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Induced abortion and breast cancer

An updated meta-analysis

Yongchun Deng, MD, Hua Xu, MM, XiaoHua Zeng, MD*

Abstract

Different epidemiological studies have indicated conflicting information about the association of induced abortion (IA) with breast cancer risk. A recent meta-analysis with prospective evidences did not support the positive association between IA and breast cancer risk. Thus, we in our meta-analysis study have tried to analyze this specific association.

We searched all relevant articles from an English-language literature using Pubmed, Embase, and Cochrane databases, until December 10, 2016. All the statistical analyses were performed on case–control studies, using Review Manager Software 5.3 (Cochrane Collaboration, Oxford, UK).

Our meta-analysis results based on 25 studies, including 5 studies with Chinese patients, indicated that there was no association of IA with breast cancer (OR = 1.08, 95% CI 0.98–1.19, $P = .1$). However, significant heterogeneity was observed, and thus further subgroup analyses were conducted. The combined OR of subjects with only 1-time IA was 1.03, 95% CI 0.90 to 1.18, $P = .63$, while for subjects with 2 or more IAs, it was 1.06, 95% CI 0.86 to 1.30, $P = .58$. In addition, the ORs of subjects, with 1st IA age either less than 30 or older than 30, were 1.05, 95% CI 0.88 to 1.26, $P = .59$, and 1.18, 95% CI 0.93 to 1.49, $P = .17$, respectively. These observations indicated that number of IAs and the age of 1st IA were not associated with breast cancer risk. Due to lack of dose–response relationships, it is difficult to say if number of IAs contributed into statistical heterogeneity. But after subgroup analysis, the age at the 1st IA appeared to impact the statistical heterogeneity. The different reproductive history appears to account for the high heterogeneity among individual studies. Also analysis of nulliparous women showed no significant difference in the association of IA and breast cancer (OR = 1.02, 95% CI 0.86–1.21, $P = .85$). However, parous women had higher IA rate in case group than control group (OR = 1.11, 95% CI 1.02–1.20, $P = .01$). Ethnicities might also result in high heterogeneity; thus, we conducted subgroup analyses on Chinese subjects, importantly, with 5 studies having Chinese patients, and did not observe any difference in the incidence of IA and its association with breast cancer between case and control groups (OR = 1.05, 95% CI 0.97–1.13, $P = .21$).

After subgroup analysis, our study showed that IA might increase the risk of breast cancer in parous women, but in the nulliparous, IA was not significantly associated with an increased risk of breast cancer.

Abbreviations: IA = induced abortion, SA = spontaneous abortion.

Keywords: breast cancer, induced abortion, meta-analysis, risk factor

1. Introduction

Breast cancer is one of the most common women cancer, both in developed and developing countries, and thus appears to be a worldwide public health problem. Global research data also indicate that breast cancer has the highest diagnosed cases and is the 2nd-leading cause of cancer deaths among women, after lung cancer.[1] Importantly, as compared to western white women, the Chinese women depict historically lower risk of breast cancer. However, recent epidemiological study in China showed that breast cancer alone accounted for 15% of all the new cancer-related cases in women, and demonstrated increasing trend in mortality. This study also emphasized that breast cancer has been the leading cause of cancer death in women younger than 45 years of age.[2]

The exact mechanism of breast cancer pathogenesis is not completely clear, but several risk factors for the disease have been established, including: female gender, increasing patient age, family history of breast cancer at a young age, early menarche, late menopause, old age at 1st live childbirth, prolonged hormone replacement therapy, previous exposure to the therapeutic chest wall irradiation, benign proliferative breast disease, increased mammographic breast density, and genetic mutation of the *BRCA1/2* genes.[3] In addition, several epidemiological studies showed number of births, alcohol use, obesity, physical inactivity, a reduced duration (or avoidance) of breast-feeding, and induced abortion (IA) as factors related with breast cancer incidence.[4–8]

Typically, there are 2 mechanisms hypothesized to underlie an association of IA to breast cancer risk. First, the women undergoing abortion usually do not experience long-term

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YD and HX contributed equally to this work.

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protection against breast cancer in comparison to full-term pregnancy. Second, the breasts of women who have undergone IA are exposed to typically high hormone levels during early pregnancy, but later they do not experience the terminal cell differentiation, a step that occurs in late pregnancy. This makes breast tissue more vulnerable to carcinogens.[9] Hence, many studies about incomplete pregnancy and development of breast cancer were conducted but did not come to a convinced conclusion. A recent meta-analysis[10] further confirmed this view of IA association with increased risk of breast cancer in Chinese females. But some of the studies in this meta-analysis review included IA data together with spontaneous abortion (SA), and thus made the conclusions doubtful. In addition, the European Prospective Investigation into Cancer and Nutrition also specifically reported about the lack of association between IA and breast cancer risk, but it did show a positive association with SA.[11] Similarly, another systematic review based on prospective studies provided an evidence about no positive association between abortion (both IA and SA) and breast cancer risk.[12] But this meta-analysis only included 1 study with Chinese subjects with high IA incidence.

