RESEARCH ARTICLE

Induced Abortion and Breast Cancer: Results from a Population-Based Case Control Study in China

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Abstract

Aim: To determine whether induced abortion (IA) increases breast cancer (BC) risk. Materials and Methods: A population-based case-control study was performed from Dec, 2000 to November, 2004 in Shanghai, China, where IA could be verified through the family planning network and client medical records. Structured questionnaires were completed by 1,517 cases with primary invasive epithelial breast cancer and 1,573 controls frequency-matched to cases for age group. The information was supplemented and verified by the family planning records. Statistical analysis was conducted with SAS 9.0. Results: After adjusting for potential confounders, induced abortions were not found to be associated with breast cancer with OR=0.94 (95%CI= 0.79-1.11). Compared to parous women without induced abortion, parous women with 3 or more times induced abortion (OR=0.66, 95%CI=0.46 to 0.95) and women with 3 or more times induced abortion after the first live birth (OR=0.66, 95%CI =0.45 to 0.97) showed a lower risk of breast cancer, after adjustment for age, level of education, annual income per capita, age at menarche, menopause, parity times, spontaneous abortion, age at first live birth, breast-feeding, oral contraceptives, hormones drug, breast disease, BMI, drinking alcohol, drinking tea, taking vitamin/calcium tablet, physical activity, vocation, history of breast cancer, eating the bean. Conclusions: The results suggest that a history of induced abortions may not increase the risk of breast cancer.

Keywords: Breast cancer - induced abortion - case control study

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Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in female worldwide, accounting for 23% (1.38 million) of the total new cancer cases and 14% (458, 400) of the total cancer deaths in 2008. About half the breast cancer cases and 60% of the deaths are estimated to occur in economically developing countries. In general, incidence rates are high in Western and Northern Europe, Australia /New Zealand, and North America; intermediate in South America, the Caribbean, and Northern Africa; and low in sub-Saharan Africa and Asia (Jemal et al., 2011). Although developed countries report higher rates of breast cancer incidence and mortality, changes in the incidence of breast cancer are dramatic in developing countries including China in recent years (Dandan et al., 2010; Yan et al., 2010).

The potential causes of breast cancer remain unclear, despite intense studies were conducted in the world. Numerous epidemiological studies over the last decade worldwide have revealed a number of risk factors associated with breast cancer and most of them have produced evidence on the association of reproductive factors with breast cancer risk (Hulka et al., 2001; Hadjisavvas et al., 2010; Jemal et al., 2010). Reproductive factors are clearly of importance, but the mechanism of their influence on breast cancer is still complex and need to have more reassessment. It was difficult to disentangle their possible effects and the degree of the effectiveness if positive. The main reasons are reproductive factors might related to other multiple factor, which might unidentified underlying causal factors and might be weakly related to the risk of breast cancer.

Exact statistics on the number of abortions in China performed annually are hard to come by as not all abortions are registered. However experts in China noted that induced abortions are more common in urban areas, where couples may only have one child and unmarried women could have unplanned pregnancy which lead to the induced abortion. Abortion in China is legal and is a government service available on request for women and women who have several induced abortions do not feel stigmatized. The incidence rate of induced abortion is high in China. According to the China Statistical Yearbook,

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there were 9.17 million IA cases in 2008 and 6.11million in 2009 (Ministry of Public Health of the People's Republic of China, 2010). Shanghai is more developed city in China with highest induced abortion and highest breast cancer. The crude incidences of breast cancer were about 44.86 per 100 thousands in 2002, while increased to 59.14 in 2008. The prevalence of breast cancer was 9.6, 19.7 and 19.1 per 100 thousands respectively in 2007, 2008 and 2009 in Shanghai (Ministry of Public Health of the People's Republic of China, 2010). The clarification of the association of IA with breast cancer may shed light on a deeper understanding of the roles of pregnancy-related factors in the natural history of breast cancer development and this owns public health significance in China. The present study was conducted to determine whether induced abortion is risk factor of breast cancer.

