed, and classified by using categorical groups. For PS, two questions were asked: (1) "Did any person, living in the same house/room with you, smoke near you? If yes, how many smokers were there?" (2) " In general, how much did they smoke? [1=less than 3 cigarettes/day (light), 2=3 to 9 cigarettes/day (medium), 3=10 to 19 cigarettes/day (heavy) and 4=20 and more cigarettes/day (very heavy)] ". In adulthood, subjects were also asked about their PS status in the workplace: (1) "Are you employed? If yes, do any of your co-workers smoke near you, whilst indoors at work? If yes, how many smokers are there? " (2) "In general, how much do they smoke?" (1=light, 2=medium, 3=heavy and 4=very heavy, the same coding as the above). A question referring to previous body weight was asked "Please describe your body weight during your childhood or youth, compared to average levels for those who had the same age as you, such as your neighbor or classmates" (1=low, 2=slightly low, 3=normal (average), 4=slightly overweight and 5=overweight). For adulthood, we asked, "Do you feel that your body weight appears to have changed over the two years before you were diagnosed as having BC? Or for controls, "do you feel that your body weight appears to have changed over the last two years? ". The question for height was "How do you compare your height during your childhood and youth in relation to averages for those who were of the same age as you?" (1=below average, 2=average and 3=above average). The question referring to a past history of suffering from a hospitalized disease (HSHD) was "Have you ever been hospitalized owing to any diseases when aged 16 or less (0=no, 1=yes). The question for family economic situation was "Please describe your family economic status compared to average levels in those who were living around you when you were in childhood, in your youth, or as an adult? (1=poor, 2=slightly poor, 3= average and 4=above average). We also assessed stress throughout life by asking "Did you have any serious experiences, which you felt caused great troubles in you life, such as parents/relatives dying, disease, unexpected events, unhappy love affairs, divorce, unemployment, etc (0=no, 1=yes)?". Before the formal study was carried out a pilot study with ten pairs of cases and controls was conducted, so as to test and modify the research questionnaire.

Statistics

Crude odds ratio (OR) and 95% confidence intervals (95%CI) were calculated initially (with adjustment for the matching variables, only). Chi square tests for 2 by 2 tables and for trends were used where appropriate. Multiple conditional logistic regression models were performed to examine the independent effects of PS and other early life experiences factors on risk of BC. All data analyses were conducted using PC-SAS version 6.06 (SAS Institute 1990).

Results

Selected characteristics of the study subjects

The mean ages were 41 years [standard deviation (SD)=5.9] in the cases, and 40 (5.9) in the control group, with no significant difference between cases and controls across age groups. Of the 186 controls, 71% did not have any breast-related disease (Table 1).

Univariate analysis (adjustment for matching variables only)

Table 2 compares the results between cases and controls. Age at menarche (>=13 years) was associated with a low risk of BC [OR (95%CI): 0.43 (0.24-0.77)]. Age at first childbirth (>=30 years), age at menopause (<45 years), education level (none or primary education level as a reference), occupation status (professional as a reference) and family history of cancer did not show a statistically significant relationship with BC. A history of suffering from a hospitalized disease (HSHD) was also not associated statistically with a high risk of BC in the univariate analysis. A history of benign breast disease (histologically proven) and life stress appear to have a significant association with

Table 1 Main Demographic Variables for Cases and Controls, and Disease Status for the Control Group