Thus, due to conflicting reports about the association of IA with risk of breast cancer, we decided to undertake a new meta-analysis by selecting studies which specifically tested the association of IA only, with breast cancer, and also included more number of Chinese subjects than in the previously published studies. For avoiding repetitive analysis as done in study by Guo et al, and obtaining larger samples including Chinese, we have chosen only case–control studies.

2. Methods

2.1. Search strategy

All the relevant clinical studies were searched from the English-language literature using Pubmed, Embase, and Cochrane databases, until December 10, 2016. The following key words, "breast cancer," "breast carcinoma," "breast neoplasm," "breast tumor," "mammary cancer," "mammary carcinoma," "mammary neoplasm," "mammary tumor," and "induced abortion" were used for literature search, by 2 individual authors. We also performed a full manual search of the bibliographies of selected studies to identify additional studies. To maximize data acquisition, we contacted authors whose articles contained insufficient information.

2.2. Inclusion and exclusion criteria

The following inclusion criteria were used to select relevant studies: case–control studies about the association between IA and breast cancer risk (case group, breast cancer patient group; control group, healthy controls); all subjects in the case group were histopathologically diagnosed for having primary breast cancer; and all controls were without prior breast cancer diagnoses, any known chronic diseases, or any hormone-related diseases. However, the reviews, meta-analyses, or case reports with no appropriate controls, and studies focusing on SA or which did not differentiate between SA and IA, and with incomplete or unavailable data, were excluded from our meta-analysis.

2.3. Data extraction

Two authors (Deng and Xu) separately evaluated the retrieved studies, according to the eligibility criteria. The following information was extracted from each paper study; number of subjects in each study; details on the study design, including first author, year of publication, region, and type of study; and sample size of each arm and subgroup. In addition, when there was any discrepancy, 3rd author (Zeng) was consulted for consensus.

2.4. Study quality

The quality of each study was independently assessed by the same 2 authors (Deng and Xu) according to the following criteria: studies designed with case characteristics matched to controls; followed strict inclusion and exclusion criteria for patients; and the methodological quality of included studies described by Newcastle–Ottawa scale.[13]

2.5. Statistical analysis

All statistical analyses were performed with Review Manager Software 5.3 (Cochrane Collaboration, Oxford, UK). The chi-squared (I^2) test was used to detect heterogeneity, and when I^2 value exceeded 50% with 10% level of significance ($P < .10$), it represented significant heterogeneity, and thus random effect model was used for analysis, including subgroup analysis. In other instances, the fixed effect model was used for analysis. The combined ORs (measure of efficacy) with 95% CIs were calculated, and the publication bias was assessed with funnel plot analysis.

2.6. Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors, so there was not ethical approval in the study.

3. Results

3.1. Identification of relevant studies

Using the study selection criteria, we identified a total of 452 studies from the literature. After complete scanning of the titles and abstracts, only 49 clinical studies related to IA and development of breast cancer were retrieved and subjected to further detailed evaluation. Among these 47 were fully published text studies but we ultimately obtained only 43 full texts. Few more studies were excluded as, 1 was repetitive study, and another 10 studies used different styles of statistic measures, 1 was case report and another 2 were meta-analyses. The inclusion criteria, later led to exclusion of another 4 prospective studies, and thus overall only 25 studies were finally included in our meta-analysis. These studies had a total of 28,278 breast cancer subjects and 40,783 controls (Fig. 1). Complete information about the total number of cases and additional subgroups has been listed in Table 1 and Table-supplement, http://links.lww.com/MD/C80. The four[14–17] studies exclusively had the data about association between number of IAs and breast cancer, among parous women (underlined data in Table 1).

3.2. Data synthesis

The meta-analysis based on all selected studies[14–38] indicated that there was no significant association between IAs and breast cancer among patients and controls (OR = 1.08, 95% CI 0.98–1.19, $P = .1$, Fig. 2). There was no publication bias observed for this dataset as analyzed through funnel plot (Fig. S1, http://links.

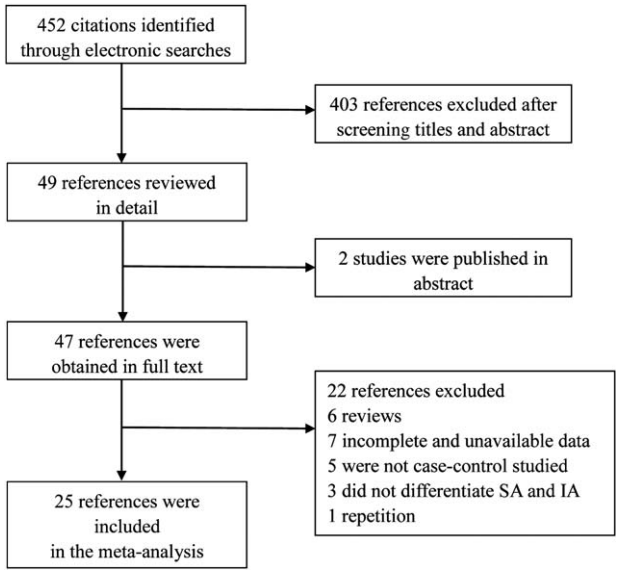

Figure 1. Flow chart depicting the literature-search and study-selection process.

lww.com/MD/C80). However, significant heterogeneity (79%) was observed, and thus we further conducted subgroup analyses based on number of IAs, age of 1st IA, childbearing history, and race, in an effort to understand the reasons of high heterogeneity.