Materials and Methods

Study participants

Total 1595 women of cases with a histological confirmed diagnosis of primary breast cancer between Dec, 2000 to Nov., 2004 were selected from the database of Shanghai Cancer Record with age under 60 years, and 1517 women completed the investigation (the response rate was 95.11%). The controls were selected randomly from the database of Shanghai Household Register System. The controls with any known chronic diseases, or any hormone related diseases were excluded. The control group consisted of 1794 women matched frequently with the case group matched on age within three years interval, and 1517 women finished the investigation with the 87.68% response rate.

Data collection

The study was approved by the Ethics Committee of Shanghai Institute of Planned Parenthood Research. The informed consents were signed by each participant before starting the investigation after the detailed introduction by trained investigator. Demographic information, detailed information about induced abortion, some confirmed risk factors, and some possible influencing factors of breast cancer were collected from both cases and controls women with specially designed questionnaire, through a face-to-face interview conducted by skilled interviewers. The questionnaire mainly included information on age, marital status, and level of education, exercise status, family history of breast cancer, use of hormone drugs and a range of reproductive characteristics such as age at menarche, any pregnancy, gestation period, parity, overall duration of breastfeeding, use of oral contraceptives and the history of abortion. The abortion information were verified and supplemented through the family planning records by family planning network.

Statistical analysis

Means and standard errors of continuous variables and frequencies of categorical variables were calculated for cases and controls, separately. The frequencies were cross-tabulated and differences in participant characteristics between cases and controls were statistically assessed using the chi-square test. The risk factors of breast cancer were identified by crude and adjusted odds ratio (OR) and related 95% confidence intervals (CI) using univariate and multivariate logistic regression analysis. The confounding risk factors identified in this study and other studies were adjusted in multivariable models. p value of < 0.05 was considered significant in the statistical analyses. In the case of ordered categorical variables (e.g. age at first IA), p-value for linear trend was reported. All analyses were performed in SAS version 9.0 (SAS Institute, Cary, NC).

A number of characteristics investigated here may be dependent on each other, or may be expected to display a high degree of colinearity, or may be nested in each other. The inter-relationships between these variables and the extent to which they are independently associated with breast cancer risk were firstly assessed in order to avoid multi-colinearity in the final model and identify appropriate course of action.

Results

Characteristics on demography of two groups

No statistically significant differences between cases and controls were observed in terms of age, marital status, and annual income per capita in the last year before the referent data, religion, and category of skin or hair and so on. In contrast, a higher proportion of cases than controls reported high level of education (15.8% *vs* 9.3%). Although the majority of the two groups were workers, more controls (41.0%) than cases (34.5%) reported being worker, and a higher proportion of cases than controls reported doing mental labor including doctor, teacher and researcher (7.6% *vs* 5.3%) and civil servant and accountant (26.2% *vs* 20.1%).

Characteristics of induced abortion distribution

In the case group and the control group, the proportions of induced abortion were 67.1% and 68.3%, respectively. In the group of age <35 years old, 55.2% reported ever having had an induced abortion, and the proportions were increasing with the age older. The proportion of induced abortion was higher in the group of low level of education. 74.1% of the group having accepted education of elementary school or lower level reported ever having had an induced abortion, while the proportion was 59.2% in the group having accepted education of university or higher level. Among nulliparous women, 12.1% reported ever having had an induced abortion, while 75.7% reported among women had having twice parity at least. The proportion of induced abortion was higher in the group whose age at first live birth was smaller, and 79.2% of the women whose age at first live birth were before 25 years old reported ever having had an induced abortion. Among the participants, 62.9% reported their induced abortion happened after first live birth. In addition, the proportions of induced abortion were higher in the groups with low annual income per capita, breast-feeding, taking oral contraceptives, alcohol drinking, worker, having a family history of breast cancer. And there was no significant difference in the proportions of induced abortion between the groups with different characteristics of menarche age,

menopause or not, taking hormones drug or not, having a history of benign breast disease or not, having tea or not, taking vitamin/calcium or not, exercise or not.

The relationship of induced abortion and breast cancer

The crude and adjusted ORs and 95% CI were calculated in this study. According to literatures, education, vocation, age at menarche, menopause, parity, hormone drug taking, history of breast cancer, history of benign breast disease, drinking alcohol, habit of tea drinking, physical activity, habit of bean eating were adjusted in multivariable logistic regression, which showed that induced abortion was not statistically significantly associated with the risk of breast cancer among all women (OR=0.94, 95%CI=0.79 to 1.11) (Table 1).