	Cases		Controls			Cases		Controls	
	No.	(%)	No.	(%)		No.	(%)	No.	(%)
Age (yrs)					**Occupation**				
24-29	9	(4.8)	9	(4.8)	Professional	85	(45.7)	46	(24.7)
30-34	16	(8.6)	24	(12.9)	Worker	54	(29.0)	122	(65.6)
35-39	42	(22.6)	47	(25.3)	Farmer	39	(21.0)	12	(6.5)
40-44	57	(30.7)	52	(28.0)	Others	8	(4.3)	6	(3.2)
45-49	51	(27.4)	44	(23.7)					
50-55	11	(5.9)	10	(5.4)					
					Disease status				
Education					Mastopathy			27	(14.5)
None/primary	7	(3.8)	6	(3.2)	Fibroadenoma			7	(3.8)
Secondary	41	(22.0)	11	(5.9)	Mastitis			2	(1.1)
High school	103	(55.4)	147	(79.0)	Others			18	(9.7)
College/above	35	(18.8)	22	(11.8)	No diseases			132	(71.0)

Table 2 Odds Ratios (ORs) and OR 95% Confidence Intervals (95%CI) for Reproductive and Demographic Variables, History of Disease and Passive Smoking in Adulthood

Factors	No. of cases	No. of controls	OR	OR 95%CI
Age at menarche (>=13 yrs) (yes/no)	140/46	163/23	0.43	(0.24-0.77)
Age at first childbirth (>=30 yrs) (yes/no)[#]	9/149	8/144	1.09	(0.37-3.19)
Age at menopause (<45 yrs) (yes/no)[##]	5/11	4/18	2.05	(0.36-12.01)
Education levels				
None or primary	7	6	1	(reference)
Secondary	41	11	3.19	(0.75-13.78)
High school	103	147	0.60	(0.17-2.06)
College or above	35	22	1.36	(0.35-5.34)
Occupation				
Professional	85	46	1	(reference)
Worker	54	122	0.24	(0.14-0.40)
Farmer	39	12	1.76	(0.79-3.95)
Other	8	6	0.72	(0.21-2.52)
Family history of cancer (yes/no)	23/163	15/171	1.61	(0.77-3.37)
Hospitalization at age <=16 yrs (yes/no)	33/153	21/165	1.69	(0.90-3.19)
History of benign breast disease (yes/no)	32/154	18/168	1.94	(1.01-3.77)
History of stress (yes/no)	38/148	22/164	1.91	(1.04-3.52)
X-ray exposure (yes/no)	94/92	76/110	1.48	(0.96-2.28)
Passive smoking in the workplace in adulthood (yes/no)	97/89	77/109	1.54	(1.00-2.37)
0 (none-smokers)	89	109	1	(reference)
1-4 smokers	61	48	1.56	(0.95-2.56)
5-9 smokers	12	19	0.77	(0.33-1.78)
>=10 smokers	24	10	2.94	(1.26-6.99)
Test for trend			p<0.05	

[#]: applies to 157 cases and 153 controls; [##]: applies to 16 cases and 22 controls

risk of BC: with ORs (95%CI) of 1.94 (1.01-3.77) and 1.91 (1.04-3.52), respectively. PS in the workplace appeared to have a statistically significant association with BC [1.54 (1.00-2.37), p=0.048]. A dose-response relationship between exposure to smokers and risk of BC was observed (test for trend p<0.05).

Table 3 shows the OR (95% CI) of BC for selected variables at three life periods. In childhood, women of low weight were at increased risk of BC [OR (95%CI): 2.43 (1.45-4.07) and 2.73 (1.32-5.68) for those with slightly low and low body weights compared to those with average levels]. Height was not a significant risk factor for BC (95% CI of OR includes 1). Exposure to PS at home and poor family socioeconomic status were associated significantly with a high risk of BC (test for trend p<0.05).

Women of low weight as teenagers (youth) were also at increased risk of BC. Again, height was not a significant risk factor. Increasing frequency of exposure to smokers and exposure to higher smoking levels at home appear to be associated with a higher risk of BC, but these effects were not statistically significant (test for trend p>0.05). Poor socioeconomic status during the teenage years increased the risk of BC (test for trend p<0.05).

In adulthood, both low weight and overweight appeared to be associated with BC. Increased level of exposure to smoking at home was associated with an increased risk of BC (test for trend p<0.01). Poor socioeconomic status again appeared as a risk factor for BC (test for trend p<0.01).