3.3. Subgroup analyses

Eight[18,22,24,25,32,34–36] studies had the data about number of IAs in cancer patients and controls. So, first the subjects were stratified based on the number of IAs, that is, one time or more than one time. Interestingly, both these subgroups did not show any significant association with breast cancer. The combined OR of one time IA was 1.03, 95% CI 0.90 to 1.18, $P=.63$, while OR of more than one time IAs was 1.06, 95% CI 0.86 to 1.30, $P=.5$ (Fig. 3). Also, no publication bias was observed in both subgroups, as shown in Fig. S2, http://links.lww.com/MD/C80. Although I^2 values were 56% and 60%, respectively, for one time and more than one time IAs, it is difficult to say heterogeneity could impact the statistical heterogeneity for lack of dose–response relationships.

Next, three[24,25,34] studies had the information about the specific age when 1st IA occurred, and thus we stratified the patients as younger (less than 30 years) or older (above 30 years of age). Again, we observed no significant difference in the association of IAs with breast cancer in both subgroups, as the observed OR in younger subgroup was 1.05, 95% CI 0.88 to 1.26, $P=.59$, $I^2=0\%$, while in older subgroup, it was 1.18, 95% CI 0.93 to 1.49, $P=.17$, $I^2=41\%$, (Fig. 4). The funnel plot analysis showed no significant publication bias (Fig. S3, http://links.lww.com/MD/C80). Importantly, the overall I^2 value was 0% in younger subgroup, which suggested that the age of 1st IA did contribute into the heterogeneity.

In addition, we also conducted a subgroup analysis based on the reproductive history. Based on the analysis of nine[14,15,17,22,23,27,30,31,33] studies about nulliparous women, it was observed that there was no difference in the association between IA and breast cancer (OR = 1.02, 95% CI 0.86–1.21, $P=.85$, $I^2=9\%$). However, opposite trend was observed when the data from parous women were analyzed. The IA did show significant association with breast cancer (OR = 1.11, 95% CI 1.02–1.20, $P=.01$, $I^2=34\%$) (Fig. 5). In addition, the funnel plot analysis revealed no significant publication bias for both nulliparous and parous group of patients (Fig. S4, http://links.lww.com/MD/C80). This analysis demonstrated that IA correlated with breast cancer rate in parous women. Additionally, there were four[14–17] studies, which typically had the data related to number of IAs and breast cancer in parous women. But, here we did not observe any significant association between one time IA (OR = 0.96, 95% CI 0.86–1.07, $P=.45$) or more than one IAs (OR = 1.03, 95% CI 0.89–1.18, $P=.07$) with breast cancer (data not shown).

Finally, five[14,18,19,25,26] studies exclusively had the data about Chinese patients, and our meta-analysis indicated that there was no significant association between IA and breast cancer (OR = 1.05, 95% CI 0.97–1.13, $P=.21$) (Fig. 6), along with no publication bias (Fig. S5, http://links.lww.com/MD/C80). The I^2 value was 81%, which emphasized that heterogeneity was not related to specific ethnicity.

4. Discussion

Multiple studies worldwide have indicated about the association between IA and breast cancer. In 1990, the study by Li et al suggested about IA as the risk factor for breast cancer.[39] Similarly, the meta-analysis by Brind et al[40] also arrived at similar conclusions. However, on the contrary, some other studies arrived at different conclusions. Specifically, the study by Mahouri et al[41] showed that there was no relationship between breast cancer and IA. The data from another study also indicated that IA was not associated with breast cancer incidence.[42] A systematic review including meta-analysis by Guo et al[12] concluded about not having sufficient evidence to support the positive association between IA and breast cancer risk. Thus, these conflicting reports posed a major question about the effects of IA on breast cancer, and led us to undertake this meta-analysis which included 25 studies. However, our study also concluded that there was no association between IA and breast cancer. But we did observe significant heterogeneity and thus further analyzed the association at the subgroup level to identify additional possible factors regulating high heterogeneity.