Characteristics of induced abortion and breast cancer among parous women

According to the results of previous studies (Costarelli et al., 2010; Hadjisavvas et al., 2010), parity is one of the risk factor of breast cancer. And in the present study, the proportion of induced abortion in the parous group was significant different with that in the nulliparous group. So parity substratification analysis was needed in order to avoid the confounding of parity. In the current study, only 14 nulliparous women reported ever having had an induced abortion, so we analyzed the relationship of characteristics of induced abortion and breast cancer in the parous women instead in the all women.

Among parous women, we observed no relationships between once or twice induced abortions, first induced abortion happening before or after first live birth, the times of induced abortion before the first live birth, the times of induced abortion after the first live birth and risk of breast cancer. Compared to the women without induced abortion, women with 3 or more times induced abortion and women with 3 or more times induced abortion after the first live birth showed the lower risk of breast cancer after adjusted by the factors of age, level of education, annual income per capita, age at menarche, menopause, parity times, spontaneous abortion, age at first live birth, breast-feeding, oral contraceptives, hormones drug, breast disease, BMI, drinking, drinking tea, taking vitamin/calcium tablet, physical activity, vocation, history of breast cancer, eating the bean (OR=0.66, 95%CI=0.46 to 0.95 and OR=0.66, 95%CI=0.45 to 0.97, respectively), while the relationships was not observed in the crude model (Table 2) .

In analyses restricted to parous women, the associations between breast cancer and the time characteristics of induced abortion including age at first induced abortion, the duration from first induced abortion to the referent data, gestational weeks at first induced abortion and the duration between first induced abortion and first live birth, were not found. The ORs for the associations between the duration from first induced abortion to the referent data and

Table 1. The Association of Induced Abortions with Breast Cancer

		Case		Control		OR	(95%CI)	OR*	95%CI
		n	%	n	%				
All women	No	492	32.9	498	31.7	1	(Ref.)	1	(Ref.)
	Yes	1003	67.1	1075	68.3	0.94	0.81-1.10	0.94	(0.79-1.11)
Nulliparous women#	No	68	90.7	51	87.9	1	(Ref.)		
	Yes	7	9.3	7	12.1	0.75	(0.24-2.32)		
Parous women	No	424	29.9	447	29.5	1	(Ref.)	1	(Ref.)
	Yes	996	70.1	1068	70.5	0.98	(0.84-1.15)	0.94	(0.79-1.12)

*Adjusted for age, level of education, annual income per capita, age at menarche, menopause, parity times, spontaneous abortion, age at first live birth, breast-feeding, oral contraceptives, hormones drug, breast disease, BMI, drinking, drinking tea, taking vitamin/calcium tablet, physical activity, vocation, history of breast cancer, eating the bean. #Did no adjustment, because the number of nulliparous women was too few

Table 2. The Association between Induced Abortion with Breast Cancer among Parous Women

	Case		Control		OR	(95%CI)	OR*	95%CI
	n	%	n	%				
IA times								
0	424	29.9	447	29.5	1	(Ref.)	1	(Ref.)
1	658	46.3	714	47.1	0.97	(0.82-1.15)	0.94	(0.78-1.13)
2	266	18.7	254	16.8	1.1	(0.89-1.37)	1.06	(0.83-1.34)
3+	72	5.1	100	6.6	0.76	(0.54-1.05)	0.66	(0.46-0.95)
First IA before or after first live birth								
before	117	8.2	100	6.6	1.23	(0.92-1.66)	1.16	(0.85-1.60)
after	879	61.9	968	63.9	0.96	(0.81-1.12)	0.92	(0.77-1.09)
IA times before first live birth								
1	108	20	89	16.3	1.28	(0.94-1.75)	1.3	(0.92-1.84)
2+	9	1.7	11	2	0.86	(0.34-2.10)	0.83	(0.30-2.24)
IA times after first live birth								
1	653	48	709	48.4	0.97	(0.82-1.15)	0.93	(0.77-1.11)
2	218	16	219	15	1.05	(0.83-1.32)	1	(0.78-1.28)
3+	65	4.8	89	6.1	0.77	(0.54-1.09)	0.66	(0.45-0.97)