Multiple conditional logistic regression analysis

To explore the independent risk effects of PS, and of other early life experience factors on BC, several covariates were adjusted by using conditional logistic regression models. These variables included education (coding 1, 2, 3 and 4 for none/primary, secondary, high school and college/above levels), occupation (1, 2, and 3 for farmer, worker/other and

Table 3 Early Life Experience in Childhood, Youth and Adulthood for the Risk of Breast Cancer

Factors	In childhood (age < 10) Cases/ Controls	Odds ratio (95%CI)	In youth (age 10-16) Cases/ controls	Odds ratio (95%CI)	In adulthood Cases/ controls	Odds ratio (95%CI)
Body weight						
Low	29 / 16	2.73 (1.32-5.68)	22 / 14	2.04 (1.10-5.27)	3 / 1	4.78 (0.43-121.8)
Slightly low	66 / 41	2.43 (1.45-4.07)	59 / 25	3.61 (2.03-6.44)	59 / 22	4.28 (2.32-7.93)
Average[#]	75 / 113	1 (reference)	85 / 130	1 (reference)	69 / 110	1 reference)
S-overweight[##]	16 / 12	2.01 (0.84-4.38)	20 / 14	2.18 (0.99-4.86)	55 / 53	1.65 (0.99-2.76)
Overweight	0 / 4	-	0 / 3	-		
Test for trend	P<0.01 (average to low)		p<0.01 (average to low)		p<0.01 (no change to low)	
Height						
Below average	42 / 28	1.57 (0.88-2.79)	48 / 18	1.17 (0.70-1.93)		
Average	115 / 120	1 (reference)	109 / 127	1 (reference)		
Above average	29 / 38	0.80 (0.44-1.42)	29 / 41	0.82 (0.46-1.46)		
No. of exposed to smokers at home						
0	57 / 64	1 (reference)	59 / 611	1 (reference)	96 / 114	1 (reference)
1	101 / 112	1.01 (0.63-1.62)	94 / 107	0.91 (0.56-1.46)	84 / 65	1.53 (0.98-2.40)
2	20 / 9	2.50 (0.98-6.49)	25 / 15	1.72 (0.78-3.38)	4 / 5	0.95 (0.21-4.22)
>=3	8 / 1	8.98 (1.08-197.3)	8 / 3	2.76 (0.62-13.8)	2 / 2	1.19 (0.12-12.1)
Test for trend		p<0.05		p>0.05		p>0.05
Exposed to smoking levels at home						
0	57 / 64	1 (reference)	59 / 61	1 (reference)	96 / 114	1 (reference)
Light	27 / 44	0.69 (0.36-1.31)	34 / 45	0.78 (0.42-1.44)	8 / 20	0.47 (0.18-1.20)
Medium	50 / 43	1.31 (0.73-2.33)	63 / 58	1.12 (0.66-1.92)	51 / 37	1.64 (0.96-2.79)
Heavy	35 / 24	1.64 (0.83-3.23)	17 / 13	1.35 (0.64-3.59)	18 / 10	2.14 (0.88-5.25)
Very heavy	17 / 11	1.74 (0.70-4.36)	13 / 9	1.49 (0.55-4.14)	13 / 5	3.09 (0.98-10.3)
Test for trend		p<0.05		p>0.05		p<0.01
Family economic situation						
Poor	8 / 2	1 (reference)	5 / 3	1 (reference)	14 / 0	-
Slightly poor	50 / 45	0.28 (0.04-1.53)	50 / 33	0.91 (0.16-4.80)	16 / 6	1 (reference)
Average	114 / 117	0.24 (0.03-1.27)	121 / 135	0.54 (0.10-2.65)	123 / 69	0.67 (0.02-0.22)
Above average	14 / 22	0.16 (0.02-101)	10 / 15	0.40 (0.06-2.61)	33 / 111	0.11 (0.04-0.34)
Test for trend		p<0.05		p<0.05		p<0.01)