At the subgroup levels, 2 studies by Giangreco et al[23] and Friedman et al,[43] which were part of our analysis also, indicated that the increasing number of IAs might be associated with lowered risk of breast cancer. Although the study by Jiang et al[18] observed that IA was associated with increased risk for breast cancer. However, our subgroup analysis concluded that number of IAs were not associated with breast cancer and were also not the cause of high heterogeneity. Similar trend was observed when subgroup analysis was performed with parous women. The whole idea of subgroup analysis based on the times of IAs was based on the hypothesis which states that multiple IAs decreased nondifferentiated cells, which subsequently reduced the susceptibility of epithelial cells to future carcinogenic stimuli, and hence reduced risk of breast cancer.[14]

In terms of identifying factor regulating high heterogeneity, our data indicated that age of 1st IA might be important and can contribute toward high heterogeneity. But, in parallel our subgroup analyses did not show significant association between 1st IA age and breast cancer. In this context, a study by Janet et al[34] concluded that association of elevated breast cancer risk with IA was high in women who have undergone their 1st IA,

Table 1

Characteristics of the clinical trials included in the meta-analysis.

	Study	Area	Type		Never abortion (n)	Ever abortion (n)								
							IA times		Age at 1st IA (n)			Parous or not (n)		
						Tolal	1 time	≥2 times	<25 y	25–30 y	>30 y	Nulliparous	Parous	NOS score*
1	Jun-Qing Wu 2014	China	Population-case–control study	Case	424/1420	1003/1495	658/1420	338/1420	NR	NR	NR	7/075	996/1420	B
				Control	447/1515	1075/1573	714/1515	354/1515	NR	NR	NR	7/058	1068/1515	
2	Ai-Ren Jiang 2012	China	Population-case–control study	Case	354/669	315/669	156/669	159/669	NR	NR	NR	NR	NR	A
				Control	436/682	246/682	145/682	101/682	NR	NR	NR	NR	NR	
3	Peng Xing 2010	China	Population-case–control study	Case	NR	827/1417	NR	NR	NR	NR	NR	NR	NR	B
				Control	NR	864/1587	NR	NR	NR	NR	NR	NR	NR	
4	Vahit Ozmen 2009	Turkey	Hospital-case–control study	Case	NR	742/1492	NR	NR	NR	NR	NR	NR	NR	A
				Control	NR	930/2167	NR	NR	NR	NR	NR	NR	NR	
5	David H Brewster 2005	UK	Hospital-case–control study	Case	NR	511/2833	NR	NR	NR	NR	NR	NR	NR	B
				Control	NR	2237/9888	NR	NR	NR	NR	NR	NR	NR	
6	Kathleen Meeske 2004	USA	Population-case–control study	case	100/414	128/560	52/414	34/414	NR	NR	NR	42/146	86/414	B
				Control	134/508	134/610	68/508	34/508	NR	NR	NR	32/102	102/508	
7	MM-Giangreco 2003	USA	Population-case–control study	Case	NR	192/744	NR	NR	NR	NR	NR	74/274	118/470	A
				Control	NR	203/744	NR	NR	NR	NR	NR	94/274	109/470	
8	Gunnar E 2003	Sweden	Population-case–control study	Case	1587/1759	172/1759	144/1759	28/1759	92/172	52/172	23/172	NR	NR	B
				Control	1522/1750	228/1750	188/1750	40/1750	121/228	68/228	31/228	NR	NR	
9	Z Ye 2002	China	Population-case–control study	Case	320/652	332/652	231/652	101/652	21/332	111/332	199/332	NR	NR	A
				Control	338/694	356/694	250/695	106/694	25/356	123/356	208/356	NR	NR	
10	C Robertson 2001	Slovenia	Population-case–control study	Case	377/624	247/624	160/624	87/624	NR	NR	NR	8/47	213/577	A
				Control	381/624	243/624	152/624	91/624	NR	NR	NR	3/39	204/585	
11	Maureen S 2001	China	Population-case–control study	Case	NR	910/1381	NR	NR	NR	NR	NR	NR	NR	B
				Control	NR	991/1492	NR	NR	NR	NR	NR	NR	NR	
12	Polly A Newcomb 2000	USA	Population-case–control study	Case	NR	23/138	NR	NR	NR	NR	NR	2/025	21/113	B
				Control	NR	44/252	NR	NR	NR	NR	NR	3/041	41/211	
13	Mei-TC Tang 2000	USA	Population-case–control study	Case	366/461	95/461	56/461	39/461	NR	NR	NR	NR	95/461	B
				Control	1700/2177	477/2177	318/2177	159/2177	NR	NR	NR	NR	477/2177	
14	Mei-TC Tang 2000	USA	Population-case control study	Case	NR	43/224	NR	NR	NR	NR	NR	NR	NR	B
				Control	NR	47/300	NR	NR	NR	NR	NR	NR	NR	
15	A Tavani 1999	Italy	Population-case–control study	Case	NR	87/579	NR	NR	NR	NR	NR	NR	NR	B
				Control	NR	108/668	NR	NR	NR	NR	NR	NR	NR	
16	Julie R Palmer 1997	USA	Population-case–control study	Case	NR	223/1366	NR	NR	NR	NR	NR	69/351	154/1015	B
				Control	NR	444/3199	NR	NR	NR	NR	NR	136/860	308/2259	
17	Matti A Rookus 1996	Netherlands	Population-case–control study	Case	NR	56/918	NR	NR	NR	NR	NR	13/159	43/759	B
				Control	NR	36/918	NR	NR	NR	NR	NR	10/117	26/801	
18	Janet R Dating 1996	USA	Population-case–control study	Case	752/958	301/1261	156/958	50/958	NR	NR	NR	95/303	206/958	A
				Control	704/902	261/1146	140/902	58/902	NR	NR	NR	63/244	198/902	
19	Alessandra Tanavi 1996	Italy	Population-case–control study	Case	2255/2567	312/2567	182/2567	130/2567	NR	NR	NR	NR	NR	B
				Control	2318/2587	269/2587	145/2587	124/2587	NR	NR	NR	NR	NR	
20	Loren Lipworth 1995	Sweden	Population-case–control study	Case	NR	366/820	NR	NR	NR	NR	NR	22/144	248/675	B
				Control	NR	559/1548	NR	NR	NR	NR	NR	54/333	352/1215	
21	Janet R Daling 1994	USA	Population-case–control study	Case	479/689	210/689	150/689	60/689	NR	169/689	41/689	NR	NR	A
				Control	580/781	201/781	142/781	59/781	NR	174/781	27/781	NR	NR	
22	Fabio Parazzini 1991	Switzerland	Hospital-case–control study	Case	2135/2394	259/2394	149/2394	110/2394	NR	NR	NR	NR	NR	B
				Control	1966/2218	252/2218	131/2218	121/2218	NR	NR	NR	NR	NR	
23	H-O Adamil 1990	Sweden and Norway	Population-case–control study	Case	349/422	73/422	60/422	13/422	NR	NR	NR	NR	NR	B
				Control	427/527	100/527	87/527	13/527	NR	NR	NR	NR	NR	
24	Hoolly L Howe 1989	USA	Population-case–control study	Case	NR	65/1451	NR	NR	NR	NR	NR	NR	NR	B
				Control	NR	34/1451	NR	NR	NR	NR	NR	NR	NR	
25	LA Brinton 1983	USA	Population-case–control study	Case	NR	16/1362	NR	NR	NR	NR	NR	NR	NR	B
				Control	NR	15/1250	NR	NR	NR	NR	NR	NR	NR	