*Adjusted for age, level of education, annual income per capita, age at menarche, menopause, parity times, spontaneous abortion, age at first live birth, breast-feeding, oral contraceptives, hormones drug, breast disease, BMI, drinking, drinking tea, taking vitamin/calcium tablet, physical activity, vocation, history of breast cancer, eating the bean. #Did no adjustment, because the number of nulliparous women was too few

Table 3. The Association between the Characteristics of Induced Abortion with Breast Cancer among Parous Women

	Case		Control		OR	(95%CI)	OR*	95%CI
	n	%	n	%				
Age at first IA								
No IA	424	29.9	447	29.5	1	(Ref.)	1	(Ref.)
<25	60	4.2	86	5.7	0.74	(0.52-1.05)	0.76	(0.51-1.14)
25-	470	33.1	534	35.2	0.93	(0.77-1.11)	0.89	(0.73-1.10)
30-	341	24	333	22	1.08	(0.88-1.32)	1.02	(0.82-1.27)
35+	125	8.8	115	7.6	1.15	(0.86-1.53)	1	(0.73-1.36)
p‡					0.998			
Duration from first IA to the referent data (year)#								
<10	151	10.6	142	9.4	1.12	(0.86-1.46)	1.06	(0.79-1.43)
10-	318	22.4	313	20.7	1.07	(0.87-1.32)	1.03	(0.83-1.30)
15-	338	23.8	395	26.1	0.9	(0.74-1.10)	0.87	(0.70-1.08)
20+	189	13.3	218	14.4	0.91	(0.72-1.16)	0.82	(0.61-1.09)
p‡					0.153			
Gestational weeks at first IA (week)#								
<8	734	51.7	738	48.7	1.05	(0.89-1.24)	1.01	(0.84-1.21)
8-	205	14.4	259	17.1	0.83	(0.67-1.05)	0.79	(0.62-1.01)
12+	57	4	71	4.7	0.85	(0.58-1.23)	0.78	(0.52-1.16)
p‡					0.053			
Duration between first IA and first live birth (year)								
<2	566	56.8	626	58.6	1	(Ref.)	1	(Ref.)
2-	212	21.3	220	20.6	1.07	(0.86-1.33)	1.04	(0.82-1.32)
4-	111	11.1	98	9.2	1.25	(0.93-1.68)	1.34	(0.98-1.84)
6+	107	10.7	124	11.6	0.95	(0.72-1.27)	0.94	(0.69-1.28)
p‡					0.746			

*Adjusted for age, level of education, annual income per capita, age at menarche, menopause, parity times, spontaneous abortion, age at first live birth, breast-feeding, oral contraceptives, hormones drug, breast disease, BMI, drinking, drinking tea, taking vitamin/calcium tablet, physical activity, vocation, history of breast cancer, eating the bean. ‡Trend test. #the women without IA as reference

breast cancer were decreasing with the duration increasing and the OR for the association between 20 years or more from first induced abortion to the referent data and breast cancer reduced to 0.82 (95%CI=0.61 to 1.09), but no trend emerged for the duration from first induced abortion to the referent data (P for trend=0.153). P-value for trend between gestational weeks at first induced abortion and breast cancer risk was 0.053. The association between the first induced abortion after first live birth year and breast cancer had no statistical significance (Table 3) .

Discussion

The etiology of breast cancer is still poorly understood. Epidemiological studies conducted in different populations have identified a spectrum of well established and probable risk factors for breast cancer, but known breast cancer risk factors explain only a small proportion of cases (Naieni et al., 2007; Ozmen, et al., 2009). There is a dispute about the relationship between induced abortion and breast cancer. There are two mechanisms hypothesized to underlie an association of induced abortion to breast cancer risk. The first is that women who undergo abortion do not experience the long-term protection against breast cancer that a full-term pregnancy would provide. The second hypothesis is that the breasts of women undergoing induced abortions are exposed to high hormone levels typical of early normal pregnancy, but then do not experience the terminal cell differentiation that occurs late in a normal pregnancy, leaving breast tissue more vulnerable to carcinogens (Henderson, et al., 2008).