#: no bodyweifht change for adults. ##: slightly overweight

professional status), age at menarche (years), age at first childbirth (years), age at menopause (years), exposure to chest X-rays (0, 1 for none and yes), family history of cancer (0, 1 for none and yes), history of benign breast diseases (0, 1 for none and yes), HSHD (0, 1 for none and yes), history of stress (0, 1 for none and yes), and PS index (as a cumulative dose, calculated as the number of smokers times their smoking categories). Because either low body weight or overweight; and low or high economic status (compared to average levels) might be risk factors for BC, two dummy variables were used for each of them. There were, LBW [0, 1 for average body weight (reference) and low body weight], and OBW (0, 1 for average body weight and overweight); LES [0, 1 for average economic status (reference) and low economic status]; and HES (0, 1 for average economic and high economic status).

In the final logistic regression model, the following factors were selected into the model at $p<0.05$ (Table 4): (1) Passive smoking at home in childhood [OR (95%CI): 1.24 (1.07-1.43)]; passive smoking at home in adulthood [4.07 (2.21-7.50)] and passive smoking in the workplace [1.27 (1.04-1.55)] increased risk of BC. (2) Age at menarche was negatively associated with risk of BC [0.83 (0.72-0.95)]. (3) Low body weight in childhood and overweight in adulthood were associated with high risk of BC [1.54 (1.09-2.18) and 1.76 (1.02-3.04)], respectively). (4) Low socioeconomic status in youth was associated with risk of BC [1.03 (1.00-1.06)]. (5) HSHD in childhood/youth [2.41 (1.21-4.81)]; history of benign breast disease [2.05 (1.01-4.16)] and history of life stress [2.32 (1.54-3.48)] were associated with high risk of BC.

Discussion

The present study showed that PS and several other early life experience risk factors were associated significantly with risk of BC. These main findings are consistent with those of previous studies (Chen et al., 1995; Colditz et al., 1995; Hamajima et al., 1995; Hilakivi et al., 1994; Hsieh et al., 1990; Le-Marchand et al., 1988; Liu et al., 1995; Micozzi et al., 1987; Peters et al., 1996; Sandler et al., 1985a,b; Ursin et al., 1995; Vatten et al., 1990; Yuan et al., 1988;). Two important features of this study, however, were (1) that these results were obtained for Chinese women who have a much lower incidence and mortality rate from BC than do Caucasians. (2) Few Chinese women are smokers (about 4%), while more than 60% of Chinese men aged more than 15 years are smokers. Passive smoking status has become a serious problem in China, either in public places, workplaces or at home, in recent decades. The results of this study not only add evidence to that obtained from other etiological studies of PS in relation to BC, but also provide important messages for public health and prevention of BC.

Few studies have investigated the association between body weight in early life and subsequent risk of BC. Our results indicate that lower body weight (than average) in childhood is an independent risk factor for BC. This association remained significant after adjustment for other covariates (Table 4). Similar observations in previous studies have been reported in the West (Le-Marchand et al., 1988; Micozzi et al., 1987; Ursin et al., 1995). On the other hand, previous studies (Den et al., 1995; Lubin et al., 1985; Swanson et al., 1989) and this present study all observed that women who are overweight as adults have a higher risk of BC than those with an average (normal) body weight. Some studies suggest that being overweight is associated with high risk of postmenopausal BC, while low body weight has been observed to be a risk factor in pre-menopausal women (Paffenbarger et al., 1980 and Walter et al., 1985). The mechanisms are not clear. However, changes in body weight and menopausal status may both be important predictors for BC. These findings, in general, suggest that having an

Table 4 Multiple Logistic Regression Analysis Showing Statistically Significant Risk Factors for Breast Cancer