NOS = Newcastle–Ottawa scale, NR = not reported.

* An NOS score of 4 or less indicates a high risk of bias, A, NOS score = 8–9; B, NOS score = 5–7.

The underline means these data only involved parous women in the original.

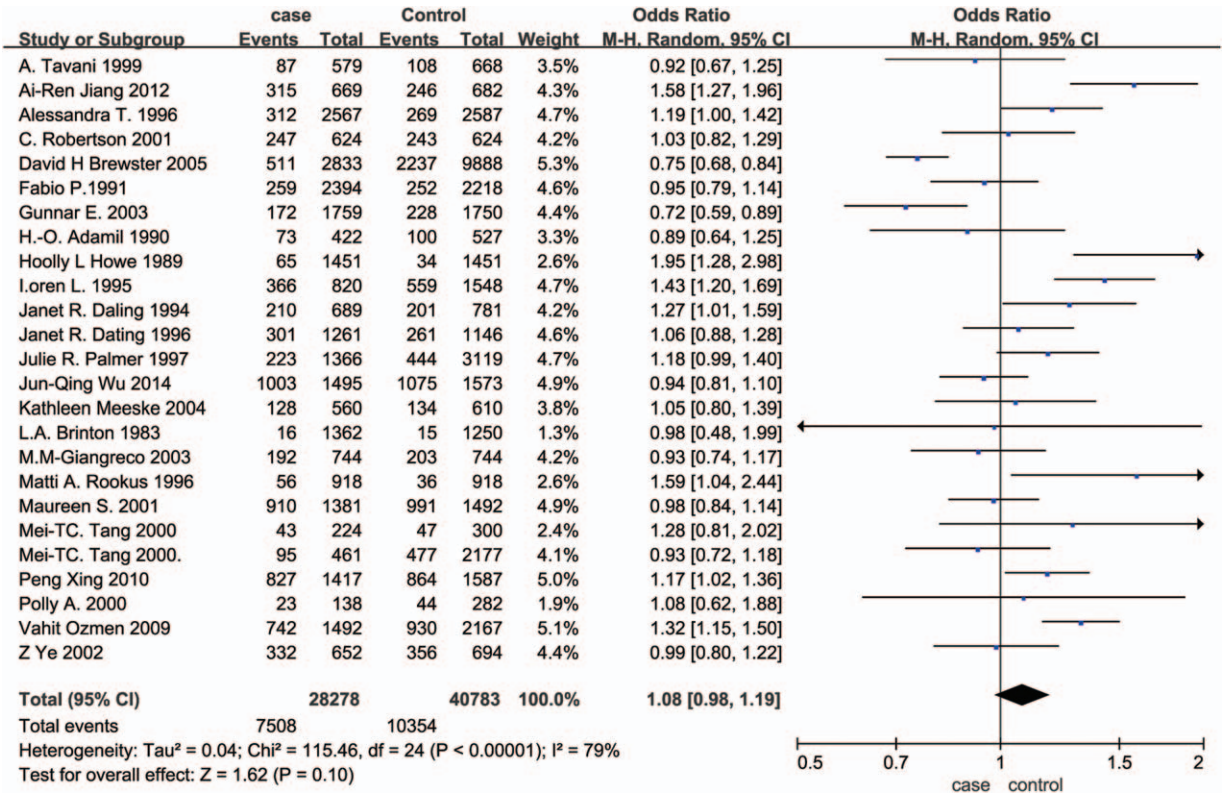

Figure 2. Forest plot of association between breast cancer and induced abortion (IA).