The controversial effects of induced abortion on breast cancer have been studied extensively. But the results of these studies are also not consistent, and public concern regarding the relationship between induced abortion and breast cancer risk continues to be voiced. Some studies (Daling et al., 1996; Yanhua et al, 2012; Toleutay, et al., 2013) found induced abortion was the risk factor of breast cancer, but the study in Yunnan province (Yanhua et al, 2012) and in Kazakhstan (Toleutay, et al., 2013) were hospital-based case-control studies, which might have the selection basis for control group. A study found a positive association between induced abortion and breast cancer risk in women younger than 50, and a negative association in older women (Michels et al., 1995) .There were other studies presented that induced abortion wasn't a risk factor or failed to detect an association between induced abortion and breast cancer (Sanderson et al., 2001; Ye et al., 2002; Michels et al., 2007), even a protective factor of breast cancer (Erlandsson et al, 2003; Mahue-Giangreco et al., 2003). In a study in Swedish, induced abortion was associated with a reduced risk of breast cancer (Lindefors-Harris et al., 1989). In our study, the proportion of nullipara was few and only 4.3% in all the participatants, the relationship of induce abortion to breast cancer in parous was analyzed more, which didn't support the hypothesis that induced abortion increase the breast cancer risk, while it showed that 3 or more times induced abortion might be a protective factor parous women.

In a study (Mahue-Giangreco et al., 2003), they found that as the number of induced abortions increased, breast cancer risk declined among nulliparous women

(trend p=0.04). Similarly, in another study (Friedman et al., 2006), having two or more therapeutic abortions might be associated with a lowered risk of breast cancer among BRCA2 mutation carriers. But another study (Jiang et al, 2012) found that women who had 3 or more times of induced abortion were at increased risk of breast cancer, but which had lower sample size (n<26, in the group of induced abortion ≥3). In our study, a strong inverse association was observed between breast cancer risk and ever having had three time or more time induced abortions. But the trend of breast cancer risk decreasing with the times of induced abortion was not observed. Generally, mammary glandular cells will proliferate and differentiate when pregnancy beginning. When the pregnancy terminated by induced abortion, the process of proliferation and differentiation would stop. But with the times of induced abortion increasing, the non-differentiated cells would be decreasing, and the susceptibility of epithelial cells to future carcinogenic stimuli would be decreasing too, so the risk of breast cancer would decline. This hypothesis provides a rational interpretation for the inverse association between breast cancer risk and the times of induced abortions.

Full-term pregnancy was reported to confer a protective effect on breast cancer risk primarily through the mechanism that permanent structural and functional changes, induced in the mammary parenchyma by the reproductive process including exposure to pregnancy hormones, may result in a lower susceptibility of epithelial cells to future carcinogenic stimuli (Russo et al., 1987; Russo et al., 1991; Ma et al., 2010). The greatest distinction between a induced abortion and a full-term pregnancy lies in the gestation weeks. In our study, p value for trend between gestational weeks at first induced abortion and breast cancer risk was 0.053 which nearly have statistical significance. So we could presume that with the gestational weeks of induced abortion increasing, the structural and functional changes of breast may be more similar with that induced by full-term pregnancy, and the association between breast cancer risk and induced abortion may be more similar with that between breast cancer risk and full-term pregnancy.

Our study was a population-based case-control study focus on induced abortion and breast cancer, details about induced abortion were collected by questionnaire survey and supplied by clients' medical records, which were accurate and the recall bias could be avoided. And the control group was sampled from all the crowd in Shanghai, not from hospital, which can eliminate some biases from hospital. This study could provide scientific evidence about the relationship between induced abortion and breast cancer. Although our results do not approve that a history of induced abortions may increase the risk of breast cancer, induced abortion could increase physical and psychological risks (Thorp et al., 2003), among females, experience of an abortion within a current relationship was associated with increased risk for various forms of sexual dysfunction (122-182%) (Coleman et al., 2009). So, we suggest that all kinds of consequence resulted by induced abortion should be consided integrately before terminating a pregnancy.

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