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
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 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-collinearity 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, breastfeeding, 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 |
|------------|--------|---------|------|----------|-----|--------|
| All women  | No     | 492     | 32.9 | 498      | 31.7 | 1      | 1 (Ref.) |
|            | Yes    | 1003    | 67.1 | 1075     | 68.3 | 0.94   | 0.81-1.10 |
|            |        |         |      |          |      | 0.94   | 0.79-1.12 |
| 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.) |
|            | 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 |
|------------|--------|---------|------|----------|-----|--------|
| IA times   | 0      | 424     | 29.9 | 447      | 29.5 | 1      | (Ref.) |
|            | 1      | 658     | 46.3 | 714      | 47.1 | 0.97   | 0.82-1.15 |
|            | 2      | 266     | 18.7 | 254      | 16.8 | 1.1    | 0.89-1.37 |
|            | 3+     | 72      | 5.1  | 100      | 6.6  | 0.76   | 0.54-1.05 |
| First IA before or after live birth | 0      | 117     | 8.2  | 100      | 6.6  | 1.23   | 0.92-1.66 |
|            | 1      | 879     | 61.9 | 968      | 63.9 | 0.96   | 0.81-1.12 |
| IA times before live birth | 1      | 108     | 20   | 89       | 16.3 | 1.28   | 0.94-1.75 |
|            | 2+     | 9       | 1.7  | 11       | 2    | 0.86   | 0.34-2.10 |
| IA times after live birth | 1      | 653     | 48   | 709      | 48.4 | 0.97   | 0.82-1.15 |
|            | 2      | 218     | 16   | 219      | 15   | 1.05   | 0.83-1.32 |
|            | 3+     | 65      | 4.8  | 89       | 6.1  | 0.77   | 0.54-1.09 |

*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
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 risk declined 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 risk was 0.053. The association between the characteristics of induced abortion with breast cancer among parous women was 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.

**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 participants, 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.

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

| Age at first IA | Case | Control | OR (95%CI) | OR* 95%CI |
|----------------|------|---------|------------|-----------|
| No IA          | 424  | 29.9    | 447        | 29.5      |
| <25            | 60   | 4.2     | 86         | 5.7       |
| 25-            | 470  | 33.1    | 534        | 35.2      |
| 30-            | 341  | 24      | 333        | 22        |
| 35+            | 125  | 8.8     | 115        | 7.6       |
| p‡             |      |         | 0.74       | (0.52-1.05)|
|                |      |         | 0.93       | (0.77-1.11)|
|                |      |         | 1.08       | (0.88-1.32)|
|                |      |         | 1.15       | (0.86-1.53)|
|                |      |         | 0.998      |           |
| Duration from first IA to the referent data (year)‡ |      |         |            |           |
| <10            | 151  | 10.6    | 142        | 9.4       |
| 10-            | 318  | 22.4    | 313        | 20.7      |
| 15-            | 338  | 23.8    | 395        | 26.1      |
| 20+            | 189  | 13.3    | 218        | 14.4      |
| p‡             |      |         | 1.12       | (0.86-1.46)|
|                |      |         | 1.07       | (0.87-1.32)|
|                |      |         | 0.9        | (0.74-1.10)|
|                |      |         | 0.91       | (0.72-1.16)|
|                |      |         | 0.998      |           |
| Gestational weeks at first IA (week)‡ |      |         |            |           |
| <8             | 734  | 51.7    | 738        | 48.7      |
| 8-             | 205  | 14.4    | 259        | 17.1      |
| 12+            | 57   | 4       | 71         | 4.7       |
| p‡             |      |         | 1.05       | (0.89-1.24)|
|                |      |         | 0.83       | (0.67-1.05)|
|                |      |         | 0.85       | (0.58-1.23)|
|                |      |         | 0.95       | (0.72-1.27)|
|                |      |         | 0.998      |           |
| Duration between first IA and first live birth (year)‡ |      |         |            |           |
| <2             | 566  | 56.8    | 626        | 58.6      |
| 2-             | 212  | 21.3    | 220        | 20.6      |
| 4-             | 111  | 11.1    | 98         | 9.2       |
| 6+             | 107  | 10.7    | 124        | 11.6      |
| p‡             |      |         | 1.07       | (0.86-1.33)|
|                |      |         | 1.25       | (0.93-1.68)|
|                |      |         | 0.95       | (0.72-1.27)|
|                |      |         | 0.94       | (0.69-1.28)|
|                |      |         | 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.
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(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 \( \geq 3)\). 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 assume that with the gestational weeks of induced abortion increasing, the structural and functional changes of breast may be more similar with that 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 for trend of female breast cancer incidence in Minhang district, Shanghai. China Cancer, 19, 108-10.

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