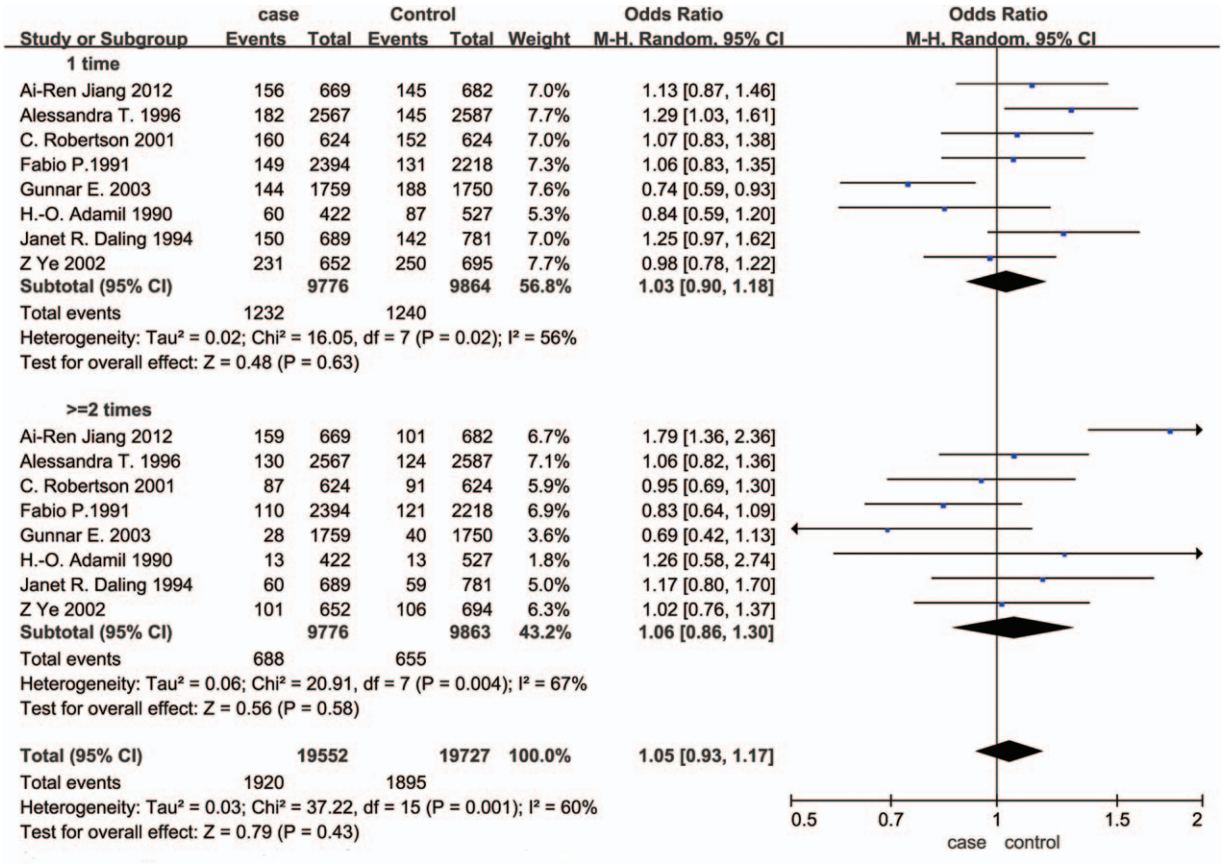

Figure 3. Forest plot of association between breast cancer and different number of induced abortions (IAs).