Factors	Regression coefficient	SE	Odds ratio (95% CI)
Passive smoking at home in childhood (PS index)	0.216	0.074	1.24 (1.07 - 1.43)
Passive smoking at home in adulthood (PS index)	1.404	0.312	4.07 (2.21 - 7.50)
Passive smoking at working places in adulthood (PS index)	0.238	0.101	1.27 (1.04 - 1.55)
Age at menarche (yrs)	-0.192	0.073	0.83 (0.72 - 0.95)
Low body weight in childhood (y/n)	0.433	0.176	1.54 (1.09 - 2.18)
Overweight weight in adulthood (y/n)	0.566	0.278	1.76 (1.02 - 3.04)
Low family economic situation in youth (y/n)	0.029	0.013	1.03 (1.00 - 1.06)
History of hospitalized diseases in childhood/youths (y/n)	0.881	0.352	2.41 (1.21 - 4.81)
History of benign breast disease (y/n)	0.717	0.362	2.05 (1.01 - 4.16)
History of life stress (y/n)	0.180	0.090	2.32 (1.54 - 3.48)

PS index is calculated as the number of smokers times their smoking categories (1=light, 2=medium, 3=heavy, 4=very heavy).

appropriate body weight at all stages of life should benefit women's health.

Although several studies have demonstrated that poor socioeconomic status is significantly associated with risk of cardiovascular disease and all causes of death, there has been no report, to our knowledge, of an association between socioeconomic status in early life and subsequent risk of BC (Van et al., 1995). In the present study, we observed that poor socioeconomic situation in early life was associated significantly with a subsequent high risk of BC. Although poor socioeconomic status may be a marker for other factors, such as previous history of suffering from hospitalized disease, benign breast disease or life stress, the association between early life economic situation and risk of BC was still statistically significant after adjustment for several covariates. Benign breast disease and life stress, in particular, have been described as risk factors in other studies (Chen et al., 1995; Colditz et al., 1995; Hislop et al., 1981), and we have also observed this in the present investigation.

No published data have previously examined a relationship between HSHD (history of suffering from a hospitalized disease) in early life and subsequent risk of breast cancer. Our results showed that HSHD may be an independent risk factor for breast cancer. This may also indicate that poor health status in early life could play an important role in the subsequent development of breast cancer.

Vatten et al. reported (Vatten et al., 1990) a positive association between height and risk of breast cancer, but other studies (Le-Marchand et al., 1988 and Kenji et al., 1994) did not find an association between children's height and subsequent risk of breast cancer. Similarly, our study found no such association.

A family history of breast cancer and exposure to chest X-rays were observed as risk factors for breast cancer in other studies (Colditz et al., 1993; Segala et al., 1991; Slattery et al., 1993; Yuan et al., 1988), but not in the present case (we used family history of cancers as the index, because there were few subjects with family history of BC). Possible limitations in our study are (1) the sample size was too small to test a significant association between family history of BC and risk of BC; (2) our controls were selected from those who sought breast examination and/or routine health examination, so that the controls with chest X-rays may be more prevalent than in the general population. Furthermore, in the study, all cases were survivors, as in most case-control studies. Fatal cases were not included, and those may have had more serious risk profiles than had survivors. This may have led to an underestimation of risk in relation to BC (survival bias). Our present results for odds ratios gave somewhat small values [range of 1.03 (family economic status in youth) to 4.07 (PS at home as adults), Table 4]. The true odds ratios may be even bigger. Therefore, we should to keep in mind of these possible limitations while interpreting our results overall.

In conclusion, our results indicate that PS in early and later life is associated significantly with risk of BC in Chinese women who have never smoked. These findings highlight the importance of control of smoking. The present study also confirms that other factors, such as age at early menarche, benign breast disease, lifelong stress, as well as being overweight as an adult are important risk factors for BC. The associations between low body weight and low socioeconomic status in early life and subsequent high risk of BC require further study.

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