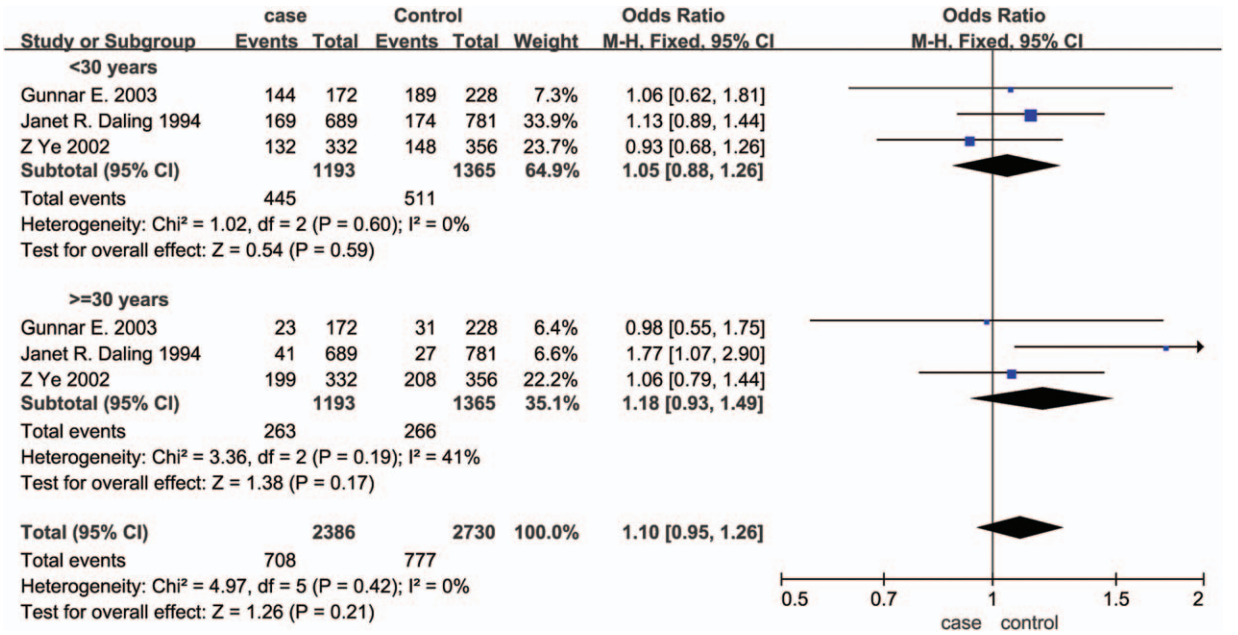

Figure 4. Forest plot of association between breast cancer and age of 1st induced abortion (IA).

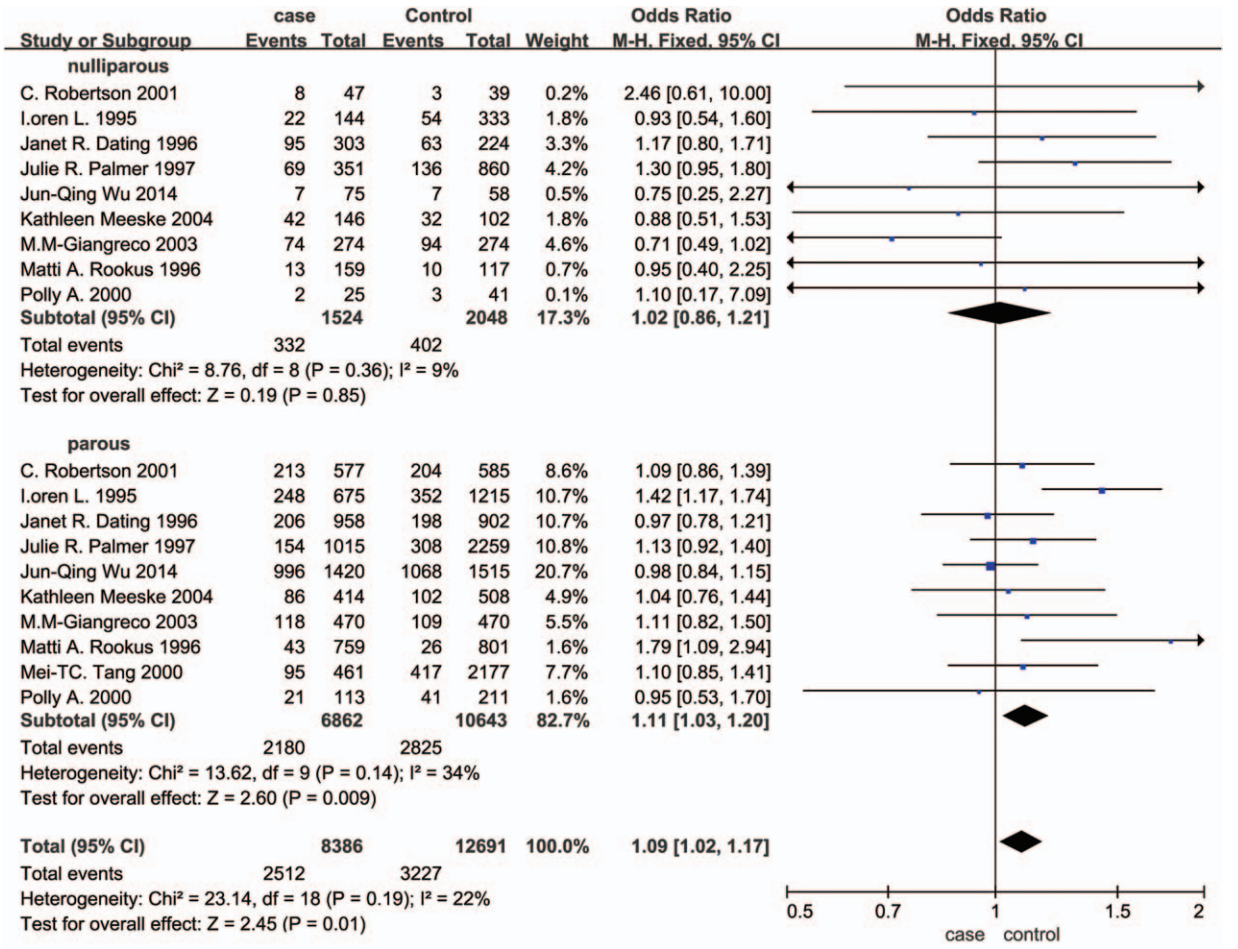

Figure 5. Forest plot of association between breast cancer and induced abortion (IA) in subjects with different reproductive history.

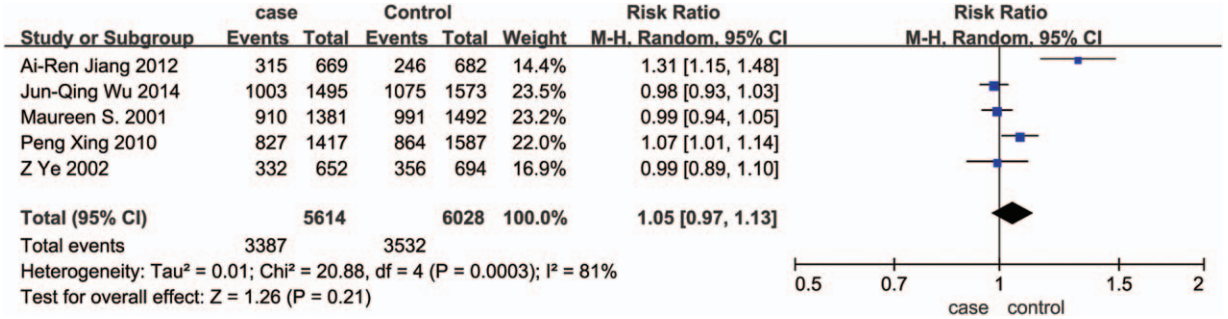

Figure 6. Forest plot of association between breast cancer and induced abortion (IA) in Chinese subjects.

either before 18 years of age or at age 30 years and older. However, in our analysis we only had 3 studies with data about age of patients with IAs, and our conclusion was based on the cutoff value "younger or older than 30." Thus, we believe that more detailed stratified analysis by age should be undertaken to further clarify the true nature of association of breast cancer with IA age.

In addition, we also performed the subgroup analysis based on different reproductive history to account for high heterogeneity among individual studies. Two epidemiological[44,45] reviews have pointed out that it would be most appropriate to separately compare the data from nulliparous and parous women. Infact, inclusion of parous women along with nulliparous may result in an increase in breast cancer risk for young women who have actually not had a full-term pregnancy due to their nulliparity and not because of incomplete pregnancy.[23] Therefore, in our analysis, we performed separate analyses for nulliparous and parous women, and observed that heterogeneity among different studies was decreased. This subgroup analysis showed that IA increased the risk of breast cancer for parous women, but not for nulliparous women. Parity, as such has been shown to be associated with reduced breast cancer risk, and the probable mechanism includes less estrogen in these women has low impact on breast tissues during pregnancy. For nulliparous women, the nulliparity is the main risk factor of breast cancer and might dilute the effect of IA. Thus, in parous women, IA might contribute to the breast cancer, as significant risk factor.

The use of IAs have been widely used in China, and 2 recent meta-analyses[10,12] investigating association between breast cancer and IA were conducted. The meta-analysis by Huang et al[10] showed that IA was a risk factor for breast cancer, but their subgroup analyses observed no significant associations between IA and breast cancer in the cohort of studies with Newcastle–Ottawa scale score of 8–9, despite high heterogeneity. Our analysis also conducted subgroup analyses exclusively using data from Chinese subjects. Ultimately, our analyses demonstrated no significant association between IA and breast cancer, and appeared that ethnicities might not contribute to the overall heterogeneity.

Importantly, there appeared to be several limitations to our meta-analysis and should be considered in parallel. First, all our studies were case–control studies, but still more high quality, well designed trials including cohort or prospective studies, and prospective cohort studies would be necessary those are less vulnerable to bias. Second, we only identified studies published in English literature, and this means that some high-quality studies published in other language might have been left out. Third, despite subgroup analyses undertaken by us, more detailed stratified studies about Chinese population would be required to get high confidence level in the results. Fourth, the studies used in our analysis were not exactly matched in terms of age at 1st birth, duration of breast-feeding, histopathological classification, and these differences also might contribute to the statistical heterogeneity.

In conclusion, despite several limitations, we have demonstrated that IA might increase the risk of breast cancer in parous women, but in the nulliparous, IA was not observed to be significantly associated with an increased risk of breast cancer. We did not observe any association between breast cancer risk and the times of IAs. The specific association between breast cancer and the 1st age of IA would require more high quality and detailed studies for further verification.

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